Anticorpi monoclonali nel trattamento del mieloma multiplo

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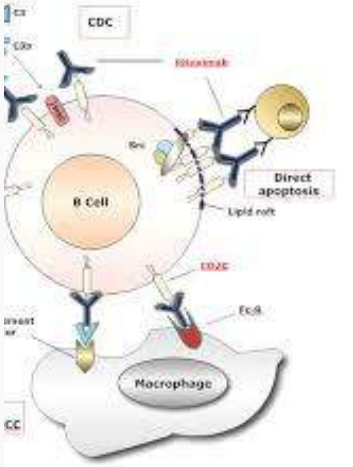
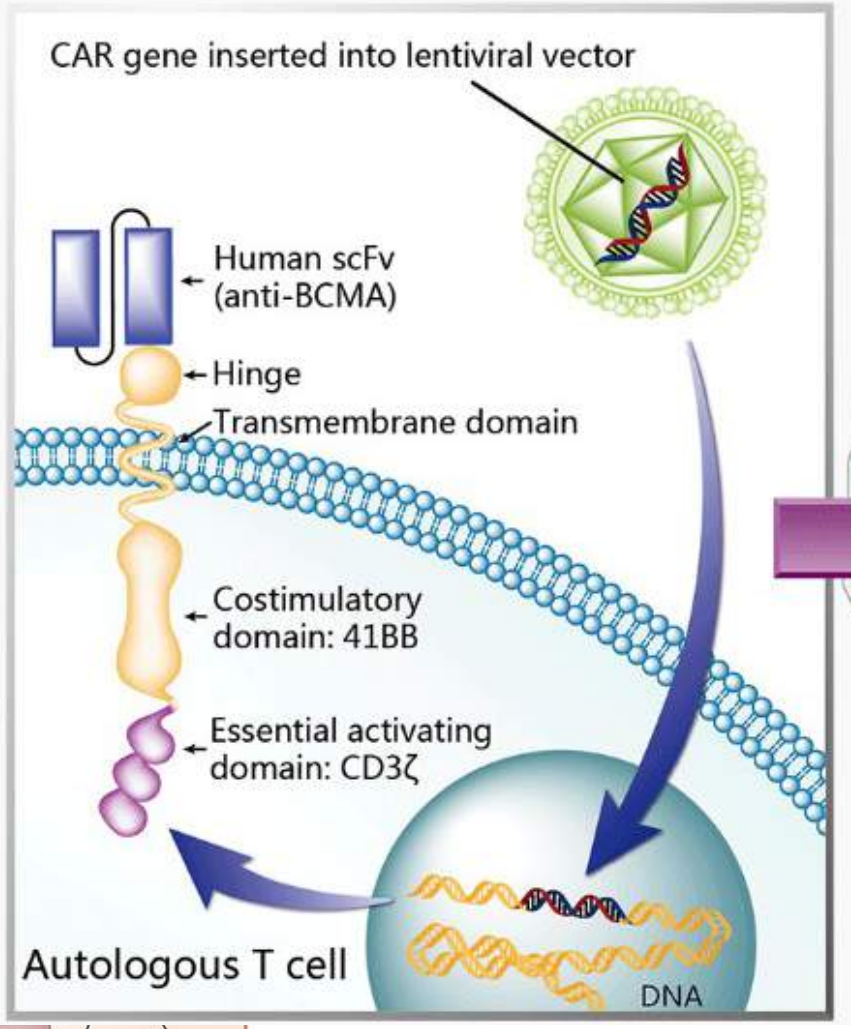
MM outcome and treatment options

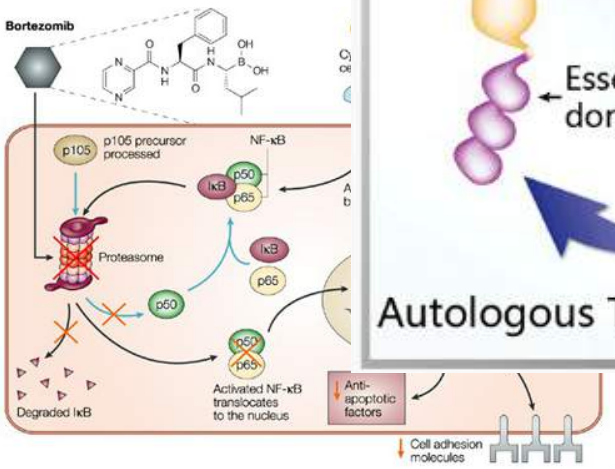
Chemotherapy

Monoclonal antibody

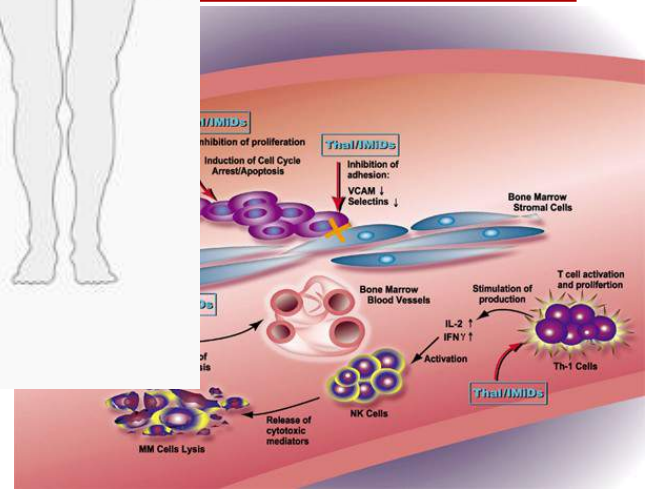




Proteasome inh



nunomodulators



MoAb is a new therapeutic strategy: target approach and favourable tolerability

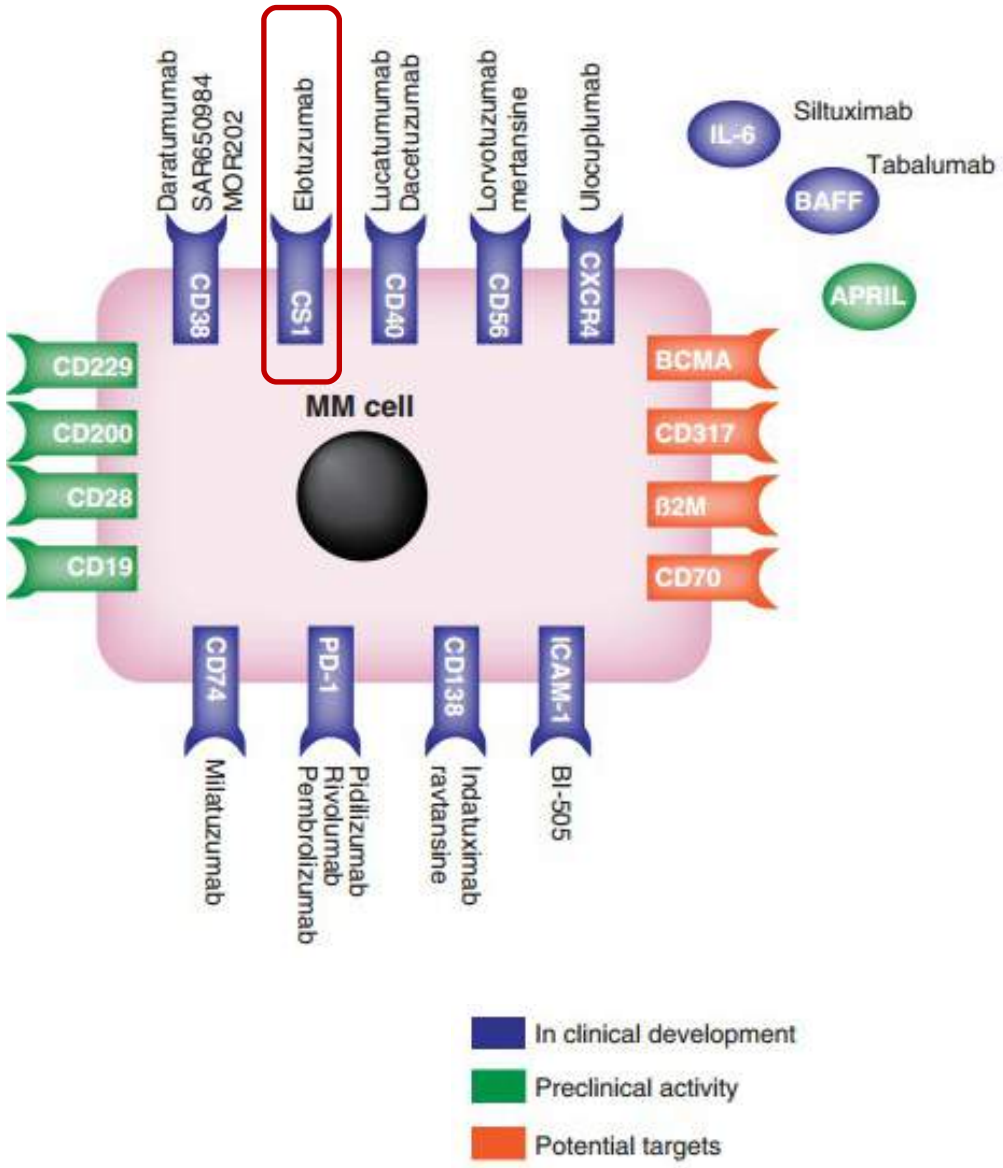
- ✓ New kind of treatment with distinct mode of action (CHT, IMIDS, PIs) to improve outcome in incurable disease

- ✓ Emergent potential strategy based on the range of antigens highly expressed on the surface of MM cells

- ✓ Potential benefit
  - ➢ Target approach to treatment
  - ➢ Favorable tolerability profile in usual elderly population

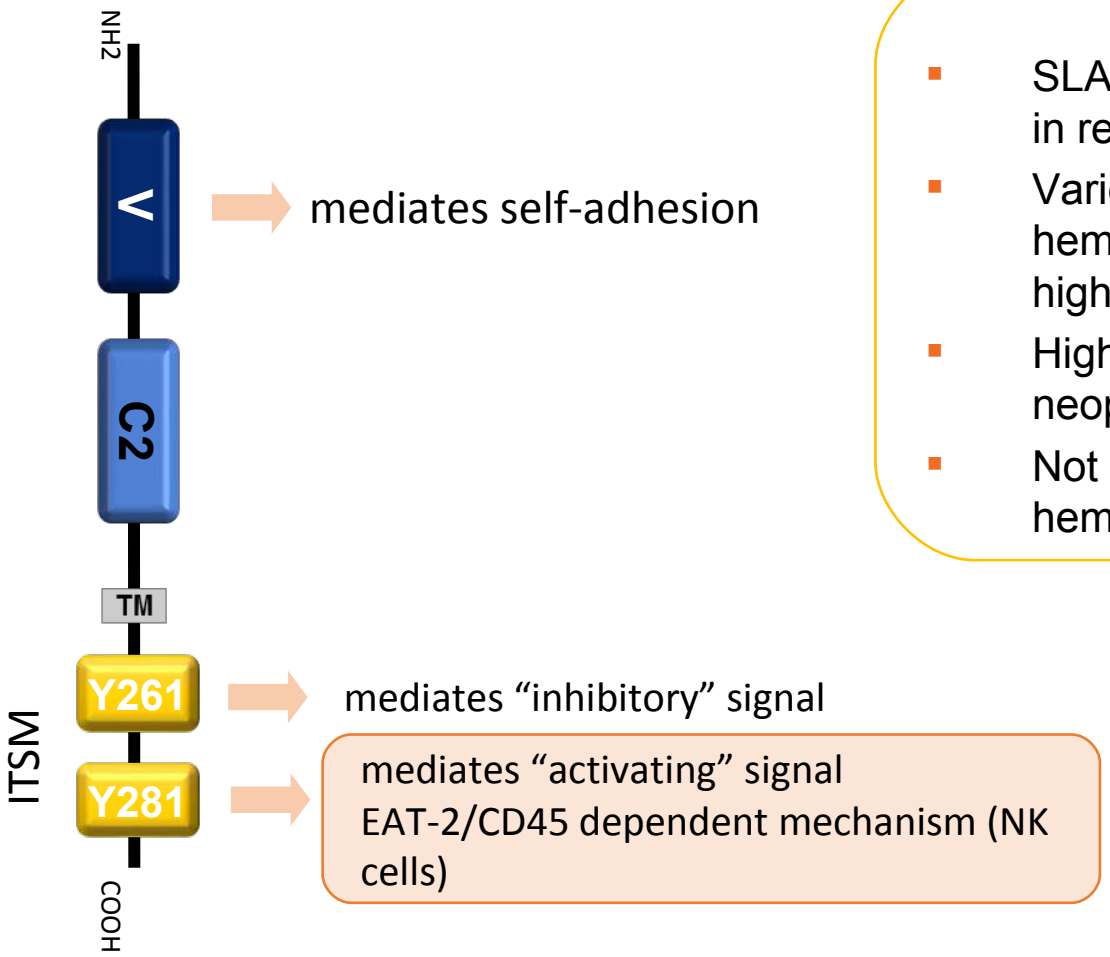
MM cells and its microenvironment: target molecules

- ✓ Ab anti SLAMF7 or CS1
- ✓ Ab anti CD38
- ✓ Ab anti PD-1/PDL-1
- ✓ Denosumab
- ✓ Other Ab targets



Lonial S, Leukemia 2016

SLAMF7: receptor involved in regulating immune response, expressed in hematopoietic cells and MM cells

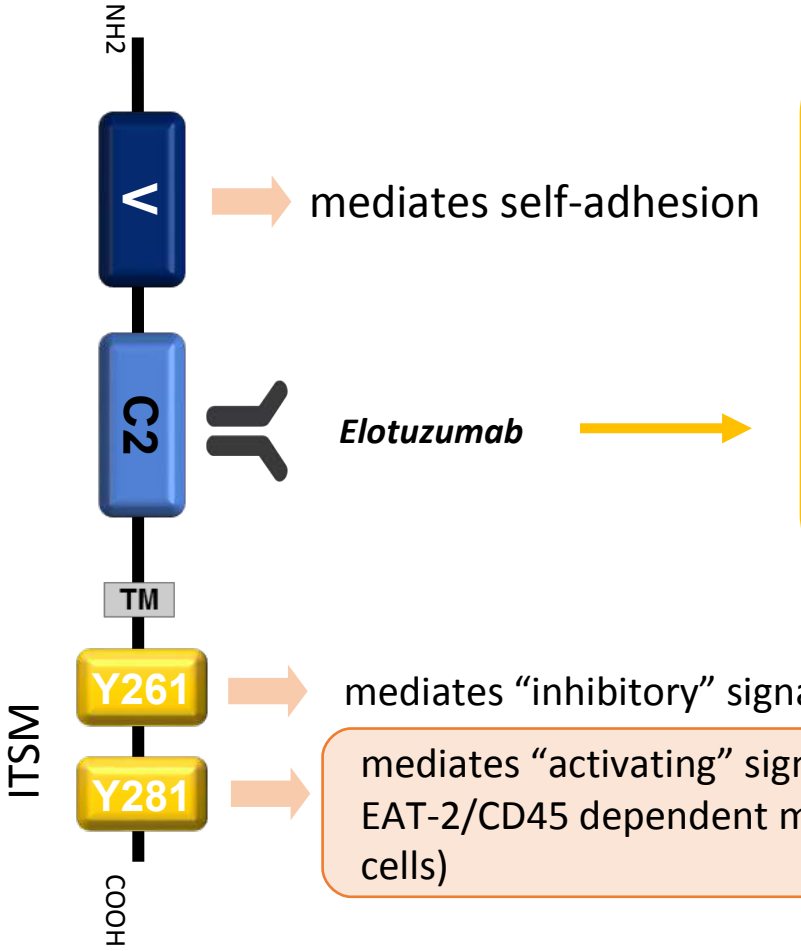


SLAMF7

- SLAM family receptor involved in regulating immune response
- Varied expression across hematopoietic cells: PC (very high), NK, TCD8+
- High expression in plasma cell neoplasia
- Not express on non-hematopoietic cells

Veillette et al, Critical Reviews in Onc and Heme, 2013
Cruz-Munoz et al, Nature Immunology, 2009.

Elotuzumab, a monoclonal Antibody targeting SLAMF7 that activates NK cells, but not MM cells



mediates self-adhesion

Elotuzumab

mediates "inhibitory" signal

mediates "activating" signal
EAT-2/CD45 dependent mechanism (NK cells)

Iotuzumab

umanized, IgG1 mab specific for human SLAMF7

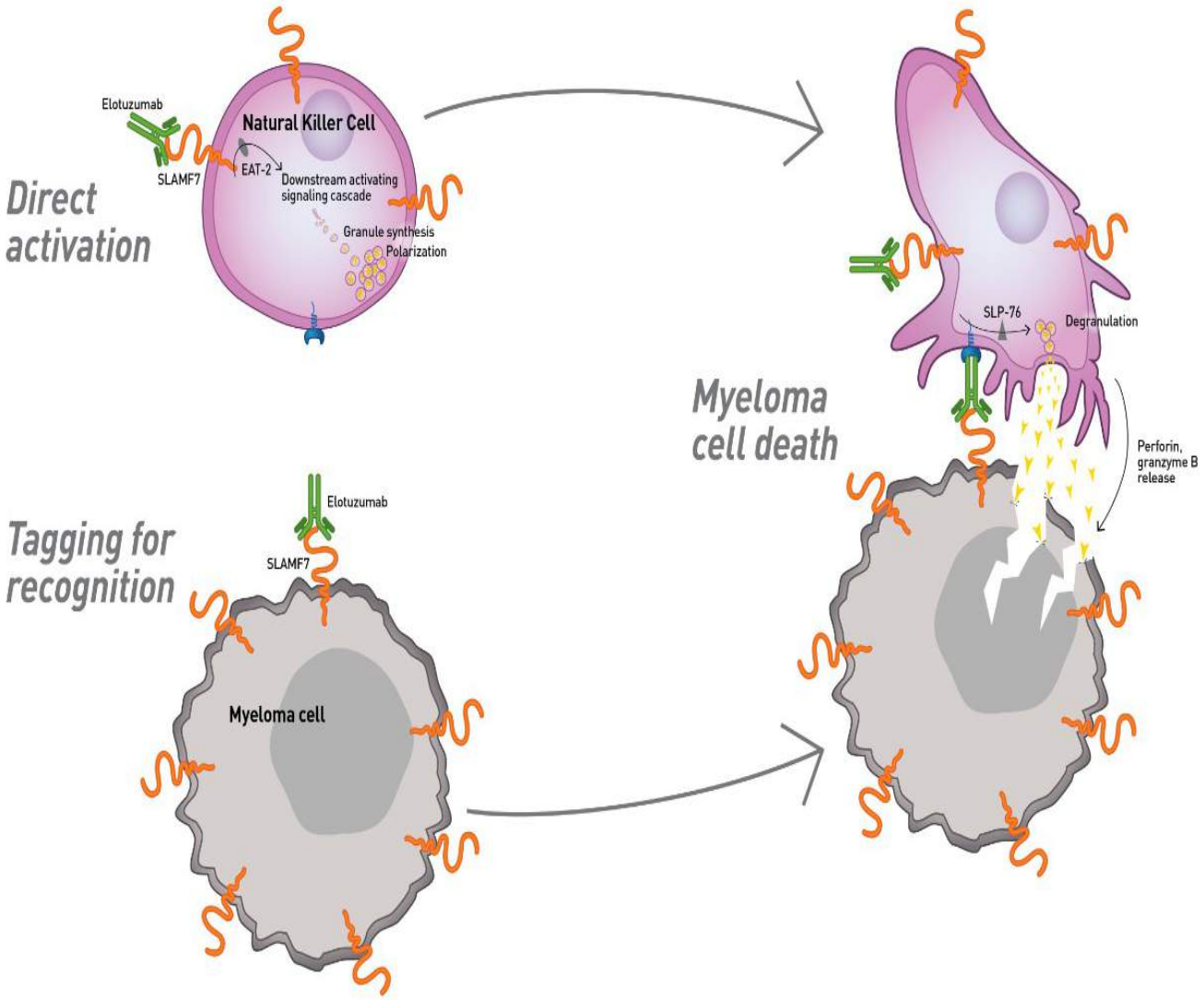
inds to a membrane-proximal motif of SLAMF7

- Critical for mediating killing of target cells (in vitro)

ctivates NK cells (EAT-2 +), but not myeloma cells (EAT-2 -)

Veillette et al, Critical Reviews in Onc and Heme, 2013
Cruz-Munoz et al, Nature Immunology, 2009.

Elotuzumab activates NK cells and ADCC in order to cause myeloma cells death

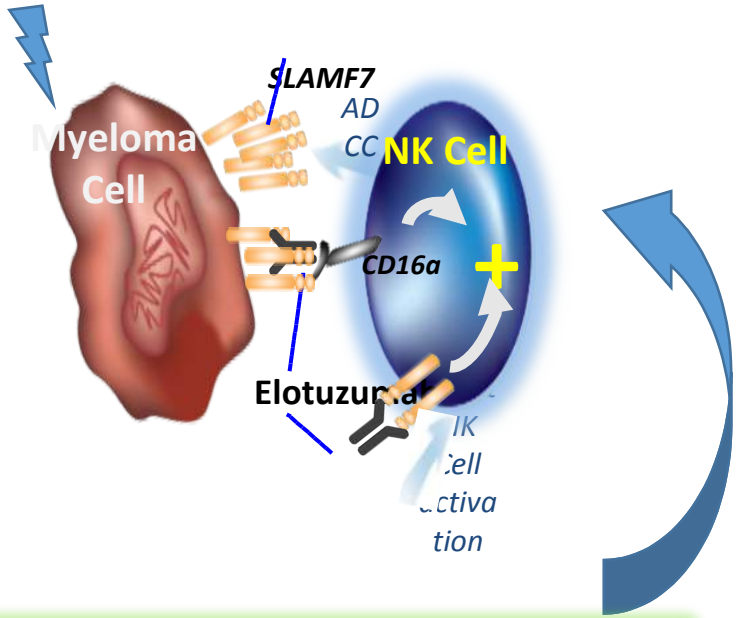


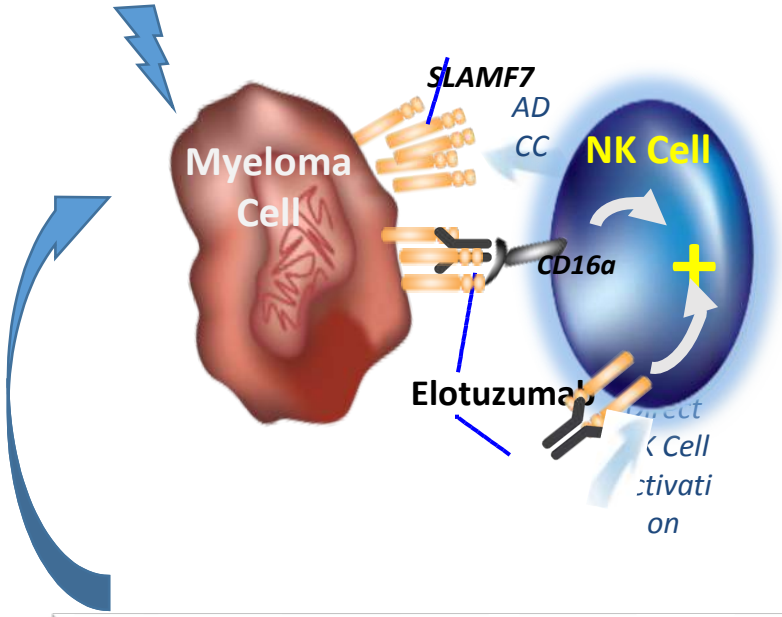
Veillette et al, Critical Reviews in Onc and Heme, 2013
Cruz-Munoz et al, Nature Immunology, 2009.

Elotuzumab synergizes with lenalidomide and bortezomib to enhance myeloma cell death

Lenalidomide
Induces myeloma cell injury and lowers threshold for NK cell-mediated killing of myeloma cells by elotuzumab

Bortezomib
Induces myeloma cell injury and lowers threshold for NK cell-mediated killing of myeloma cells by elotuzumab





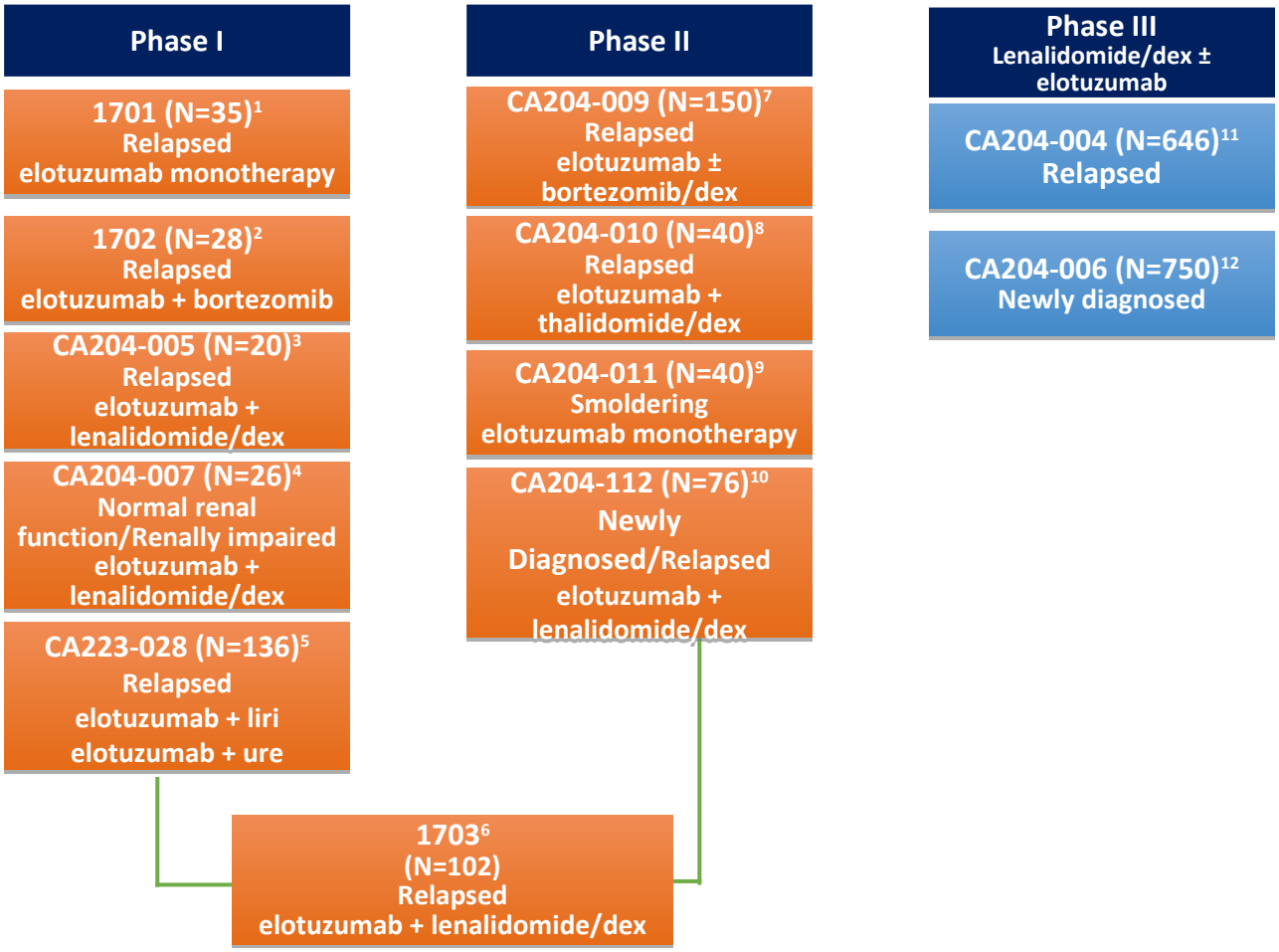
Lenalidomide
Enhances adaptive and innate immune system including production of IL2 to increase NK cell activity

Bortezomib
Sensitizes MM cells to killing by NK cells by enhancing activating ligands and reducing inhibitory ligands on MM cells

Balasa et al, Cancer Imm and Immunotherapeutics, 2015

Van Rhee et al (Molecular Cancer Therapeutics), 2009.

Elotuzumab Clinical Development Program



1. Clinicaltrials.gov. NCT00425347. 2. Clinicaltrials.gov. NCT00726869. 3. Clinicaltrials.gov. NCT01241292. 4. Clinicaltrials.gov. NCT01393964. 5. Clinicaltrials.gov. NCT02252263. 6. Clinicaltrials.gov. NCT00742560. 7. Clinicaltrials.gov. NCT01478048. 8. Clinicaltrials.gov. NCT01632150. 9. Clinicaltrials.gov. NCT01441973. 10. Clinicaltrials.gov. NCT02159365. 11. Clinicaltrials.gov. NCT01239797. 12. Clinicaltrials.gov. NCT01335399.

Phase 1 and 2 elotuzumab Trials in RRMM

Author	Phase study	Combination	Number of pts	Median n. of prior Th	Response rate % (≥ PR)	PFS (months)
Zonder Blood 2012 (1701)	1	none	35	4.5	SD 26.5%	-
Jakuboviak JCO 2012 (1702)	1	BOR	28	2 (BOR refractory 2/3)	48	9.46
Jakuboviak ASCO pres 2015	2	BOR-DEX	77	≥ 2 in 29%	65	9.7
Lonial JCO 2012 (1703)	1	LEN-DEX	28	3 (previous LEN 21%)	82	33
Richardson Lancet Hematol2015 (1703)	2	LEN-DEX (ELO 10 mg vs 20 mg)	73	1-3	92 vs 76	33 vs 18.6

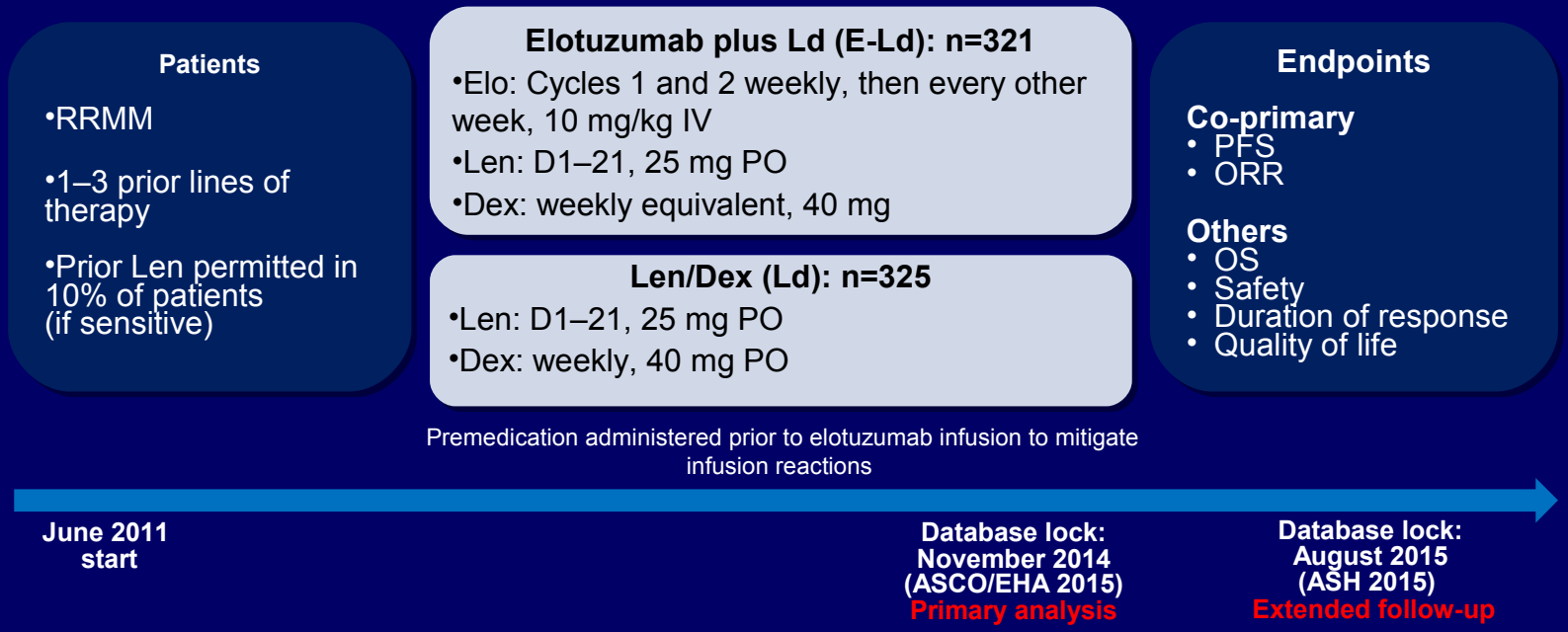
NO EFFICACY

ORR in BOR combination with mild increase in PFS (9.7 vs 6.9 mos)

Good ORR and PFS in LEN combination Reccommended dose: 10 mg

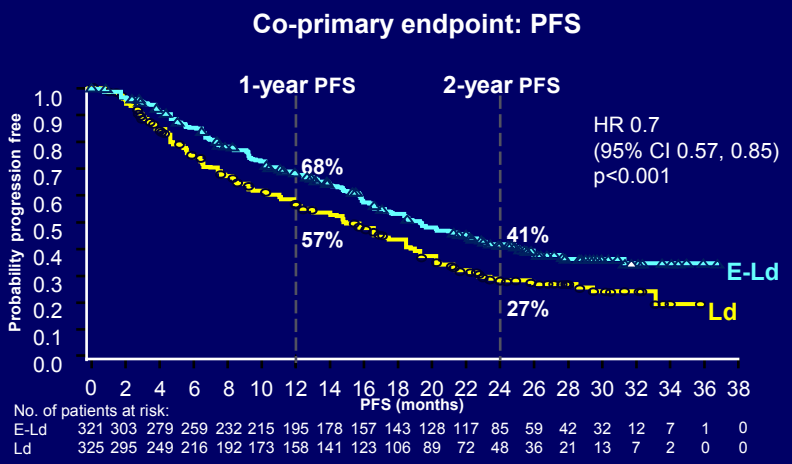
ELOQUENT-2: Study Design

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

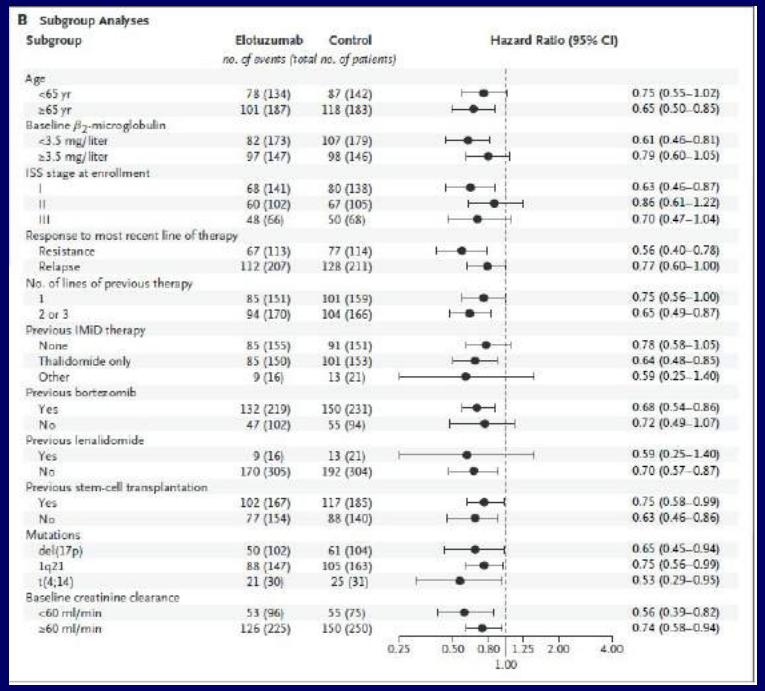


- **Statistical analysis**
  - **Threshold for interim OS significance was 0.014 based on 295/427 events required for final analysis**

ELOQUENT-2: Primary Analysis



From *N Engl J Med*, Lonial S et al, Elotuzumab therapy for relapsed or refractory multiple myeloma, 373, 621–31.
Copyright © 2015, Massachusetts Medical Society. Reprinted with permission

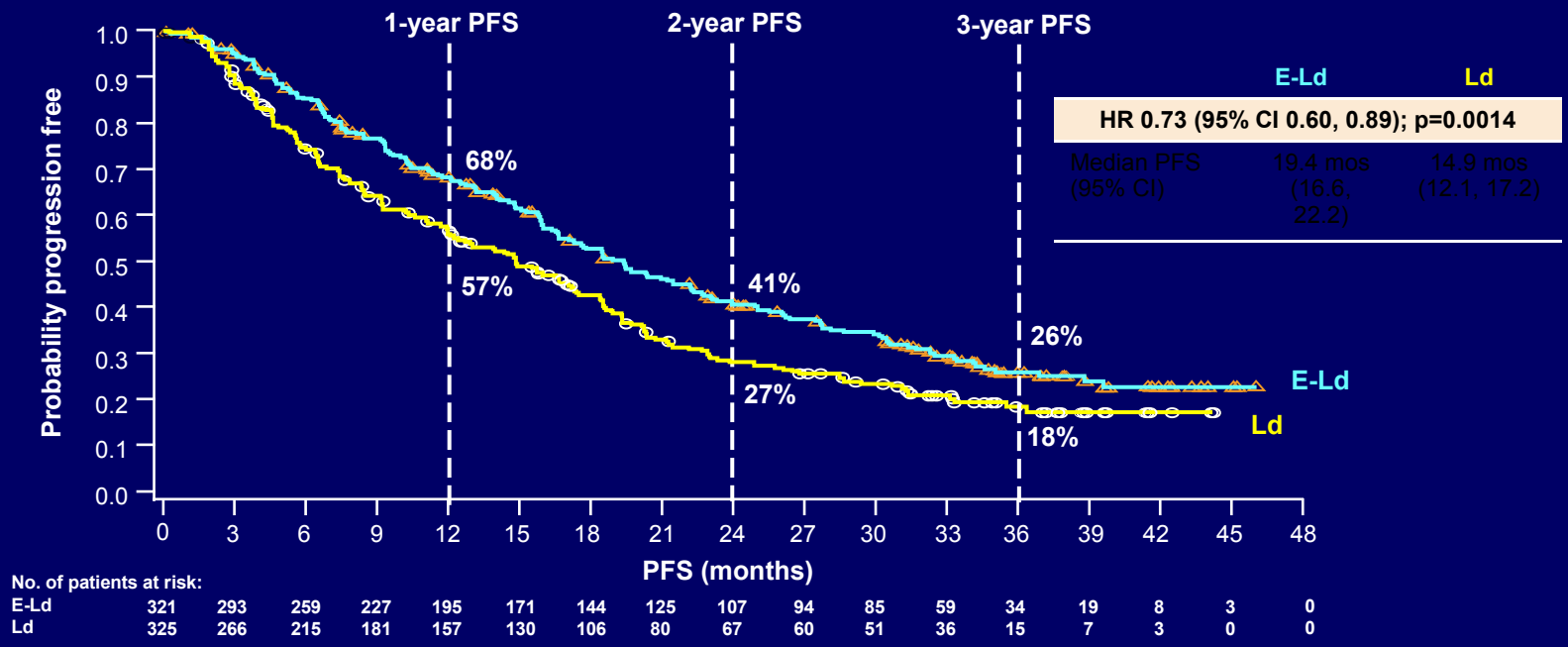


Co-primary endpoint: ORR	E-Ld	Ld
%	79	66
95% CI	74, 83	60, 71

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

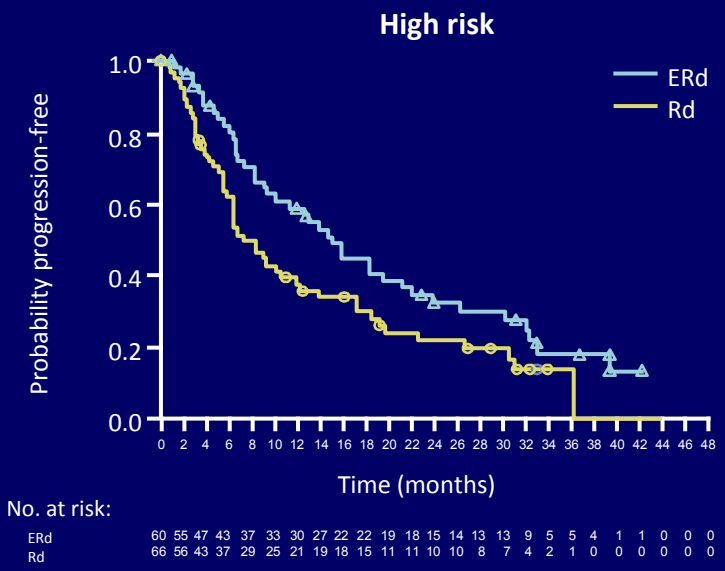


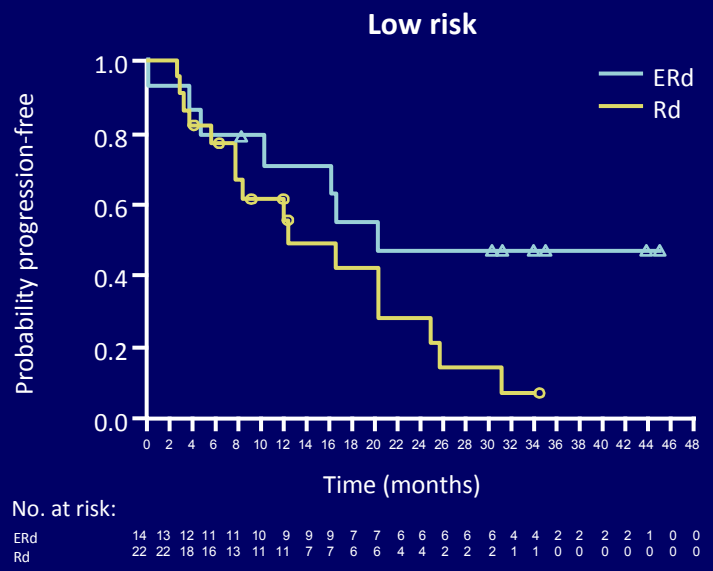
	E-Ld	Ld
HR 0.73 (95% CI 0.60, 0.89); p=0.0014		
Median PFS (95% CI)	19.4 mos (16.6, 22.2)	14.9 mos (12.1, 17.2)

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





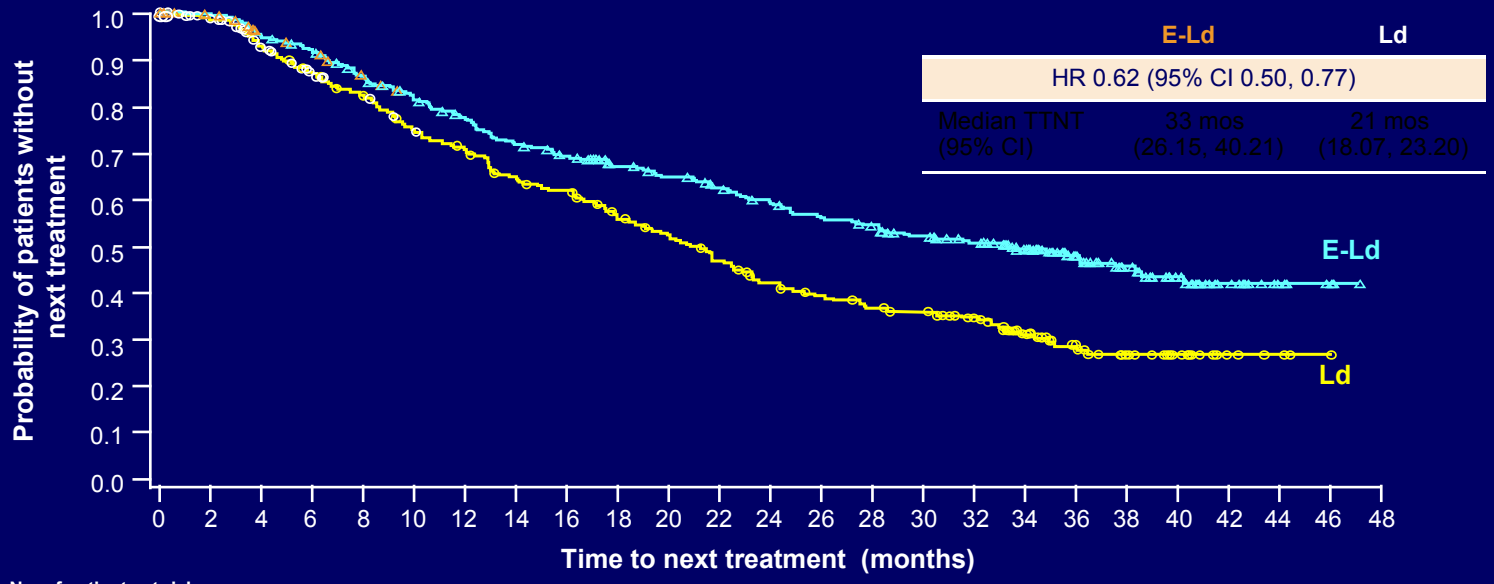
Adapted from Lonial S et al. 2016.[1]

- 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.

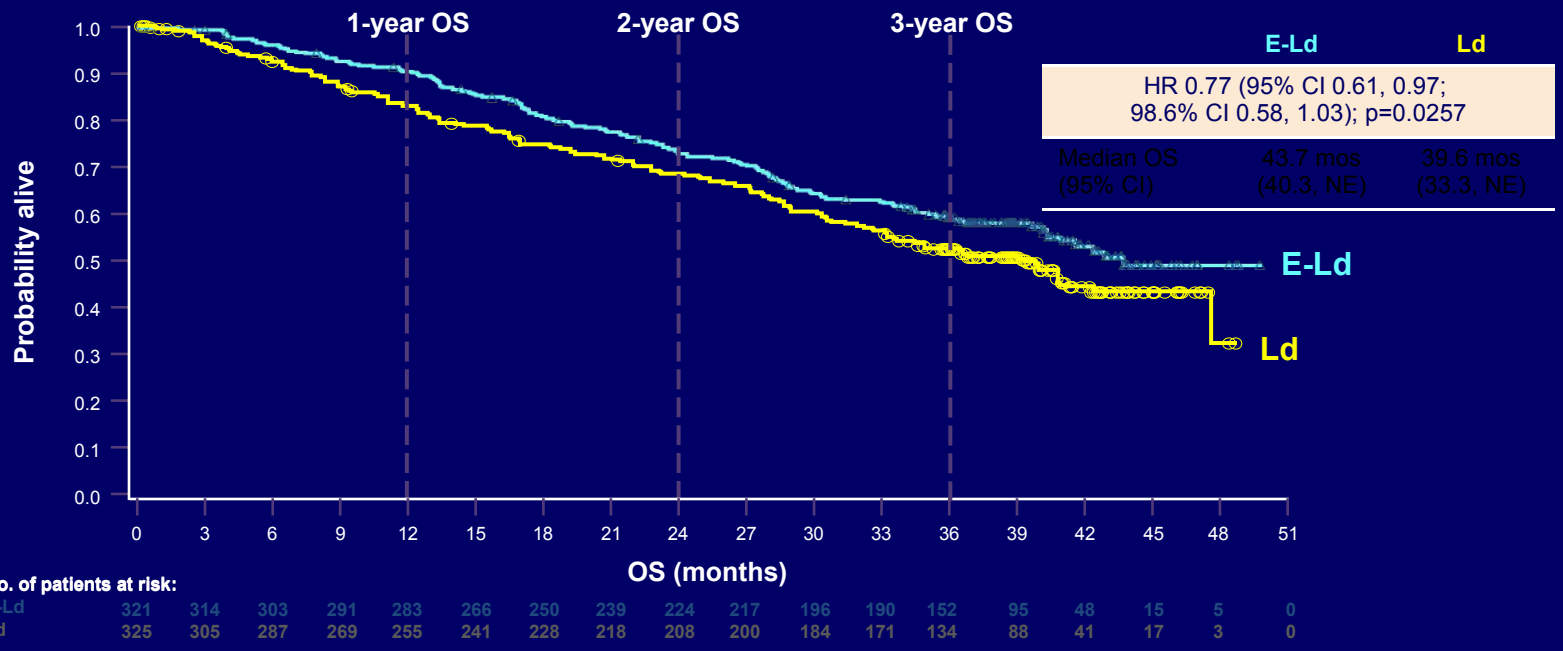
1. Lonial S et al. Poster presentation at ASCO 2016. Abstract 8037.

Time to Next Treatment



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

Interim Overall Survival



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

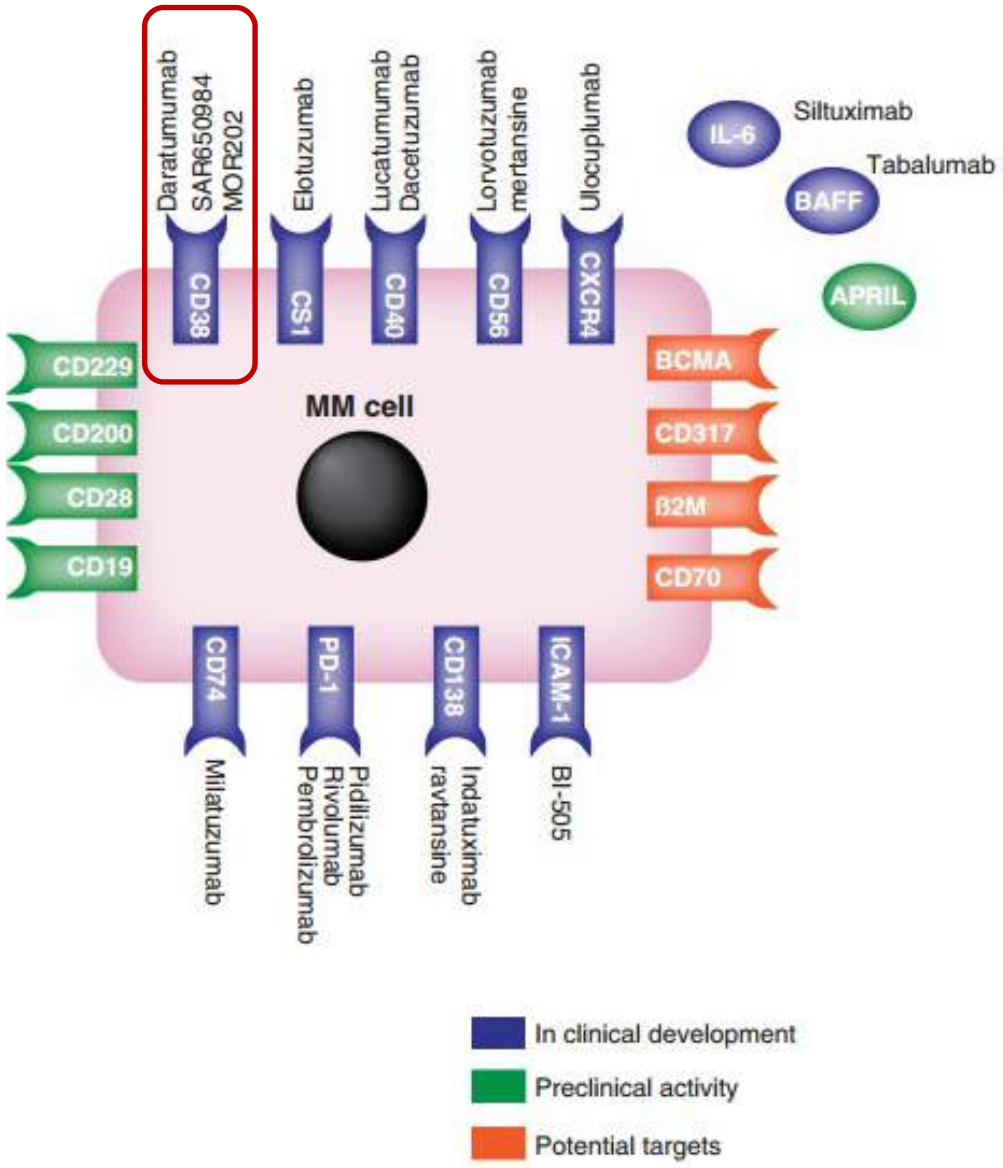
Lonial S et al N Engl J Med, 2015: 1-11

Summary

- ✓ Phase 1 study demonstrated no efficacy of Elotuzumab in monotherapy
- ✓ Phase 1 and 2 studies demonstrated significant anti-tumor activity of Elotuzumab in combination with Lenalidomide and bortezomib in R/R MM setting
- ✓ In Phase 3 Elotuzumab in combination with lenalidomide and dexametasone demonstrates a durable and clinical relevant improvement in PFS and ORR in R/R MM
- ✓ Elotuzumab is well tolerated and principal AEs are related to infusion reactions: pre-medication regimen successfully mitigated infusion reactions

MM cells and its microenvironment: target molecules

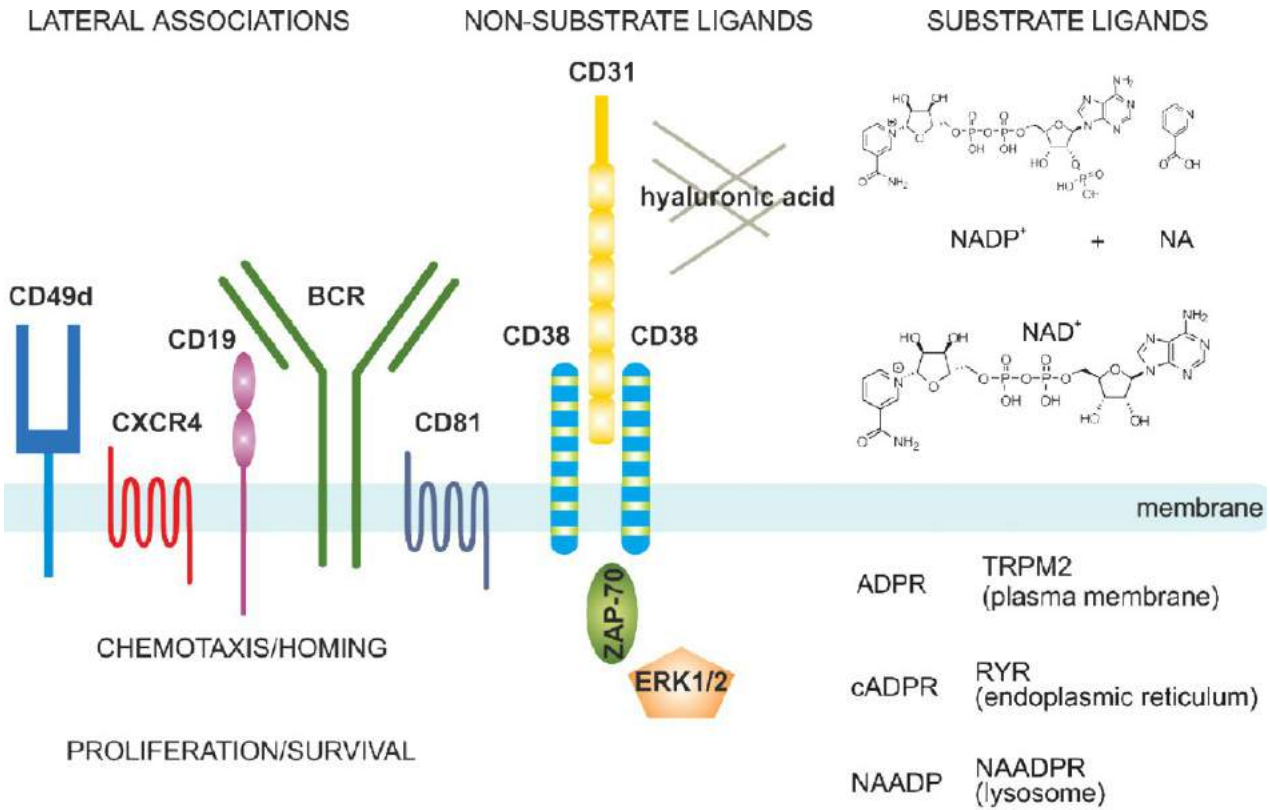
- ✓ Ab anti SLAMF7 or CS1
- ✓ Ab anti CD38
- ✓ Ab anti PD-1/PDL-1
- ✓ Denosumab
- ✓ Other Ab targets



Lonial S, Leukemia 2016

CD38

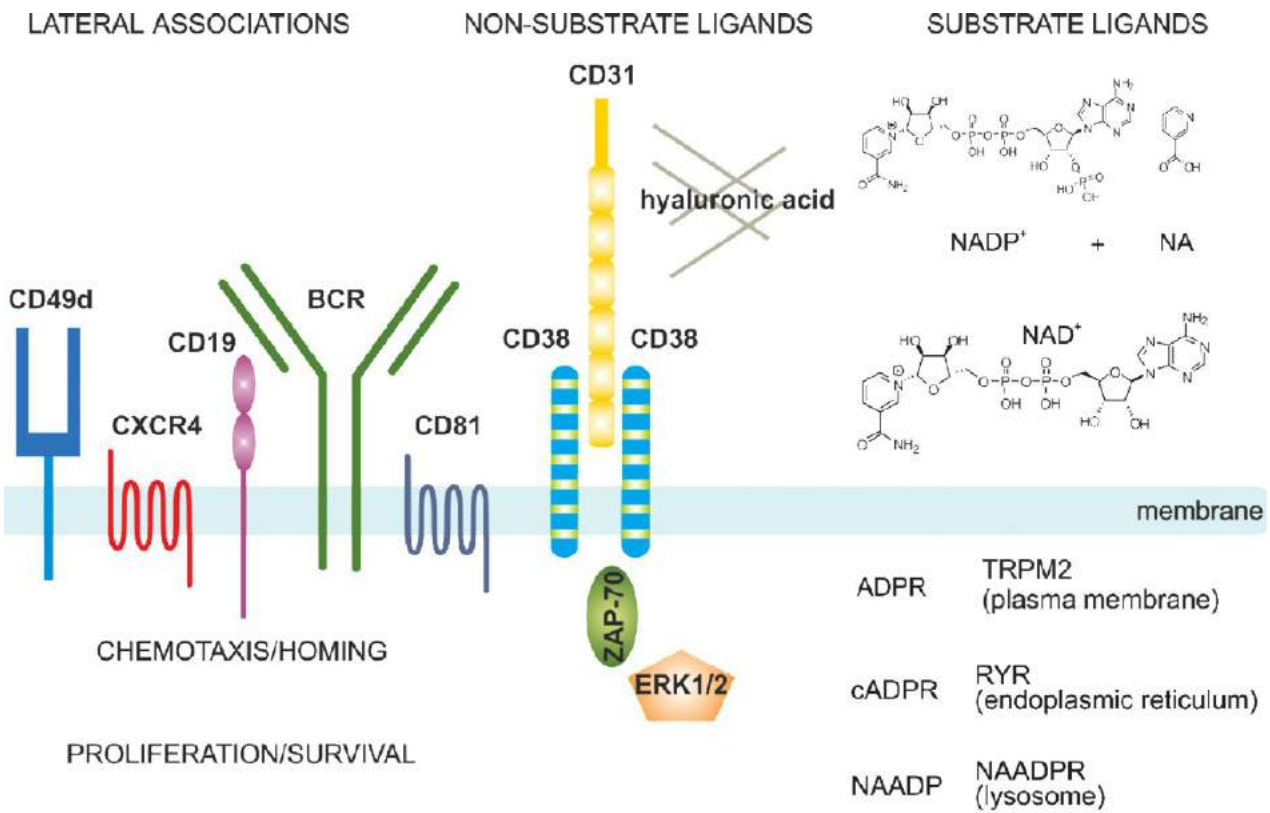
- Cell surface receptor close to BCR complex that regulates T cells activation/proliferation
- Ectoenzyme involved in calcium signaling
- low expression in hematopoietic cells (NK B and T cells) and non –hematopoietic cells
- High expression in MM cells



Malavasi F, et al. *Physiol Rev*. 2008; Lin P, et al. *Am J Clin Pathol*. 2004; Santonocito AM, et al. *Leuk Res*. 2004; Deaglio S, et al. *Leuk Res*. 2001

Anti CD38 mAbs in clinical development for MM

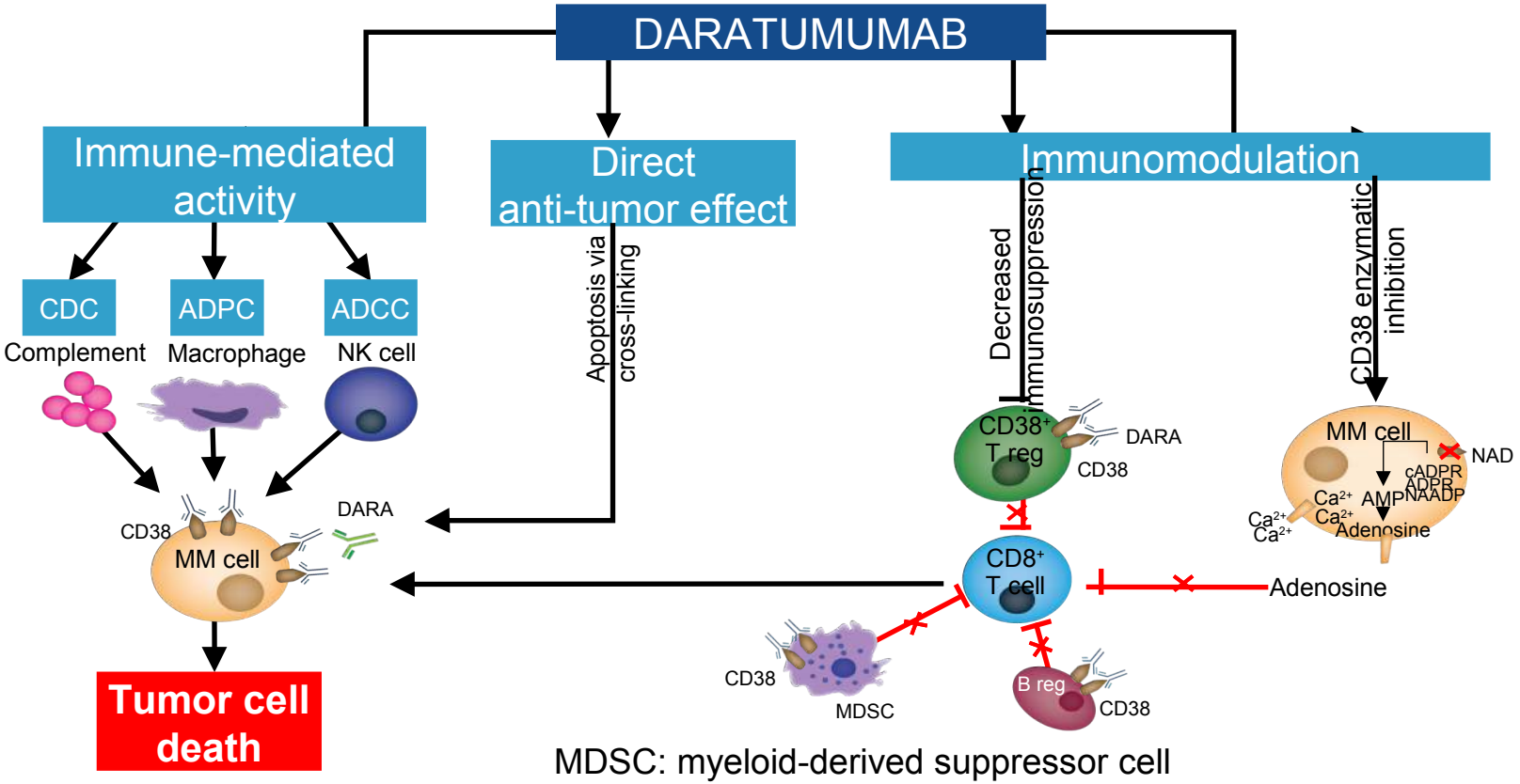
- ✓ Daratumumab
- ✓ SAR650984 (isatuximab)
- ✓ MOR202



Malavasi F, et al. *Physiol Rev*. 2008; Lin P, et al. *Am J Clin Pathol*. 2004; Santonocito AM, et al. *Leuk Res*. 2004; Deaglio S, et al. *Leuk Res*. 2001

Daratumumab: IgG/K human moAb anti CD38 and mechanisms of action

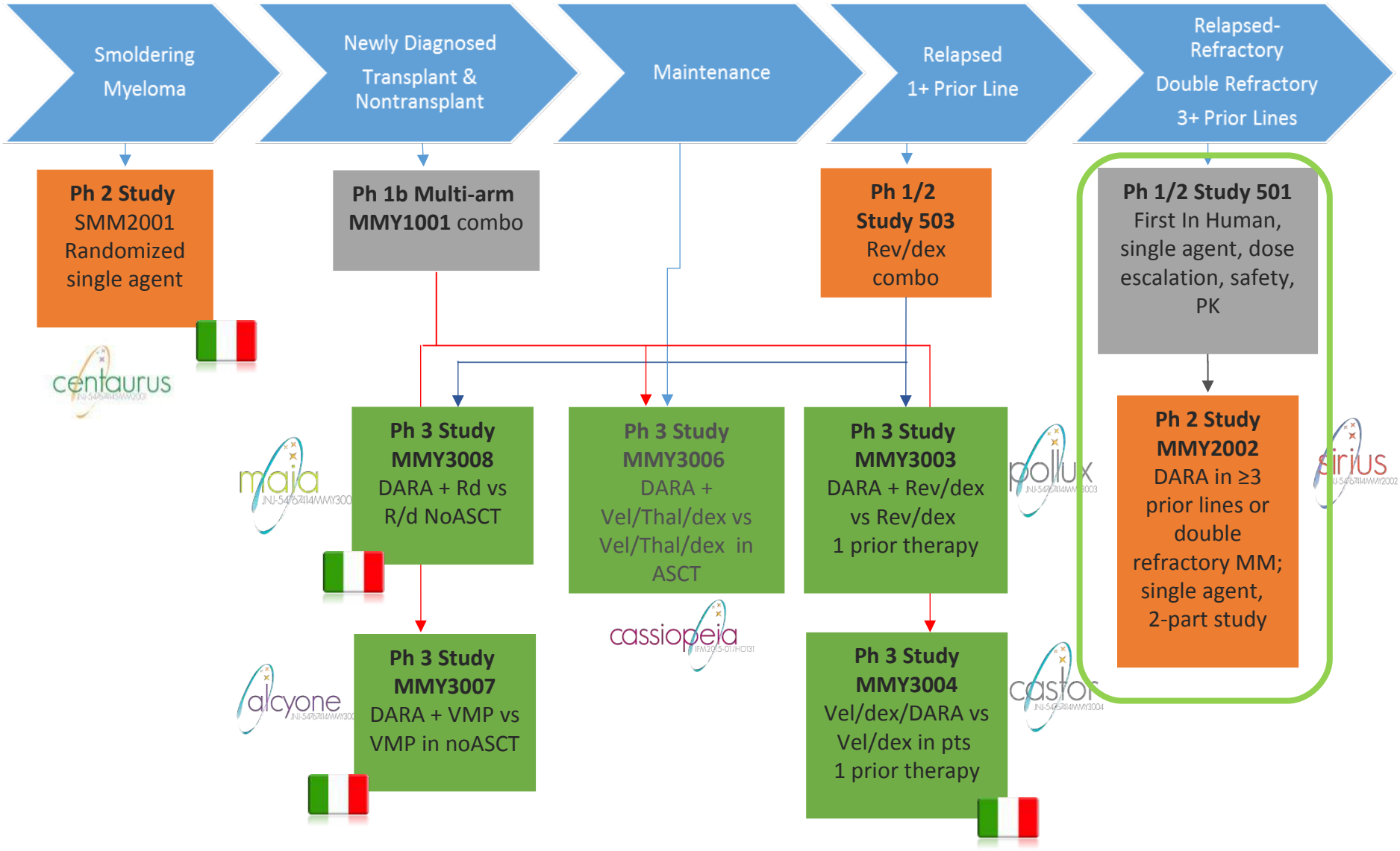
- Complement-dependent cytotoxicity (CDC)
- Antibody-dependent cell-mediated phagocytosis (ADCP)
- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Induction of apoptosis
- Modulation of cellular enzymatic activities associated with calcium mobilization and signaling



MDSC: myeloid-derived suppressor cell

Usmani, SZ et al. Presented at ASH 2015 (Abstract 29), oral presentation

Daratumumab development in all MM settings



Daratumumab: phase 1 and 2 trials

Author	Phase study	Combination	Number of pts	Median n. of prior Th	Response rate % (≥ PR)	PFS (months)
Lokhorst (501) NEJM 2015	1-2	None (arm 16 mg)	20	4	35	5.6
Lonial SIRIUS trial Lancet 2016	2	None (16 mg)	106	5	29	3.7
Plesner (503) ASH pres 2015	2	LEN-DEX	45	2	91	-
Mateos EHA pres 2015	1b	BORT-DEX	6	0	100	-
Mateos EHA pres 2015	1b	BORT-MEL-PRED	8	0	100	-
Mateos EHA pres 2015	1b	BORT-THAL-DEX	11	0	100	-
Mateos EHA pres 2015	1b	POM-DEX	24	≥ 2	55	-

Single agent, ORR:
✓dose-related;
✓also in R/R MM

Good ORR in combination with LEN

ORR 100% in 1°line in combnation with BOR

Good ORR in combination with POM in R/R MM

Daratumumab single agent: pooled analysis

ASH | 57th Annual Meeting & Exposition
Orlando, FL · December 5-8, 2015

Oral #29

Clinical Efficacy of Daratumumab Monotherapy in Patients with Heavily Pretreated Relapsed or Refractory Multiple Myeloma

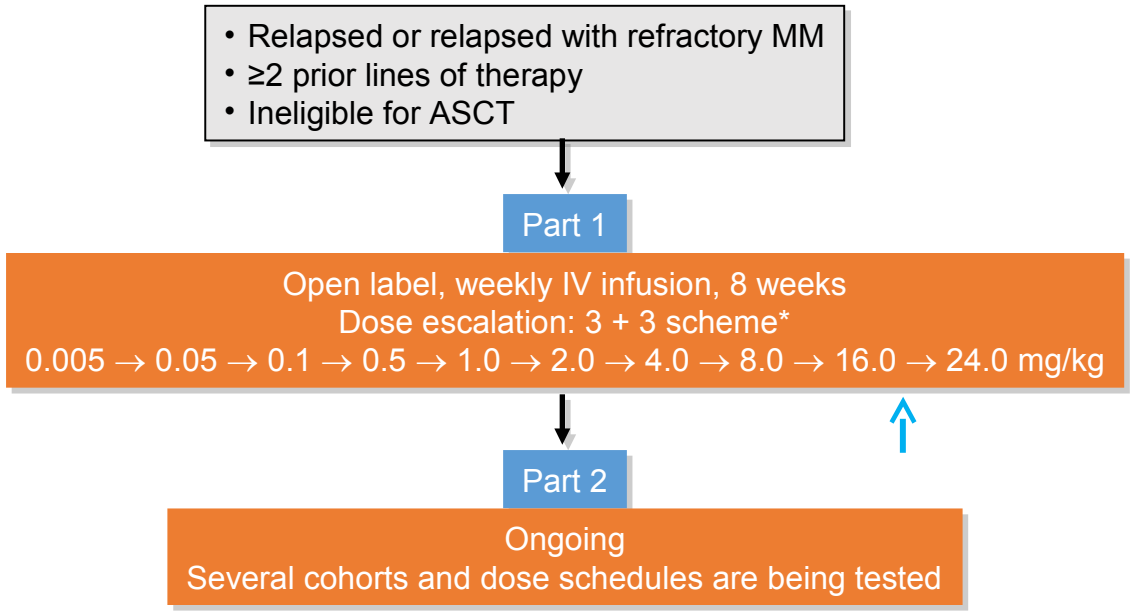
Pooled analysis Studies GEN501 and MMY2002 (Sirius)

Median follow-up: 14.8 months

Usmani et al Abs #29 Orlando, ASH 2015

Daratumumab single agent: GEN501

Phase I/II Study Design



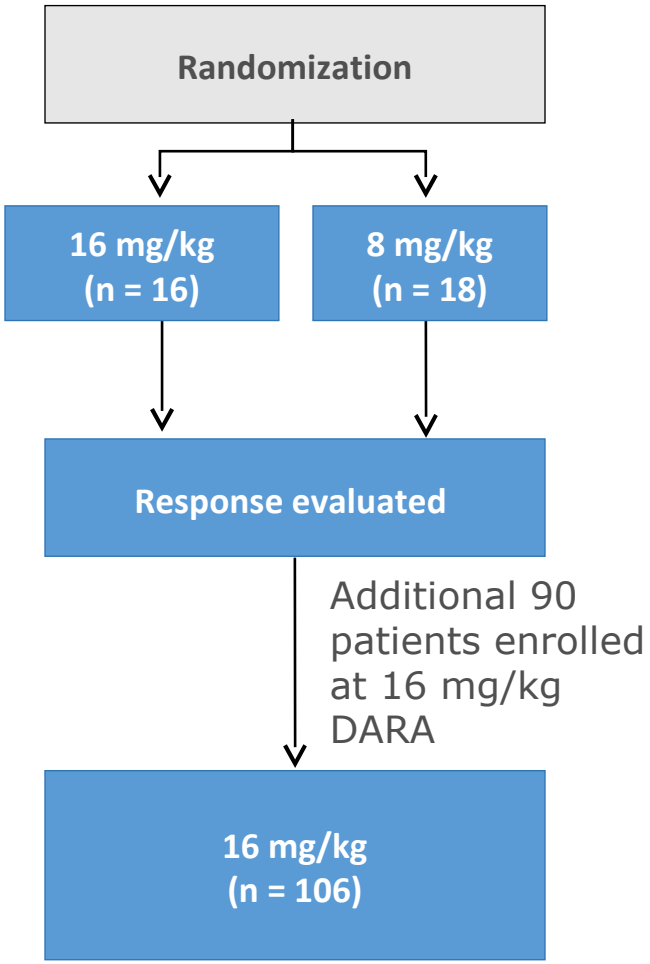
Dose-escalation cohorts

Expansion cohorts

Lokhorst HM, et al NEJM 2015

Daratumumab single agent: MMY2002 (SIRIUS)

- Open-label, international, multicenter study of Simon-2-stage design
- Initially, patients randomized 1:1 to receive DARA
  - 8 mg/kg Q4W or
  - 16 mg/kg every week (QW) for 8 weeks, Q2W for 16 weeks, then Q4W thereafter
- 16 mg/kg DARA was established as the recommended dose for further study
- Results are reported for all patients who were treated with 16 mg/kg DARA (n = 106)



Lonial S, et al. Lancet 2016

Daratumumab single agent dosing: GEN501/SIRIUS trials

- ✓ Median age of pts: 64y
- ✓ Median time since disgnosis: 5.1 y
- ✓ Median number of prior lines: 5
- ✓ Baseline refractory status: 91% last line; 86% both PI and IMID

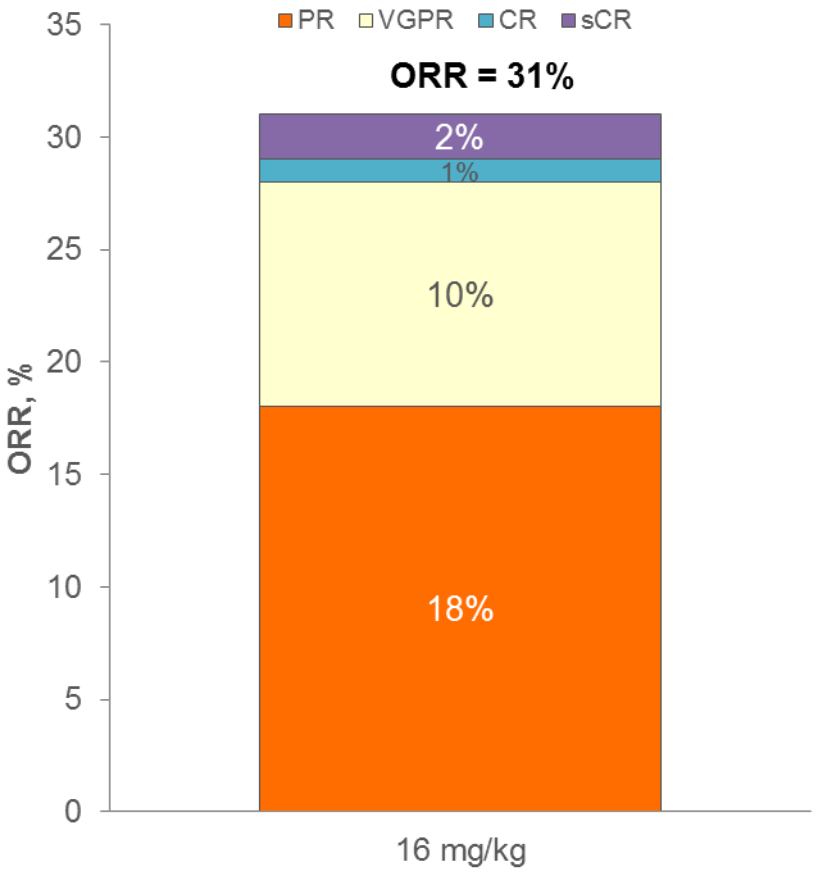
Schedule	Weeks
Weekly	Weeks 1 to 8
Every two weeks	Weeks 9 to 24
Every four weeks	Week 25 onwards until disease progression

	Dilution volume	Initial rate (first hour)	Rate increment	Maximum rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

MMY2002 SIRIUS Duration of infusion (hr)	1st Infusion n = 106	2nd Infusion n = 104	Subsequent Infusions n = 103
Median	**7.0**	**4.2**	**3.4**
Range	1.5-14.3	2.7-8.5	1.1-6.7

Daratumumab efficacy: ORR in combined analysis

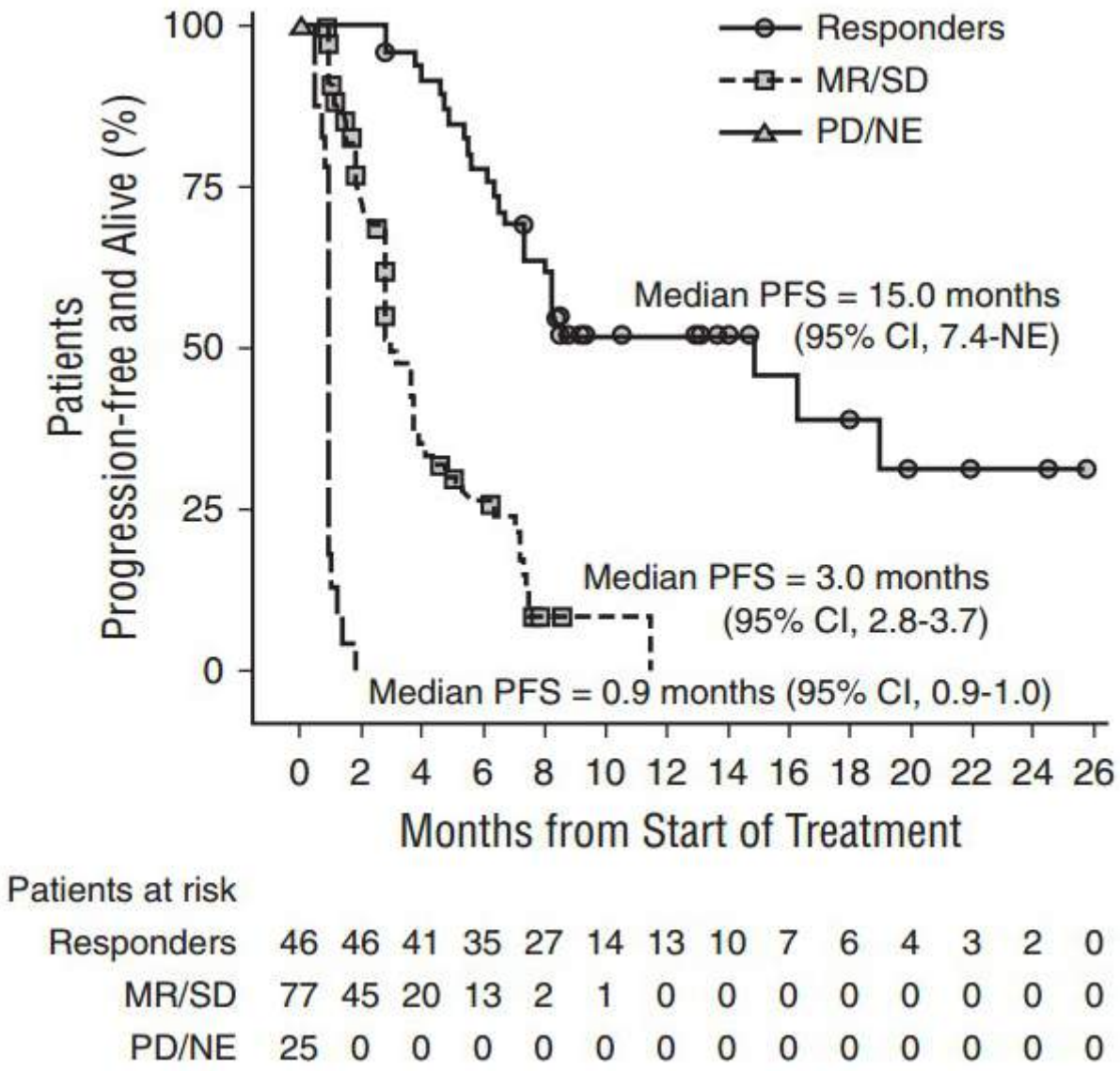
	16 mg/kg (N = 148)	
	n (%)	95% CI
ORR (sCR+CR+VGPR+PR)	**46 (31)**	**23.7-39.2**
Best response		
sCR	3 (2)	0.4-5.8
CR	2 (1)	0.2-4.8
VGPR	14 (10)	5.3-15.4
PR	27 (18)	12.4-25.4
MR	9 (6)	2.8-11.2
SD	68 (46)	37.7-54.3
PD	18 (12)	7.4-18.5
NE	7 (5)	1.9-9.5
VGPR or better (sCR+CR+VGPR)	19 (13)	7.9-19.3
CR or better (sCR+CR)	5 (3)	1.1-7.7



- ORR = 31%
- ORR was consistent in subgroups including age, ISS, number of prior lines of therapy, refractory status, or renal function

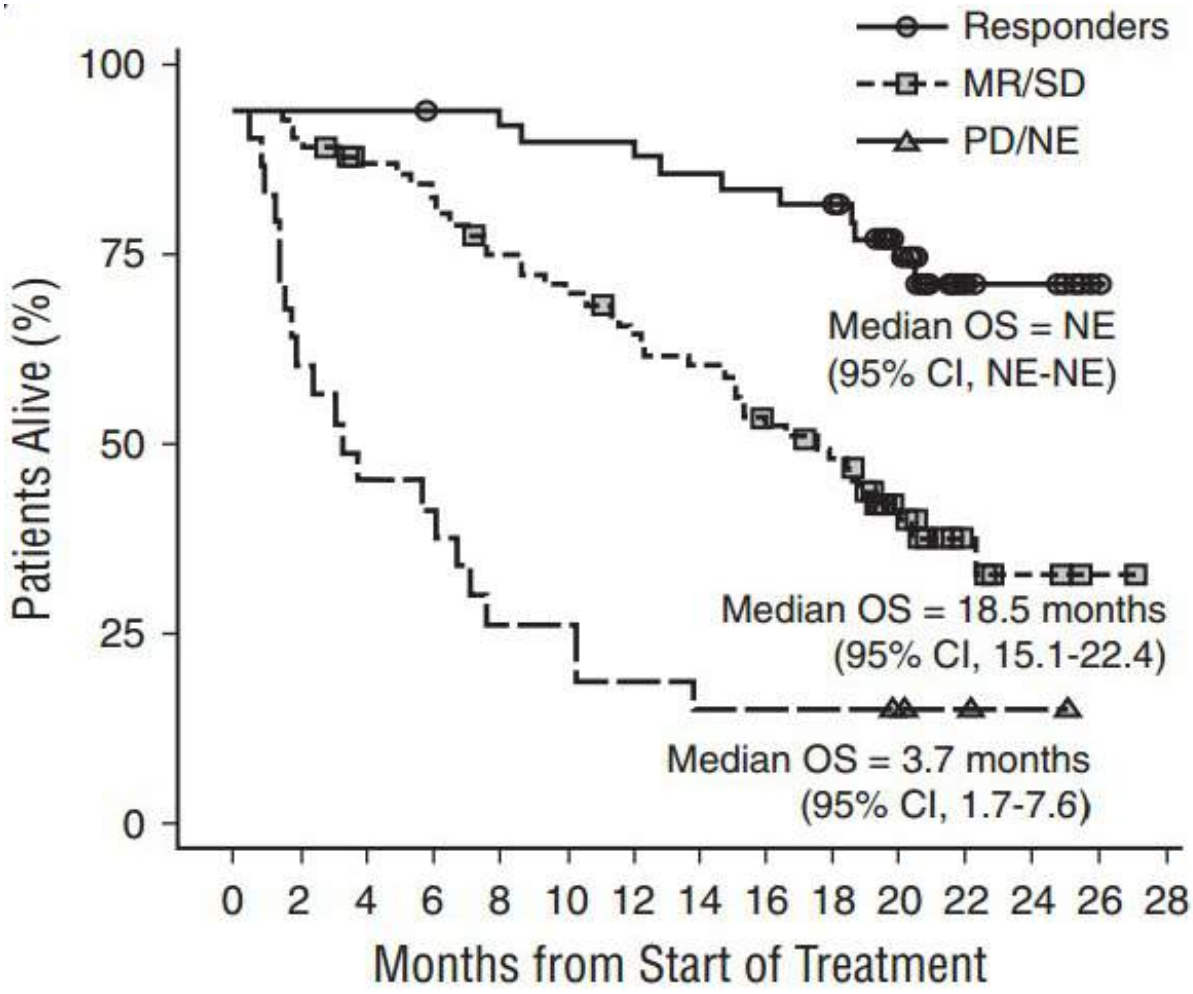
Usmani S, et al. Oral presentation: ASH 2015; Abstract 29

Daratumumab efficacy: median PFS (4 months) and in specific subgroups



Usmani S, et al, Blood 2016

Daratumumab efficacy: median OS (20 months) and in specific subgroups



tients at risk

Responders	46	46	46	45	44	43	43	41	40	39	28	12	11	2	0
MR/SD	77	74	67	63	57	53	48	45	38	34	20	8	4	1	0
PD/NE	25	16	12	11	7	7	5	4	4	4	3	2	1	0	0

Usmani S, et al, Blood 2016

Daratumumab: summary of clinical safety

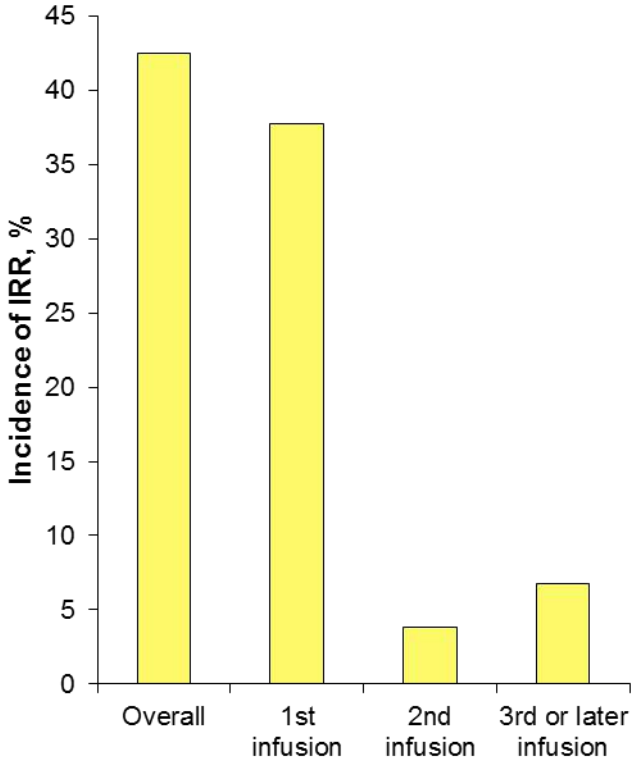
TEAE, n (%)	Any grade N = 148	Grade ≥3 N = 148
Fatigue	61 (41)	3 (2)
Nausea	42 (28)	0
Anemia	41 (28)	26 (18)
Back pain	36 (24)	3 (2)
Cough	33 (22)	0
Neutropenia	30 (20)	15 (10)
Thrombocytopenia	30 (20)	21 (14)
Upper respiratory tract infection	30 (20)	1 (<1)

- AEs were consistent with the individual GEN501 and SIRIUS studies; no new safety signals were identified
- 48% of patients had infusional reactions: 46%, 4%, and 3% occurred during the first, second, and subsequent infusions, respectively

Usmani S, et al. Oral presentation: ASH 2015; Abstract 29

Special consideration in management in daratumumab: Infusional reactions

- Occurred in 43% of patients
- Predominantly Grade 1 or 2 (Grade 3: 5%; no Grade 4)
- >90% of IRRs occurred during the first infusion
- 7% of patients had an IRR at >1 infusion
- Most common IRRs included nasal congestion (12%); throat irritation (7%); cough, dyspnea, chills, and vomiting (6% each)
- No patients discontinued treatment due to IRRs



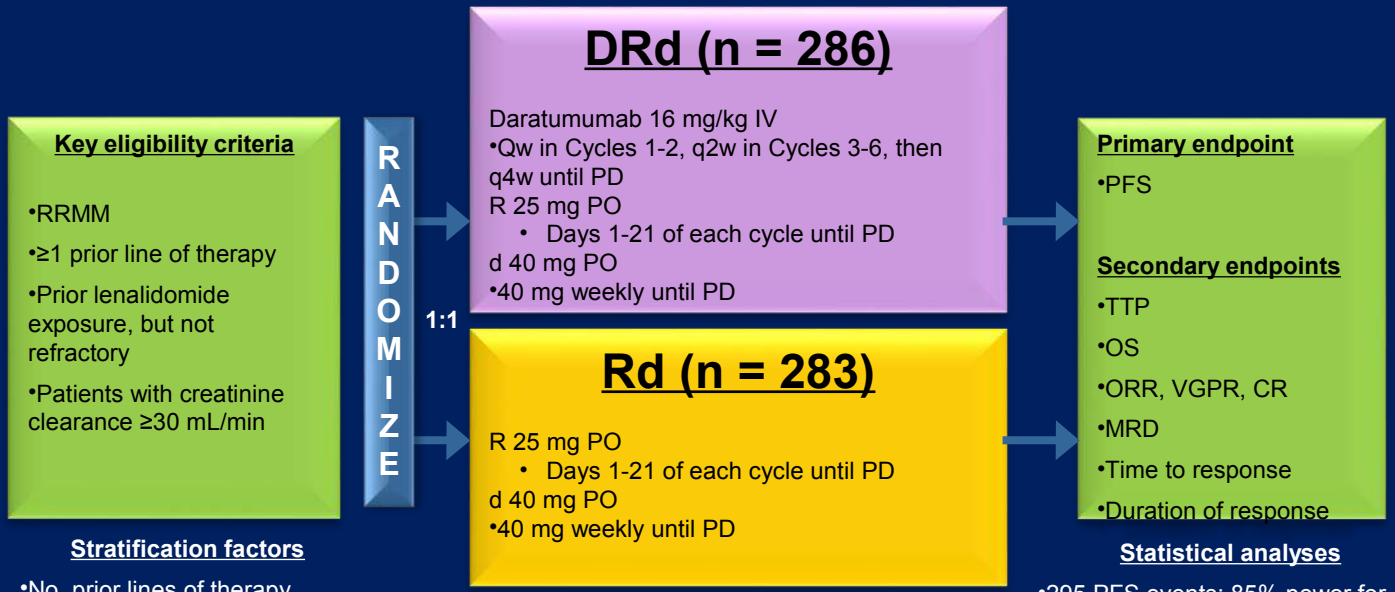
Pre-medication to reduce the risk of IRRs:
- ✓intravenous corticosteroid (methylprednisolone 100 mg or an equivalent)
- ✓oral antipyretic (paracetamol at 650-1000 mg)
- ✓oral or intravenous antihistamine (diphenhydramide 25-50 mg or equivalent)

Post-medication corticosteroids on 1st and 2nd day after all infusions

Lonial S, et al. Oral presentation, ASCO 2015; Protocol for: Lokhorst et al. N Engl J Med 2015

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

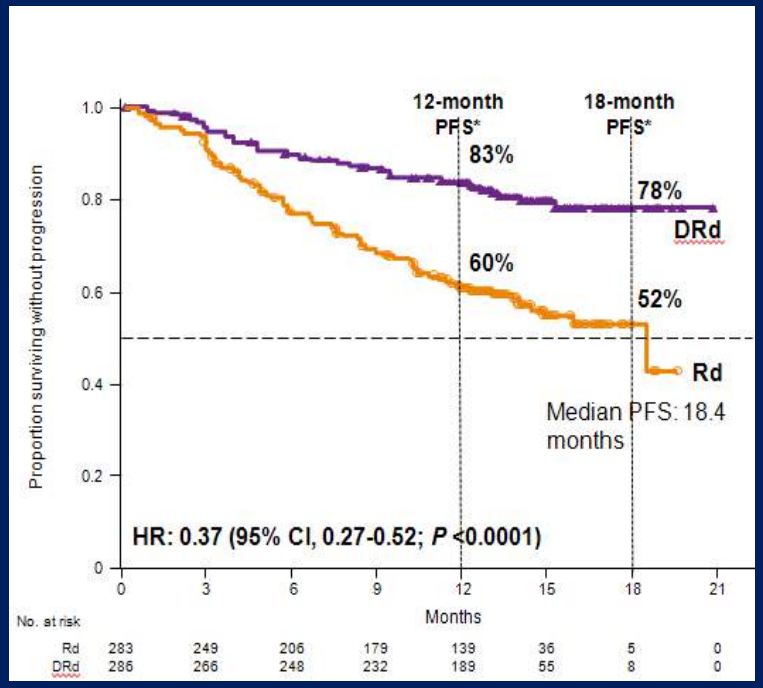
Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg[a], paracetamol, and an antihistamine

[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

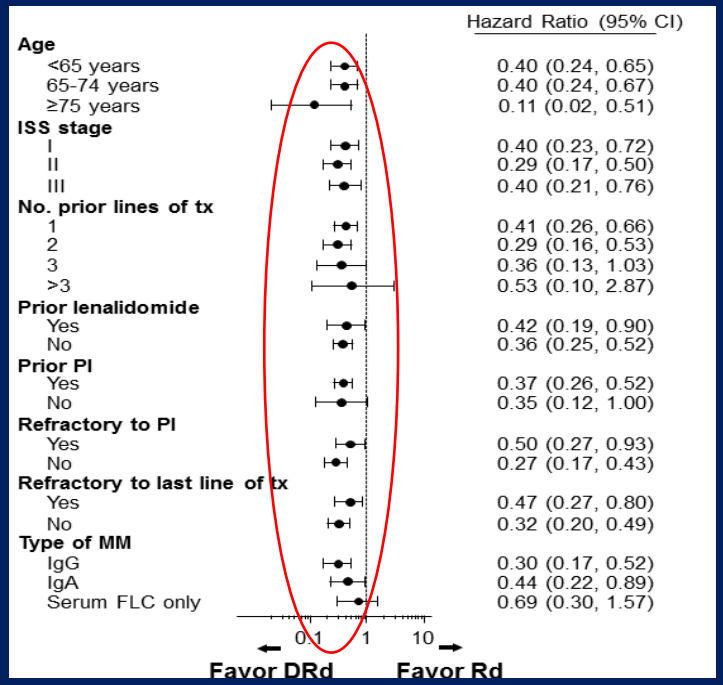
POLLUX: Study Design

Progression-free Survival (PFS)



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

PFS: Subgroup analysis



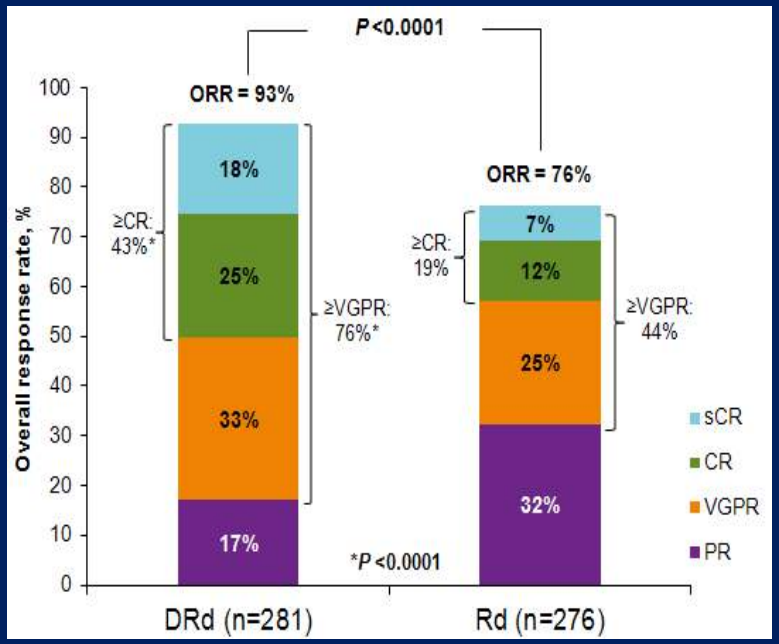
Higher efficacy was observed for DRd versus Rd across all subgroups

DRd: Daratumumab lenalidomide dexamethasone; Rd: lenalidomide dexamethasone

Dimopoulus et al. EHA 2016

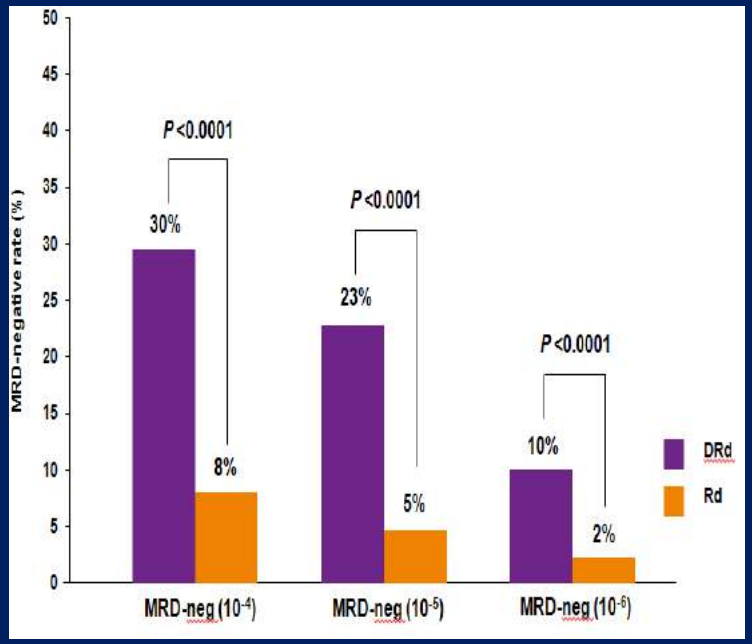
POLLUX: Study Design

Overall response rate



- 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

MRD negative rate

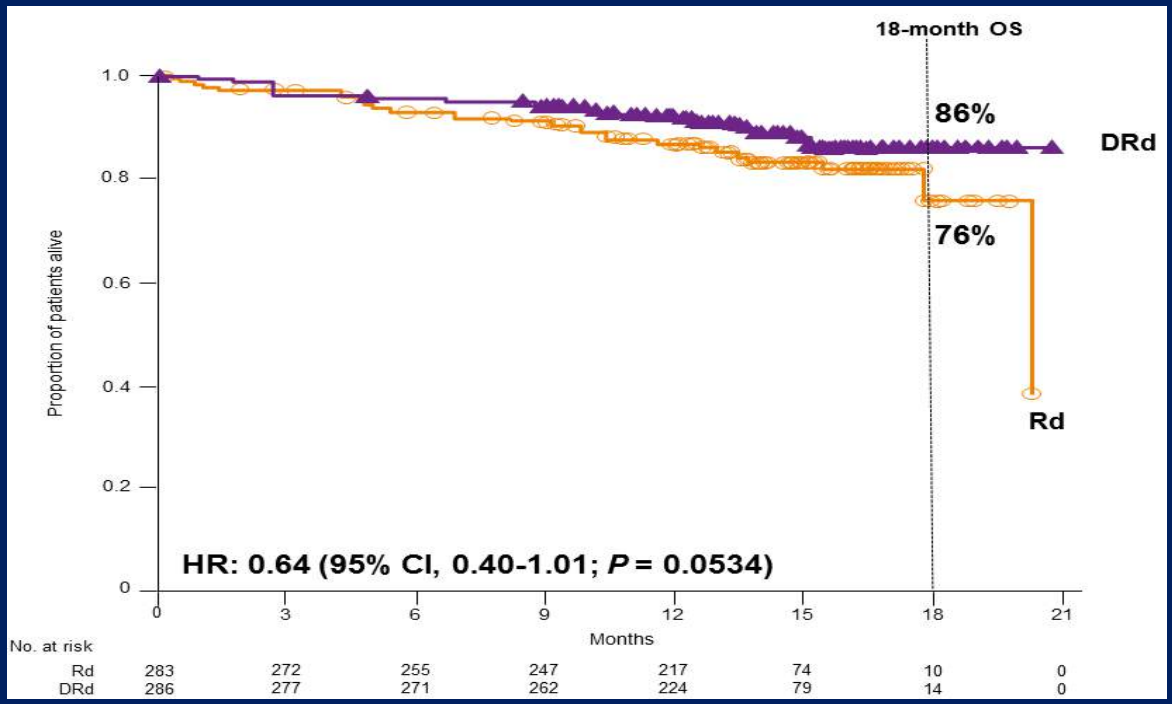


Significantly higher MRD-negative rates for DRd vs Rd

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

o grade 4 or 5 IRRs were reported

2% of all IRRs occurred during the first infusion

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.

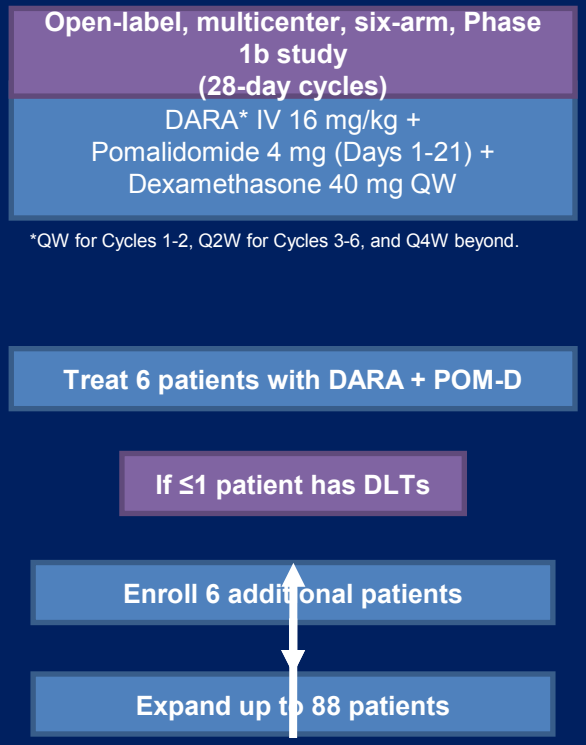
DRd: Daratumumab lenalidomide dexamethasone; Rd: lenalidomide dexamethasone

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



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

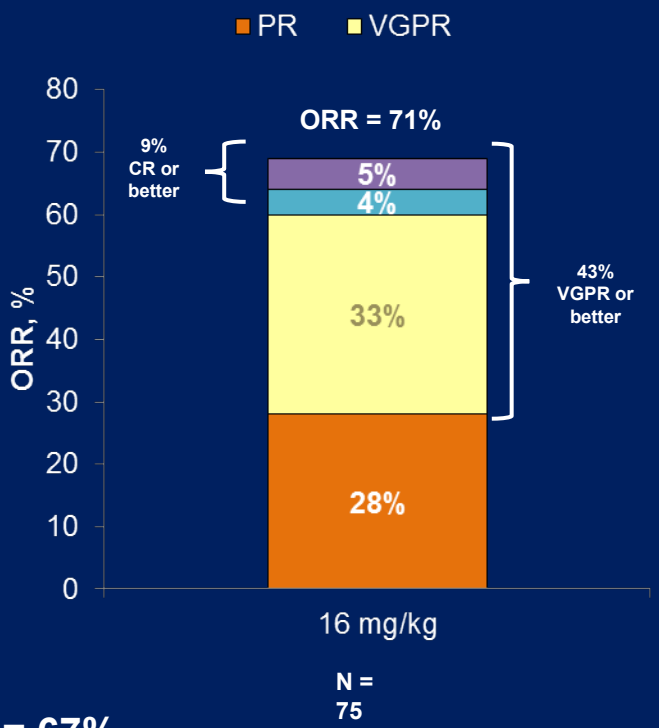
- IRRs were predominantly grade ≤2
  - 6 (6%) patients had grade 3 IRRs
  - Only 2 patients discontinued due to an IRR
- 53%, 1%, and 0% of patients had IRRs during the 1st, 2nd, and subsequent inf., respectively
- IRRs were managed with premedication and reduced infusion rates

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

Phase 3 study: Dara + Bor dex

- Multicenter, randomized, open-label, active-controlled, phase 3 study

N = 498

Key eligibility criteria

- RRMM
- ≥1 prior line of therapy
- Prior bortezomib exposure, but not refractory

RANDOMIZE 1:1

DVd (n = 251)
Daratumumab (16 mg/kg IV)
Every week: Cycles 1-3
Every 3 weeks: Cycles 4-8
V: 1.3 mg/m² SC on Days 1, 4, 8, and 11 of Cycles 1-8
d: 20 mg PO-IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of Cycles 1-8

Vd (n = 247)
V: 1.3 mg/m² SC on Days 1, 4, 8, and 11 of Cycles 1-8
d: 20 mg PO-IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of Cycles 1-8

- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

D only
Every 4 weeks: Cycles 9+

Obs only

Primary endpoint
- PFS

Secondary endpoints
- TTP
- OS
- ORR, VGPR, CR
- MRD

Stratification factors
- ISS (I, II, and III)
- Number of prior lines (1 vs 2 or 3 vs >3)
- Prior bortezomib (no vs yes)

Statistical analyses
- Planned to enroll 480 patients
- Primary analysis: ~177 PFS events

- Premedication for the DVd treatment group consisted of dexamethasone 20 mg, acetaminophen, and an antihistamine

DVd, daratumumab, bortezomib and dexamethasone; IV, intravenous; V, bortezomib; SC, subcutaneously; d, dexamethasone; PO, orally; VD, bortezomib and dexamethasone; D, daratumumab; Obs, observation; PFS, progression-free survival; TTP, time to progression; OS, overall survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; ISS, International Staging System.

Mateos M-V, et al. Oral presentation at: 58th American Society of Hematology (ASH) Annual Meeting and Exposition; December 3-6 2016; San Diego, CA, USA.

Baseline demographic and clinical characteristics

Characteristic	DVd (n = 251)	Vd (n = 247)
Age, y		
Median (range)	64 (30-88)	64 (33-85)
≥75, n (%)	23 (9)	35 (14)
ISS staging, n (%)[a]		
I	98 (39)	96 (39)
II	94 (38)	100 (41)
III	59 (24)	51 (21)
Creatinine clearance (mL/min), n (%)		
N	243	233
>30-60	49 (20)	59 (25)
>60	186 (77)	163 (70)
Median time from diagnosis, y (range)	3.87 (0.7-20.7)	3.72 (0.6-18.6)
Cytogenetic profile, n (%)[b]		
N	167	186
Standard risk	123 (74)	135 (73)
High risk	44 (26)	51 (27)

Characteristic	DVd (n = 251)	Vd (n = 247)
Prior lines of therapy, n (%)		
Median	2 (1-9)	2 (1-10)
1	122 (49)	113 (46)
2	70 (28)	74 (30)
3	37 (15)	32 (13)
>3	22 (9)	28 (11)
1-3[c]	229 (91)	219 (89)
Prior ASCT, n (%)	156 (62)	149 (60)
Prior PI, n (%)	169 (67)	172 (70)
Prior IMiD, n (%)	179 (71)	198 (80)
Prior PI + IMiD, n (%)	112 (45)	129 (52)
Refractory to IMiD only, n (%)	74 (30)	90 (36)
Refractory to last line of therapy, n (%)	76 (30)	85 (34)

ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory drug.

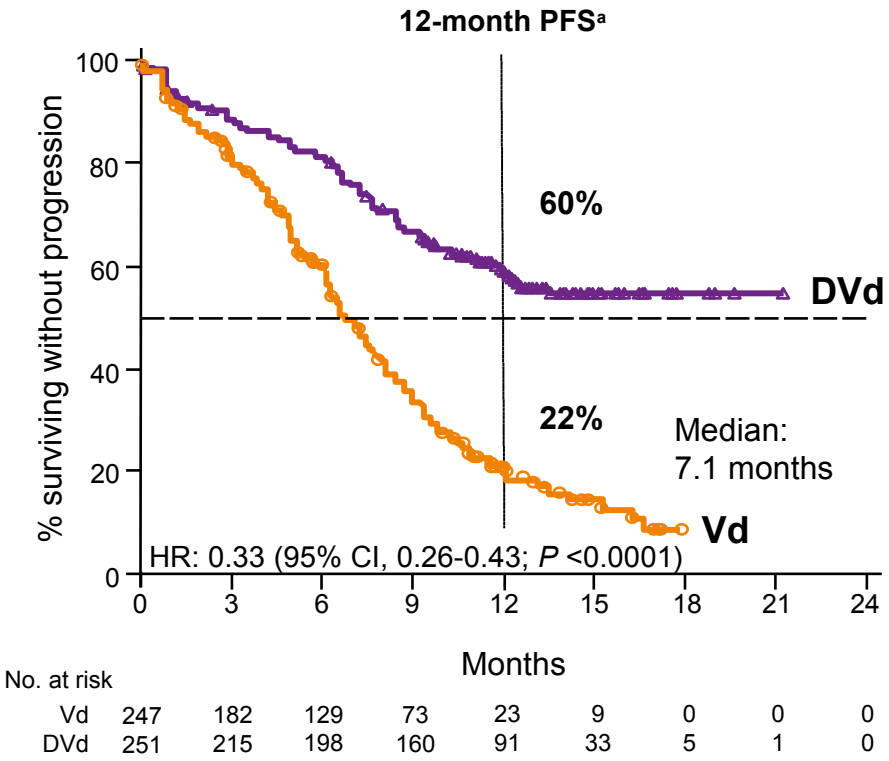
[a]ISS staging is derived based on the combination of serum β2-microglobulin and albumin.

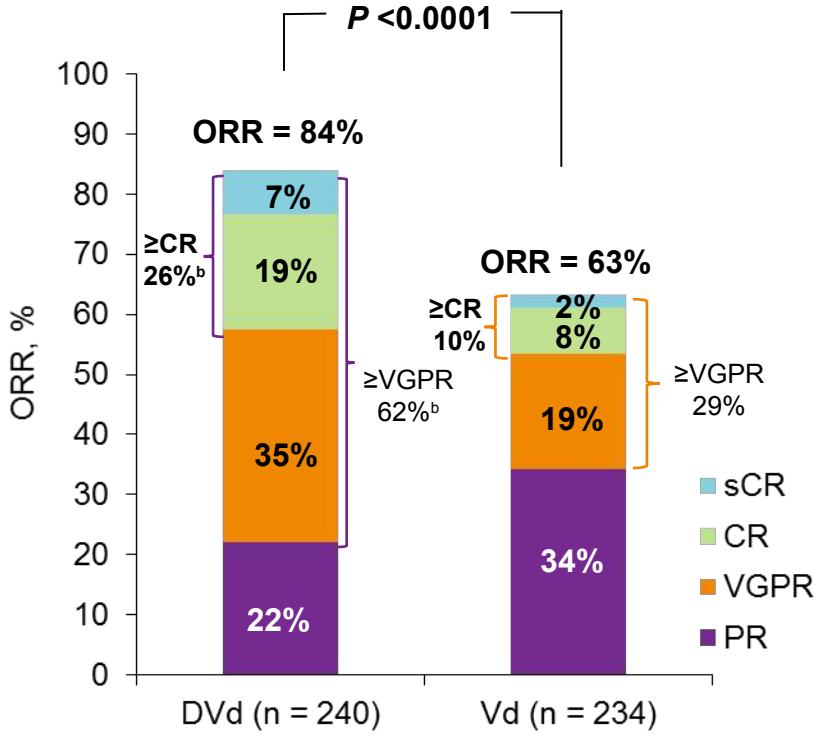
[b]Centralized analysis using next-generation sequencing. Patients with high risk had t(4;14), t(14;16), or del17p abnormalities.

[c]Exploratory.

Mateos M-V, et al. Oral presentation at: 58th American Society of Hematology (ASH) Annual Meeting and Exposition; December 3-6 2016; San Diego, CA, USA.

ORR and PFS





- Median (range) follow-up: 13.0 (0-21.3) months
- An additional 7% of patients receiving DVd achieved ≥CR with longer follow up

Responses continue to deepen in the DVd group with longer follow-up

ITT, intent to treat.
Note: PFS: ITT population; ORR: response-evaluable population.
[a]Kaplan-Meier estimate.
[b]*P* <0.0001 for DVd versus Vd.
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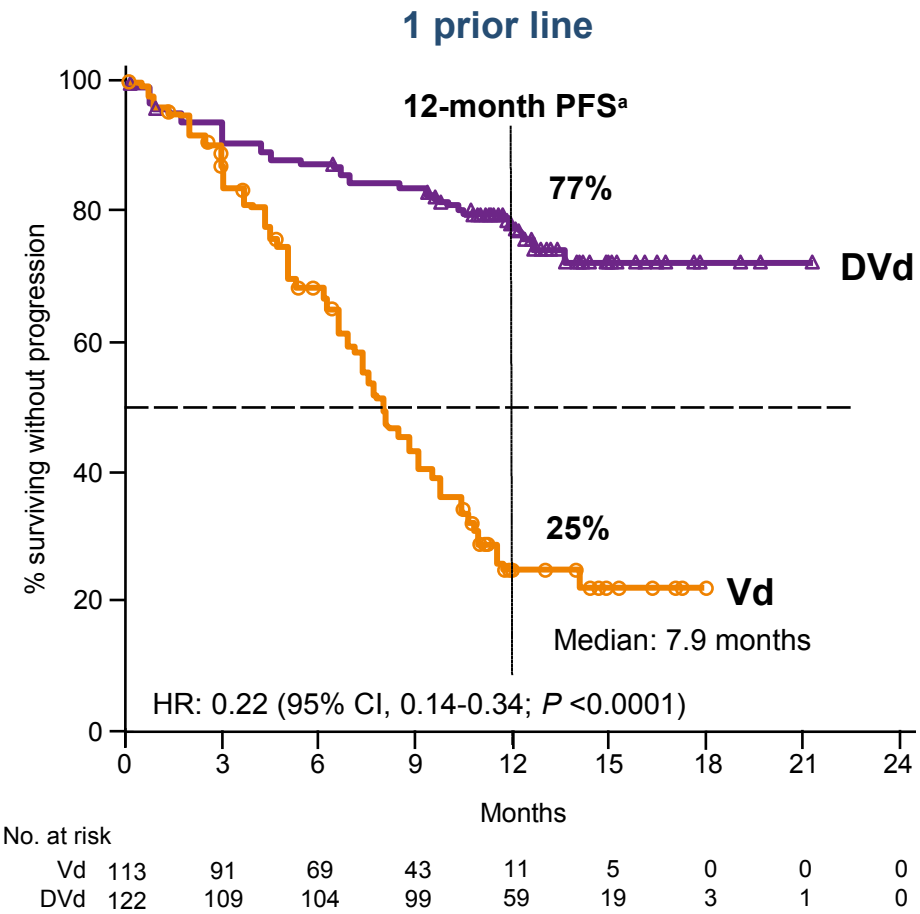
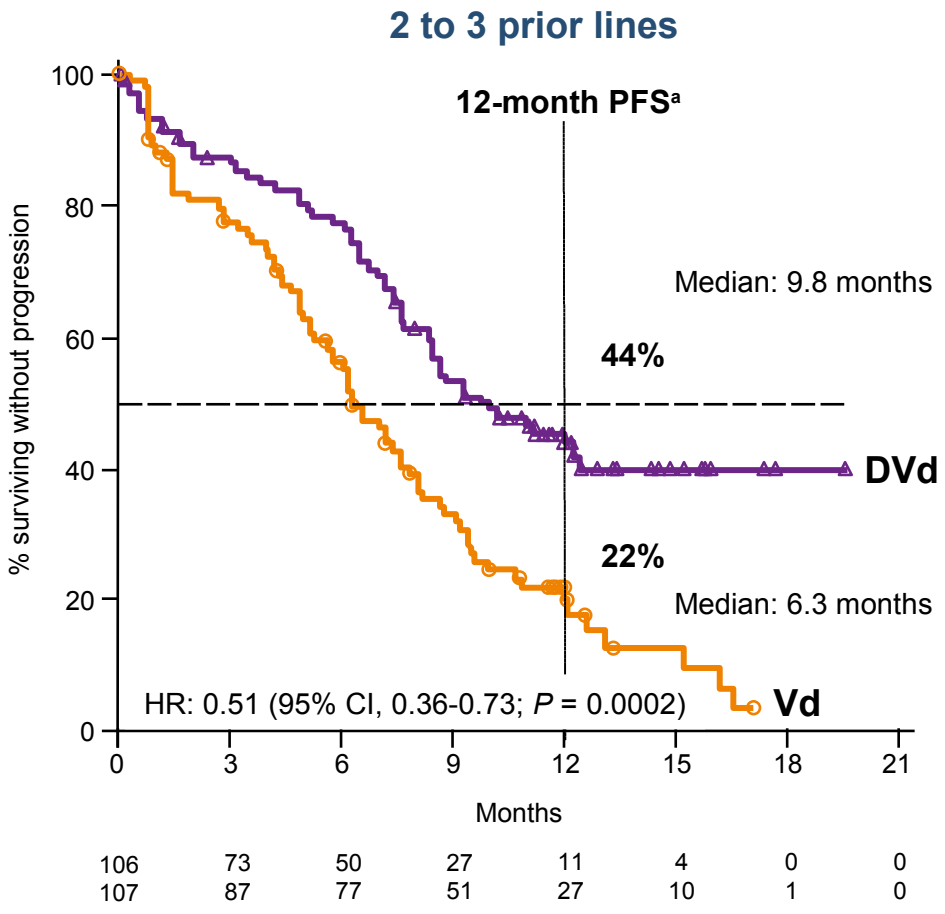
PFS:Prior Lines of treatment





DVd is superior to Vd regardless of prior lines of therapy, with greatest benefit observed in 1 prior line

[a]Kaplan-Meier estimate

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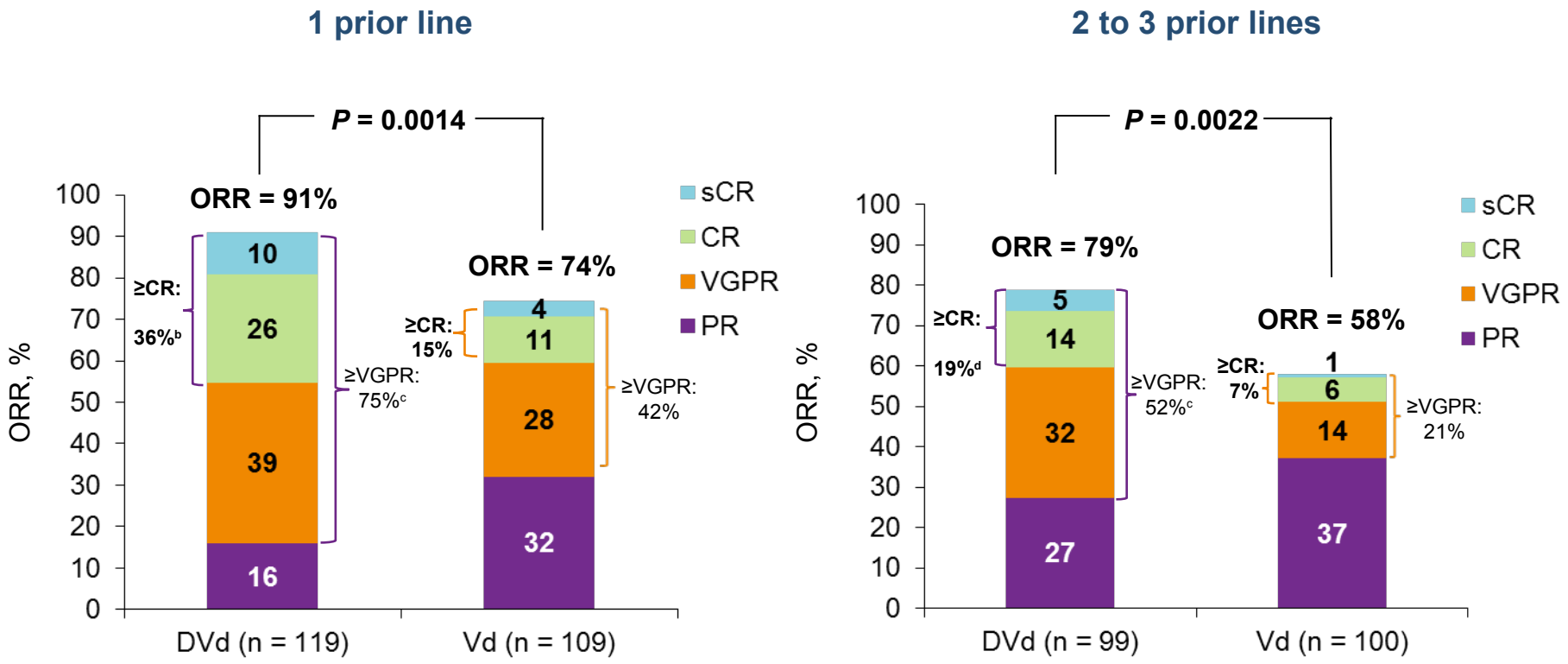
ORR by prior lines



More patients achieve a deeper response with DVd after 1 prior line of treatment

[a]Response-evaluable population.
[b]*P* = 0.0006 for DVd vs Vd.
[c]*P* <0.0001 for DVd vs Vd.
[d]*P* = 0.0133 for DVd vs Vd.
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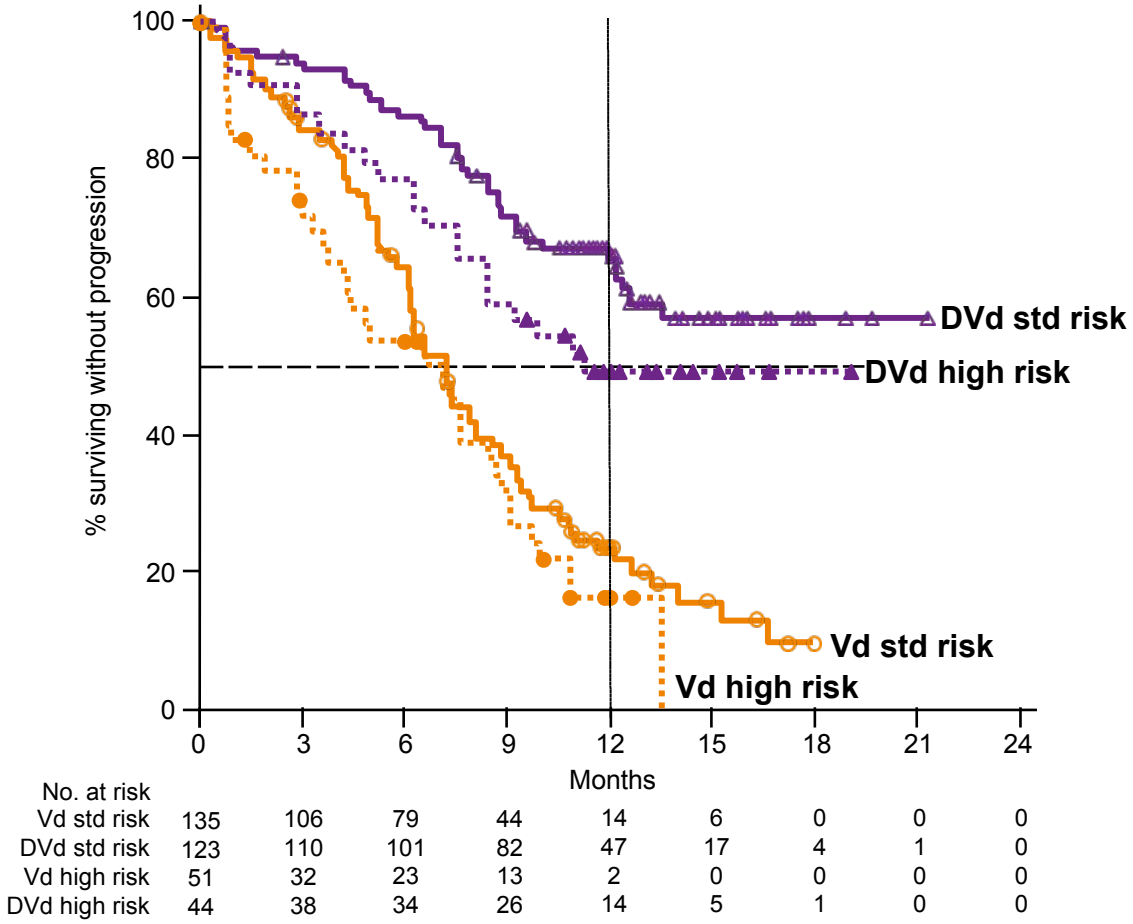
PFS: Cytogenetic Risk in all evaluable patients



High risk[b]	DVd n = 44	Vd n = 51
Median PFS, mo	**11.2**	**7.2**
HR (95% CI)	0.49 (0.27-0.89)	
P value	0.0167	
	n = 44	n = 47
ORR, %	**82**	**62**
P value	0.039	

Standard risk	DVd n = 123	Vd n = 135
Median PFS, mo	**NR**	**7.0**
HR (95% CI)	0.29 (0.20-0.43)	
P value	<0.0001	
	n = 118	n = 131
ORR, %	**85**	**64**
P value	0.0003	

DVd improves outcomes regardless of cytogenetic risk

NR, not reached.

[a]ITT/Biomarker risk–evaluable analysis set.

[b]Central next-generation sequencing. High-risk patients had any of t(4;14), t(14;16), or del17p. Standard-risk patients had an absence of high-risk abnormalities.

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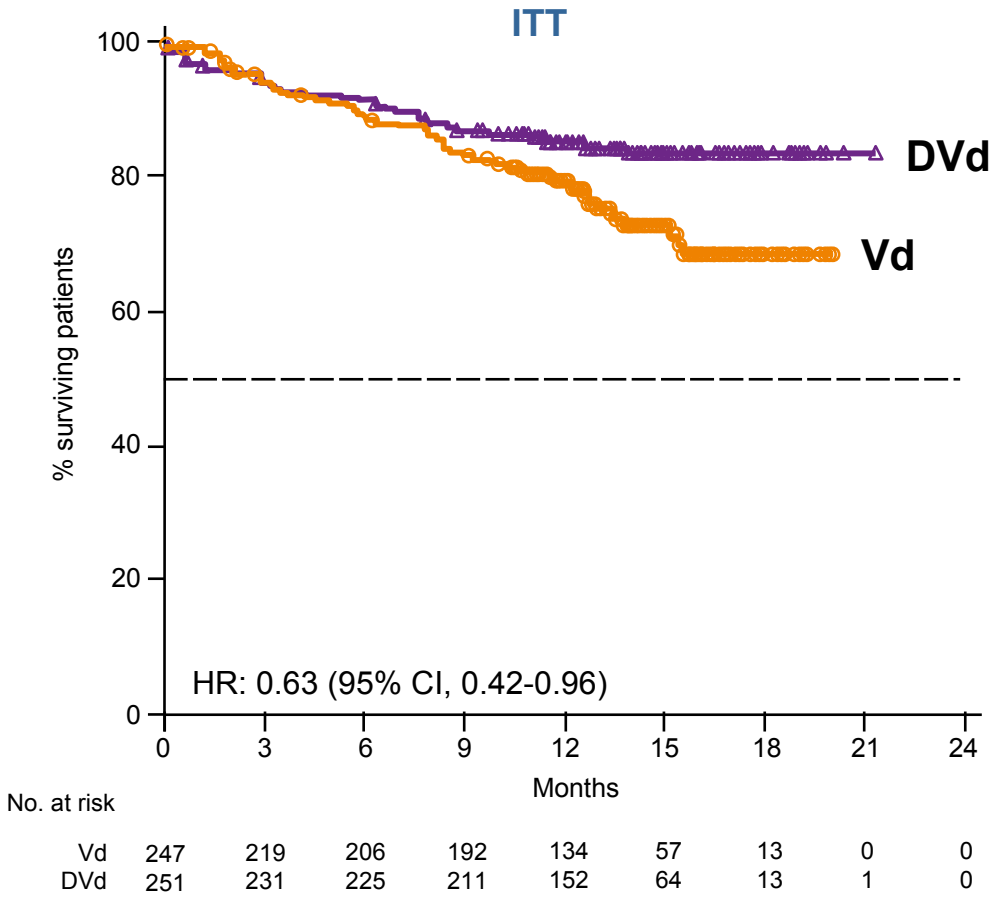
OS



- OS events
  - 37 (15%) in DVd
  - 58 (24%) in Vd
- OS HR for DVd versus Vd by prior lines:
  - 1 prior line = HR: 0.42 (95% CI, 0.19-0.93)
  - 1-3 prior line = HR: 0.54 (95% CI, 0.34-0.84)

Curves are beginning to separate, but OS data are immature

Median OS was not reached; results did not cross the prespecified stopping boundary.
Mateos M-V, et al. Oral presentation at: 58th American Society of Hematology (ASH) Annual Meeting and Exposition; December 3-6 2016; San Diego, CA, USA.

Most Common TEAEs (all patients, updated analysis)

	DVd (n = 243)		Vd (n = 237)	
Hematologic, n (%)	All-grade ≥25%[a]	Grade 3/4 ≥5%[a]	All-grade ≥25%[a]	Grade 3/4 ≥5%[a]
Thrombocytopenia	145 (60)	110 (45)	105 (44)	78 (33)
Anemia	67 (28)	36 (15)	75 (32)	38 (16)
Neutropenia	45 (19)	32 (13)	23 (10)	11 (5)
Lymphopenia	32 (13)	24 (10)	9 (4)	6 (3)
Nonhematologic, n (%)				
Peripheral sensory neuropathy	120 (49)	11 (5)	90 (38)	16 (7)
Diarrhea	83 (34)	9 (4)	53 (22)	3 (1)
Upper respiratory tract infection	72 (30)	6 (3)	43 (18)	1 (0.4)
Cough	66 (27)	0	30 (13)	0
Fatigue	53 (22)	12 (5)	58 (25)	8 (3)
Pneumonia	33 (14)	22 (9)	28 (12)	23 (10)
Hypertension	22 (9)	16 (7)	8 (3)	2 (0.8)

- Grade 3/4 TEAEs: 79% of DVd patients versus 63% of Vd patients
- Discontinuations due to TEAEs: 9% of DVd patients versus 9% of Vd patients[b]
- No new IRRs; incidence remains stable with longer follow up (45%)

TEAE, treatment-emergent adverse event; IRR, infusion-related reaction.
[a]Common TEAEs listed are either ≥25% all grade OR ≥5% grade 3/4. [b]Vd arm treated for 8 cycles and DVd arm treated until progressive disease, per protocol.
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PI-based Studies: Efficacy outcome

	Daratumumab DVd vs Vd	Carfilzomib Kd vs Vd[1]	Panobinostat PVd vs Vd[2,3]	Elotuzumab EVd vs Vd[4]
PFS HR (95% CI)	0.39 (0.28-0.53)	0.53 (0.44-0.65)	0.63 (0.52-0.76)	0.72 (0.59-0.88)
PFS, median mo	NE	18.7	12.0	9.7
≥VGPR	59%	54%	28%	36%
≥CR	19%	13%	11%	4%
Duration of response, mo	NE	21.3	13.1	11.4
OS HR (95% CI)	0.77 (0.47, 1.26)	0.79 (0.58-1.08)	0.94 (0.78-1.14)	0.61 (0.32-1.15)

1. Dimopoulos MA, et al. *Lancet Oncol*. 2016;17(1):27-38.
2. San-Miguel JF, et al. *Lancet Oncol*. 2014;15(11):1195-1206.
3. San-Miguel JF, et al. *Blood*. 2015;126(23):Abstract 3026.
4. Jakubowiak A, et al. *Blood*. 2016. Epub ahead of print.

Palumbo, A. *Oral Presentation EHA* 2016

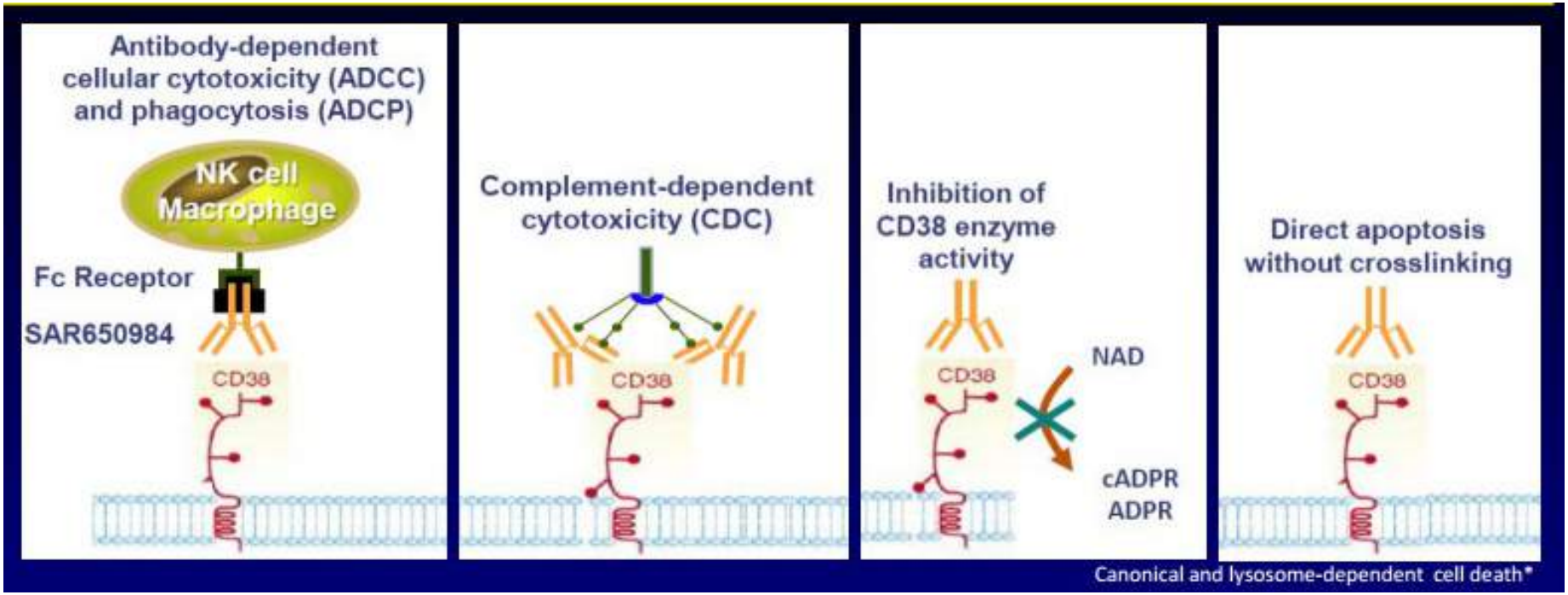
Daratumumab: summary

- ✓ As a single agent, DARA induced rapid, deep, and durable responses in a heavily pretreated/highly refractory population
- ✓ DARA conferred an OS benefit not only in responder patients, but also in patients who achieved SD or MR
- ✓ Updated analysis of the combined dataset of GEN501 and SIRIUS did not identify any new safety signals (infusional reactions)
- ✓ DARA has immune-mediated and immunomodulatory mechanisms that may be contributing to a survival benefit in combination with other drugs (IMIDs and PI)

Isatuximab: mAb anti CD38

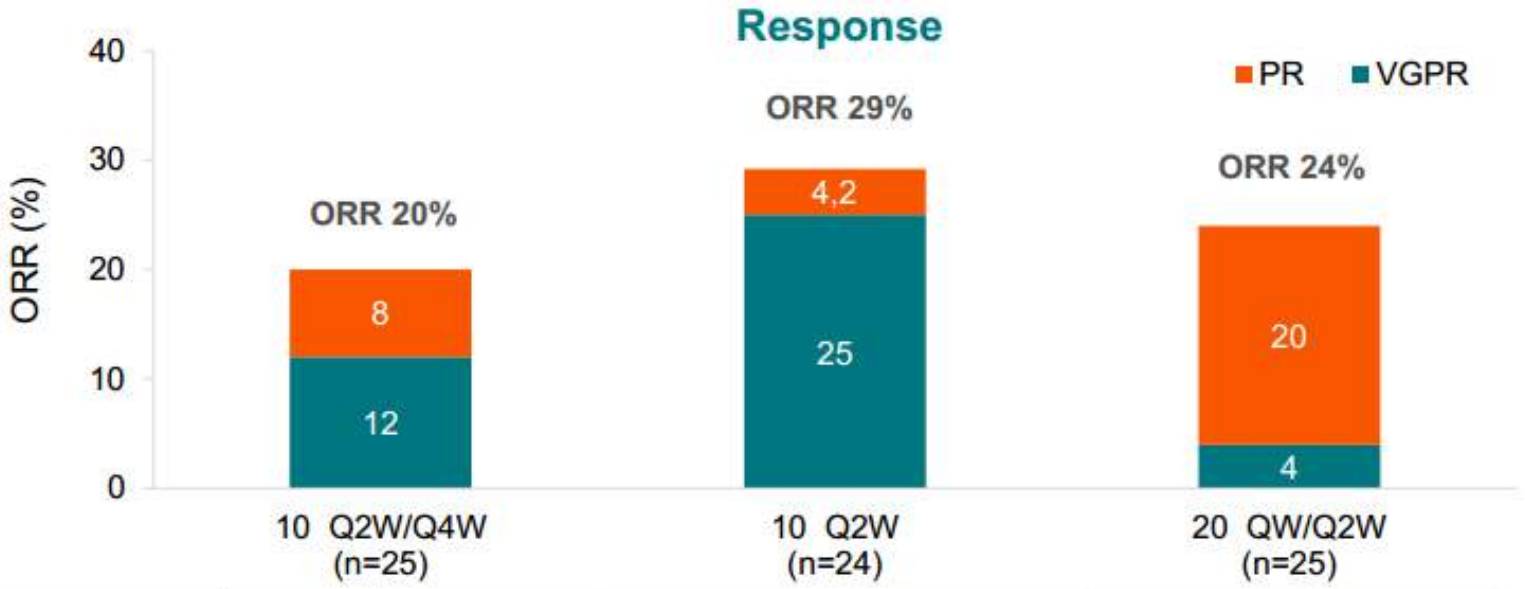
- ✓ ADCC was observed in all the CD38+ lines tested
- ✓ CDC activity was dependent on receptor density
- ✓ Crosslinking –independent apoptosis
- ✓ Inhibition of the CD38 ectoenzimes activity

→ Synergistic and/or additive effect in combination with Len, Bor, Car and Mel in animal models



Vij et al, J Clin Oncol 2016; Deckert et al, Clin cancer Res 214; Martin et al ASH 2014; Jiang et al Leukemia 2016

Isatuximab monotherapy in RRMM



Time to first response, mo	2.0 (0.8– 2.1)	0.9 (0.9–1)	1.35 (0.9–2.8)

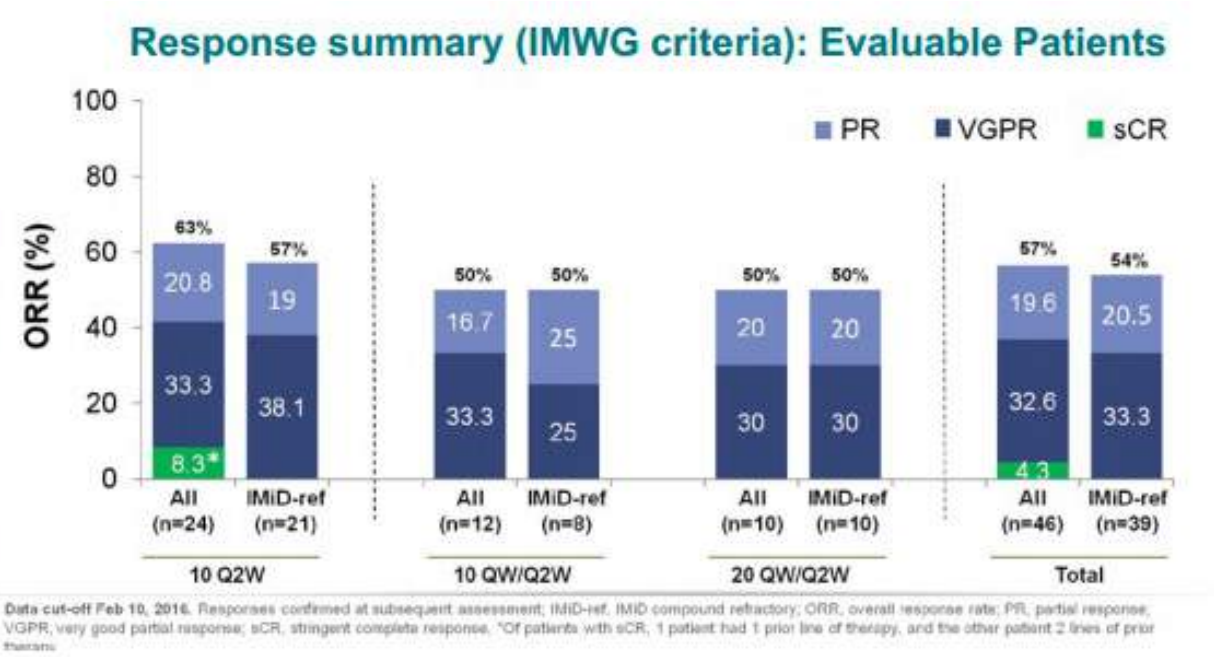
- IRRs occurred in 55% of patients receiving ≥10 mg/kg; Grade ≥3 in 2 patients (3%), both leading to discontinuation (10 mg/kg Q2W)
- Majority of IRRs occurred with first infusion; No IRRs after the 4th infusion

RRMM patients double refractory to PI and IMiDs or have received ≥3 prior lines of therapy

Vij R, et al. Presented at EHA 2016 (Abstract P274), poster presentation.

Phase 1b study: Isatuximab + Len dex in RRMM

- 3 + 3 dose escalation + expansion study
- RRMM + ≥2 prior regimens + len-exposed (for QW/Q2W cohorts)
- Median 4-6 prior lines of therapy in the 3 expansion cohorts; 85% IMiD refractory
- Median duration of response was 7.6 months
- Isatuximab 10 mg/kg QW/Q2W has been selected for further study in global phase 3 study



Data cut-off Feb 10, 2016. Responses confirmed at subsequent assessment; IMiD-ref, IMiD compound refractory; ORR, overall response rate; PR, partial response; VGPR, very good partial response; sCR, stringent complete response. *Of patients with sCR, 1 patient had 1 prior line of therapy, and the other patient 2 lines of prior therapy.

Vij, R et al. ASCO 2016 (Abstract 8009); oral presentation.

Phase 1b study: Isatuximab + Pom dex in RRMM

- 3 + 3 dose escalation + expansion study
- Adults with RRMM and ≥2 prior therapies including lenalidomide and a PI

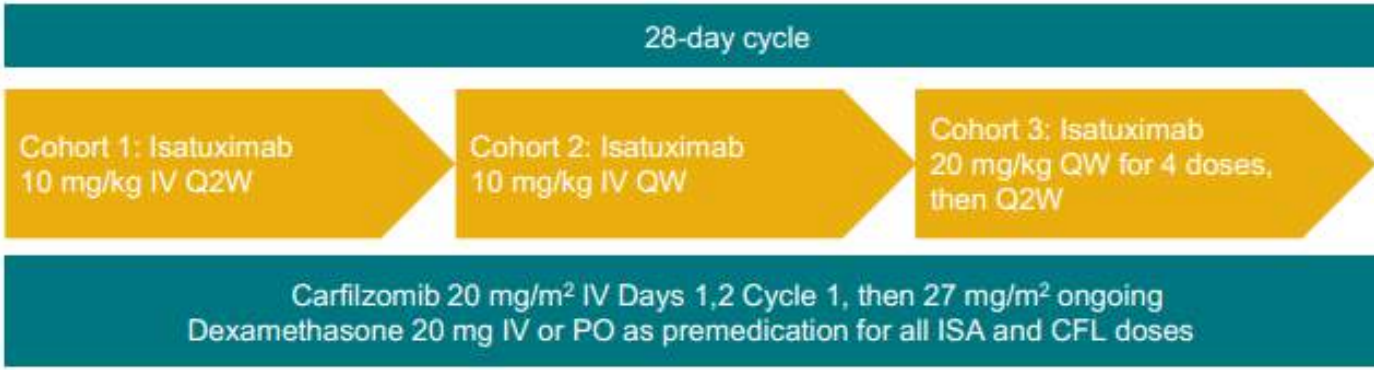
- Patients: n=20 in dose-escalation phase
  - Median (range) prior lines: 4.5 (3-11); 75% of patients refractory to IMiD
- Response data (n=14):
  - ORR 64%: 1 patient with CR, 4 with VGPR, and 4 with PR
  - Median (range) duration of response: 19.71 (8-45) weeks
- No new safety signals
- MTD not reached; Isatuximab 10 mg/kg selected for expansion cohort
- Phase III study of isatuximab plus Pom/Dex was planned to start in 2016

Interim analysis results. Data cut-off: August 15, 2016

Richardson, P et al. Presented at ASH 2016 (Abstract 2123), poster presentation.

Phase 1b study: Isatuximab + Carf dex in RRMM

- 3 + 3 dose escalation + expansion study
- Adults with RRMM and 2 prior therapies including an IMiD and PI (prior carfilzomib allowed even if refractory)



- Patients: N=12
  - Median (range) prior lines: 3.5 (2-8); 75% refractory to IMiD and PI; 65% refractory to carfilzomib
- Response data (n=12):
  - ORR 66.7%: 2 with VGPR, 6 with PR, and 2 with MR
- No new safety signals
- MTD not reached; 21 patients to be enrolled into expansion phase

Interim analysis results. Data cut-off: November 20, 2016

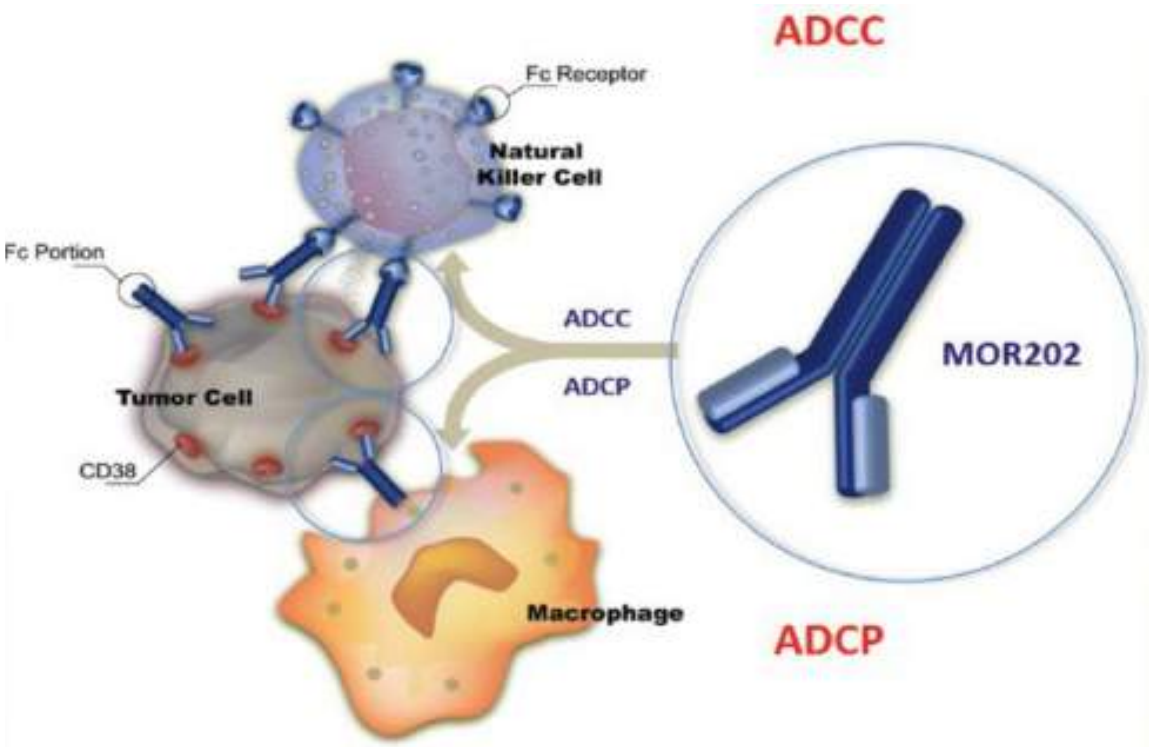
Martin, T et al. Presented at ASH 2016 (Abstract 2111), poster presentation.

MOR202 (CD38) mAb: main modes of action

- ✓ ADCC
- ✓ ADCP (phagocytosis)

→Synergistic effect in combination with Len and POM and additive with Bor

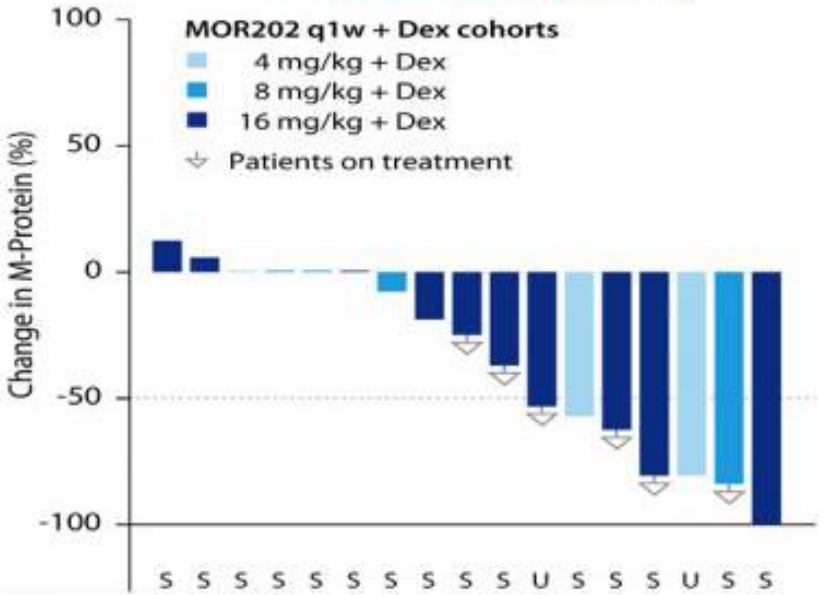
- Len and Pom showed to increase CD38 expression, and thus enhance the cytotoxic effects of MOR202 in cell lines.
- Both IMIDs induce activation of immune effector cells
- Reductions in bone lysis in combination with Len, Bor or Pom in animal models



Raab et al, ASCO 2015

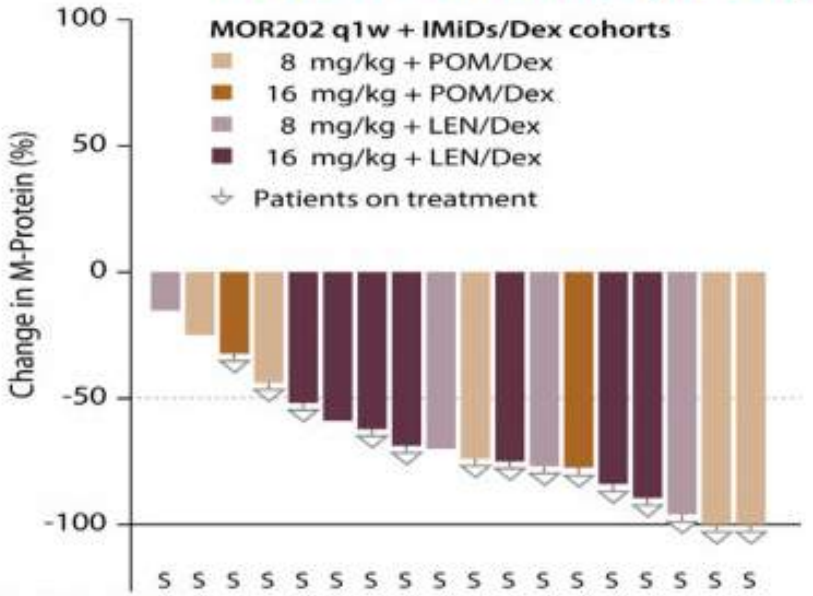
Phase 1/2 study: MOR202 in RRMM

MOR202/Dex (n=18)



- ORR: 29%
- Median of number of prior lines of therapy: 3
- 56% of pts refractory to the last line of therapy
- Median PFS: 4.7 months

MOR202 + IMiD/Dex (n=9/14)



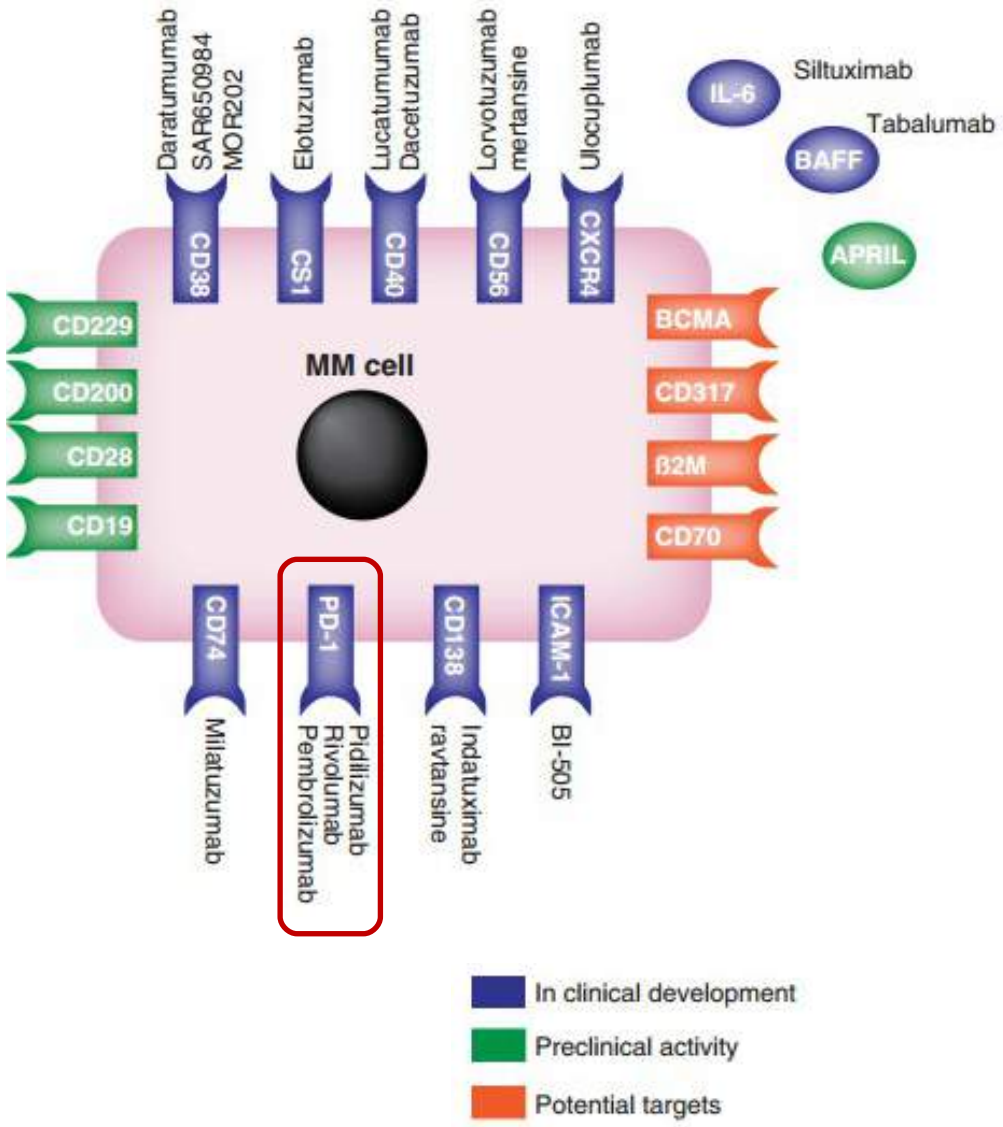
- ORR: 78%
- Median of number of prior lines of therapy: 3/2
- 100% of pts refractory to the last line of therapy for Pom-dex arm (n=9) and 50% for len-dex arm
- Median PFS: NR

Good tolerability. 7% of IRRs (grade 2)

Raab, MS et al. ASH 2016 (Abstract 1152), oral presentation

MM cells and its microenvironment: target molecules

- ✓ Ab anti SLAMF7 or CS1
- ✓ Ab anti CD38
- ✓ Ab anti PD-1/PDL-1
- ✓ Denosumab
- ✓ Other Ab targets

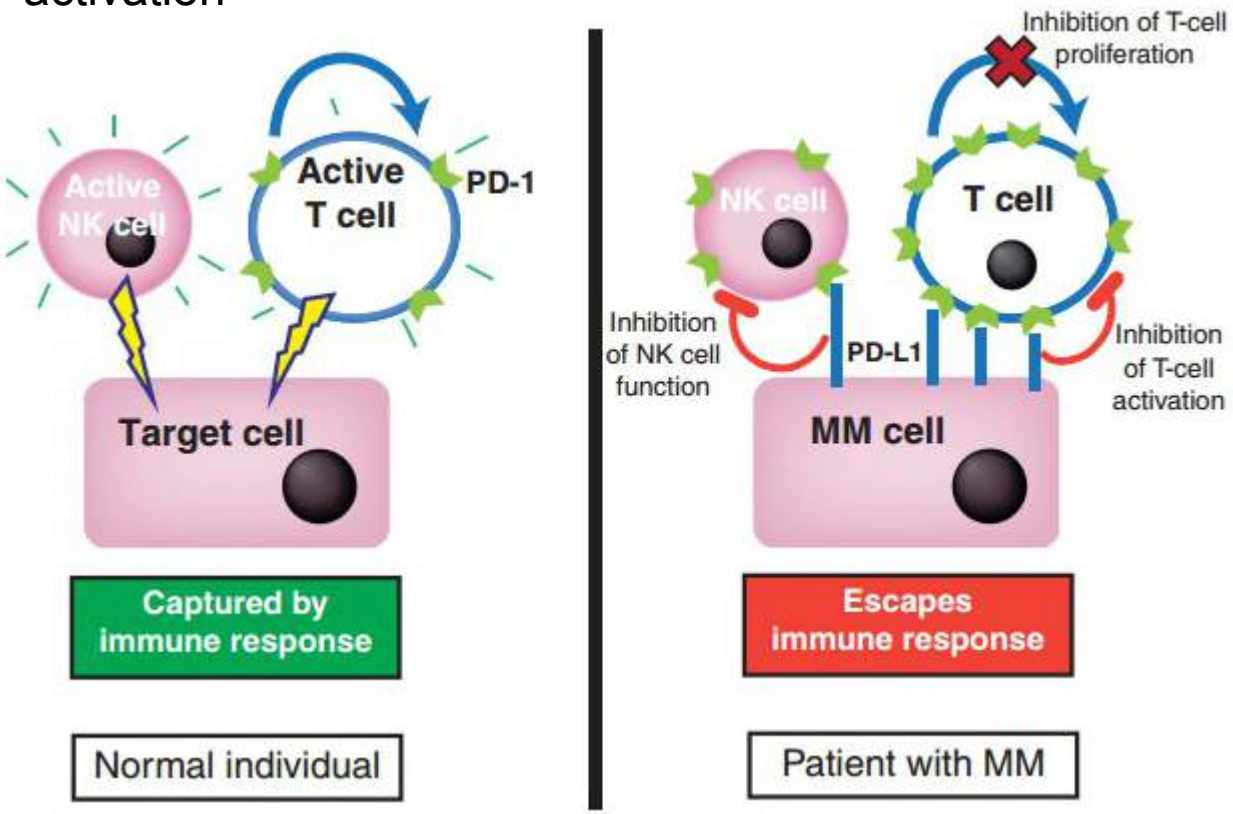


Lonial S, Leukemia 2016

PD-1 and PD-L1

- ✓ PD-1 is expressed on T and B surface and inhibits T-cell activation and proliferation through interaction with PD-L1 expressed on APC

- ✓ PD-1/PD-L1 signaling is dysregulated in MM patients:indeed PD-L1 expressed on MM cells provides an escape of immune through inhibition of NK and T cells activation



Topalian SL, Curr Opin Immunol 2012; Chen DS, Clin Cancer Res 2012

PD-1, PD-L1 and mAbs

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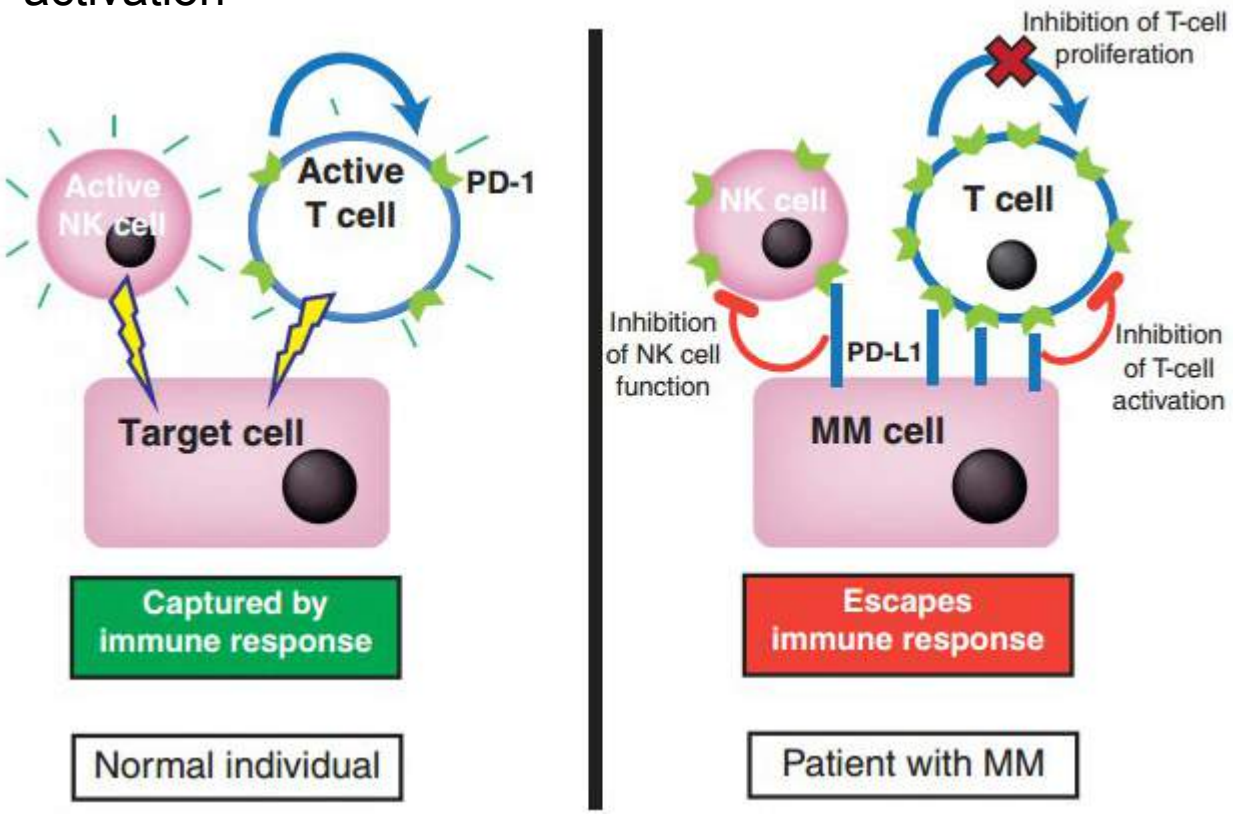


PD-1 mAbs
- ✓Nivolumab
- ✓Pembrolizumab
- ✓Pidilizumab

PD-L1 mAbs
- ✓Durvalumab

Topalian SL, Curr Opin Immunol 2012; Chen DS, Clin Cancer Res 2012

PD-1, PD-L1 and mAbs

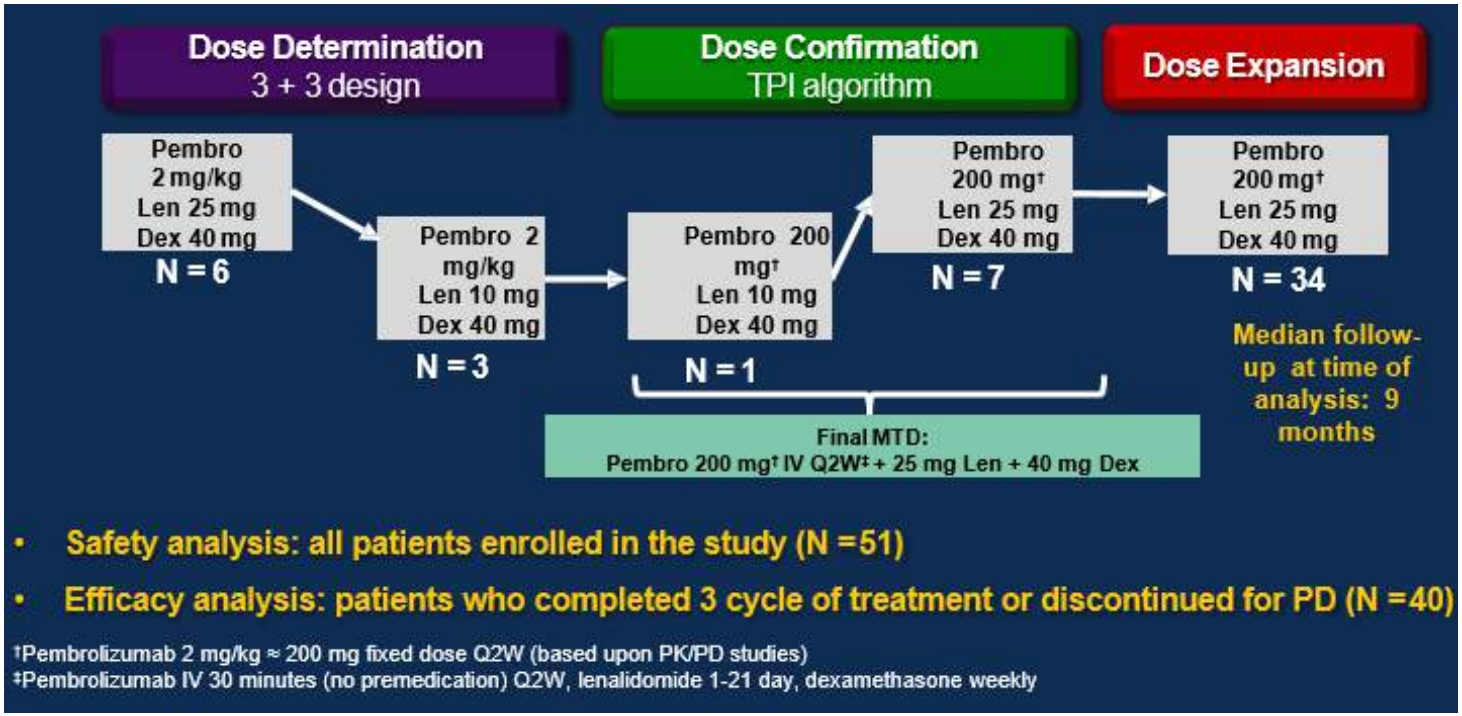
Author	Phase study	Combination	Number of pts	Median n. of prior Th	Response rate % (≥ PR)	PFS (months)
Lesokhin, 2016 J Clin Oncol (nivolumab)	1b	NIVOLUMAB alone	27	78% ≥ 3	63% SD, 4% CR	-
SanMiguel, 2015 Blood (pembrolizumab)	1	PEMBROLIZUMAB LEN-DEX	50	3	76% (76% LEN refractory)	Short follow-up
Badros, 2015 Blood (pembrolizumab)	2	PEMBROLIZUMAB POM-DEX	17	3	60% (96% LEN refractory)	Short follow-up

Modest clinical activity as single agent

Good ORR in combination with IMIDs in R/R MM (also in LEN refractory group)

Phase 1 study: Pem + Len dex in RRMM

- ✓ 51 RRMM pts, failure of ≥2 prior therapies including PI and IMIDs
- ✓ median age 61, prior lines: 4
- ✓ Refractoriness: 78% to last line, 75% to Len, 63% to Bor



- ✓ In dose determination stage, 3/6 pts treated with Pem 2 mg/kg + Len 25 mg + Dex had DLTs (1 pt TLS G3, hyperuricemia G4, neutropenia G4; 1 pt neutropenia G3, 1pt pneumonia G3)
- ✓ All pts recovered from the DLTs without treatment discontinuation
- ✓ In dose confirmation stage, 7 additional pts were treated with pembro 200 mg + Len 25 mg + Dex with no DLTs observed

Mateos et al, ASCO 2016

Phase 1 study: Pem + Len dex in RRMM

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

Immune-mediated AE

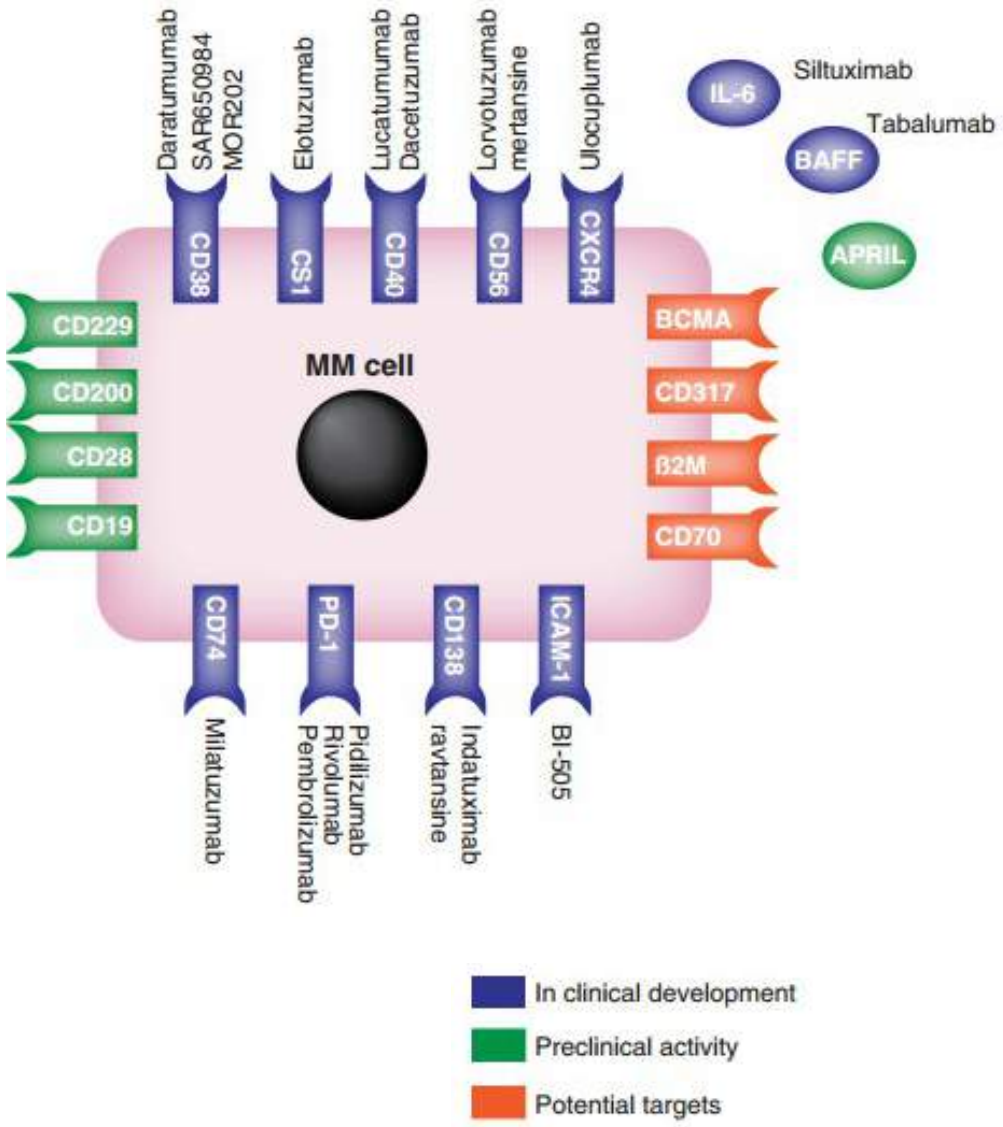
n (%)	Pembro +Len + Dex (N = 51)
Hyperthyroidism Grade 1	1 (2)
Hypothyroidism Grade 1	2 (4)
Thyroiditis Grade 1	1 (2)
Increased transaminases Grade 3	1 (2)
Renal failure Grade 3	1 (2)

- AEs associated wit PEM were similar to other indications (solid tumors)
- 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%) pts discontinued due to treatment related AEs
- No dose modification or treatment discontinuation required for management of the reported immune related AEs
- No cases of pneumonitis or colitis were reported
- No infusion reactions were reported

Mateos et al, ASCO 2016

MM cells and its microenvironment: target molecules

- ✓ Ab anti SLAMF7 or CS1
- ✓ Ab anti CD38
- ✓ Ab anti PD-1/PDL-1
- ✓ Denosumab
- ✓ Other Ab targets

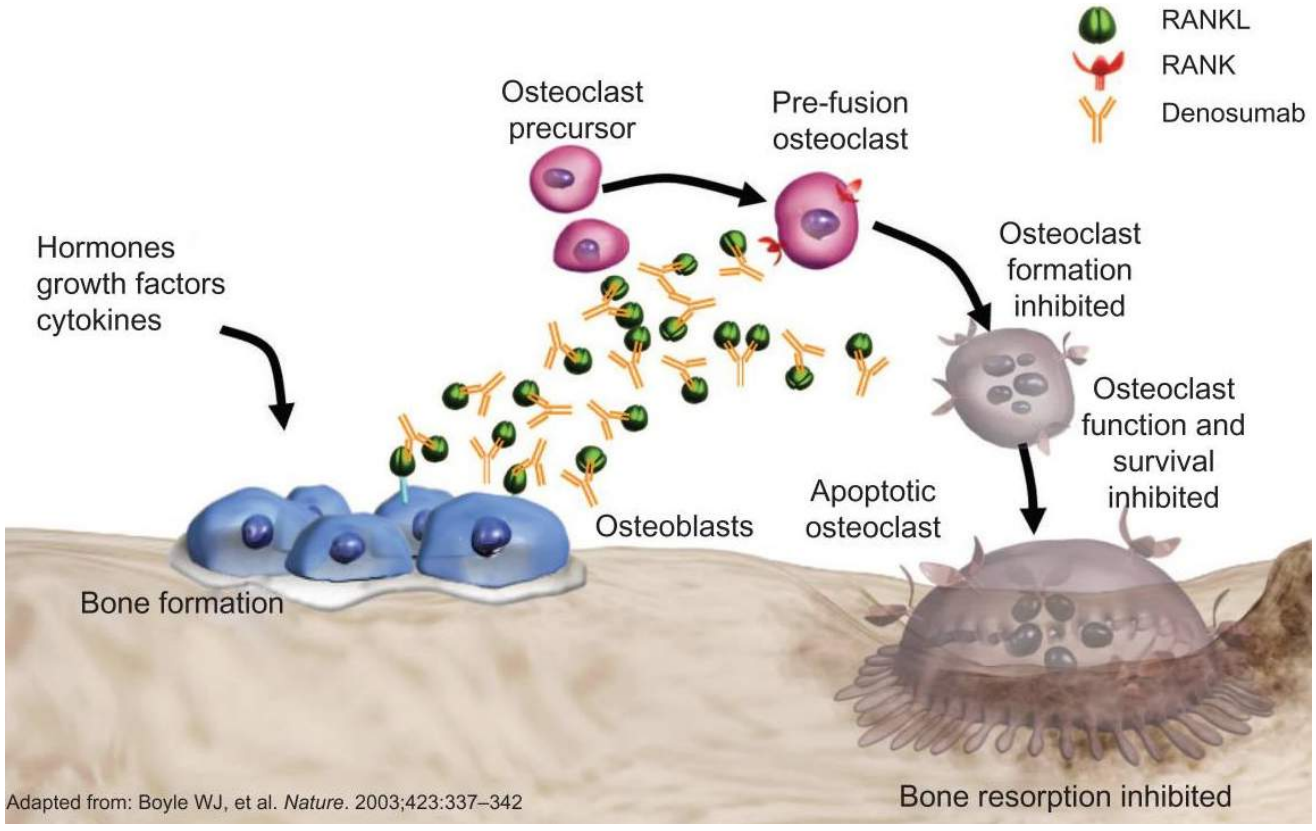


Lonial S, Leukemia 2016

Denosumab: a future option?

✓RANK ligand (RANKL) is a key driver of osteoclast-mediated osteolysis, increasing the risk of skeletal-related events and impacting morbidity, mortality and quality of life in MM pts

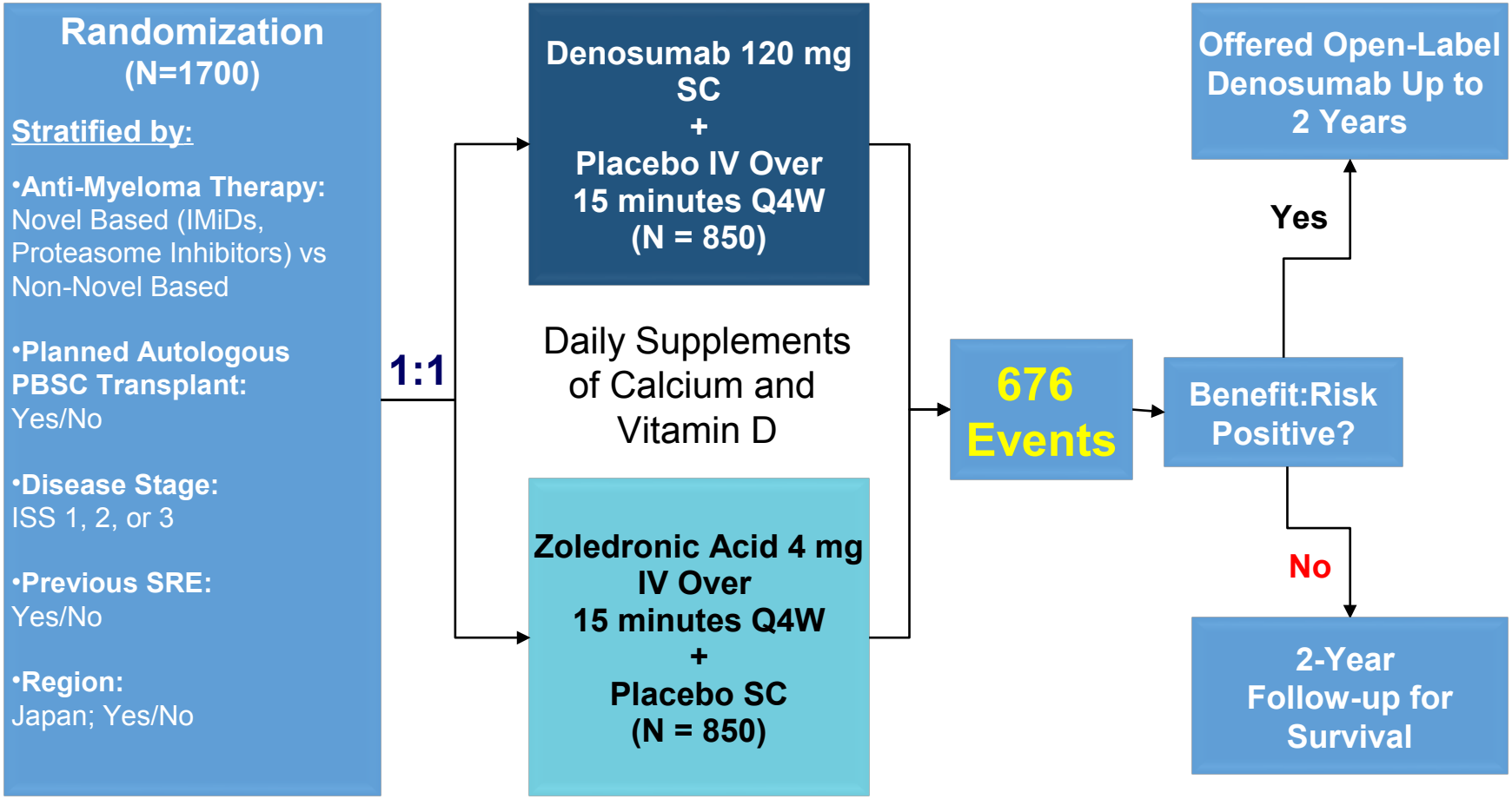
✓Denosumab, a human monoclonal antibody that binds with high specificity and affinity to RANKL, may directly inhibit RANKL-mediated myeloma growth and reactivation of dormant myeloma cells



Henry et al. J Clin Oncol, 2011,
Lawson et al, Nat Commun 2015
Raje N, Blood Cancer Journal 2016

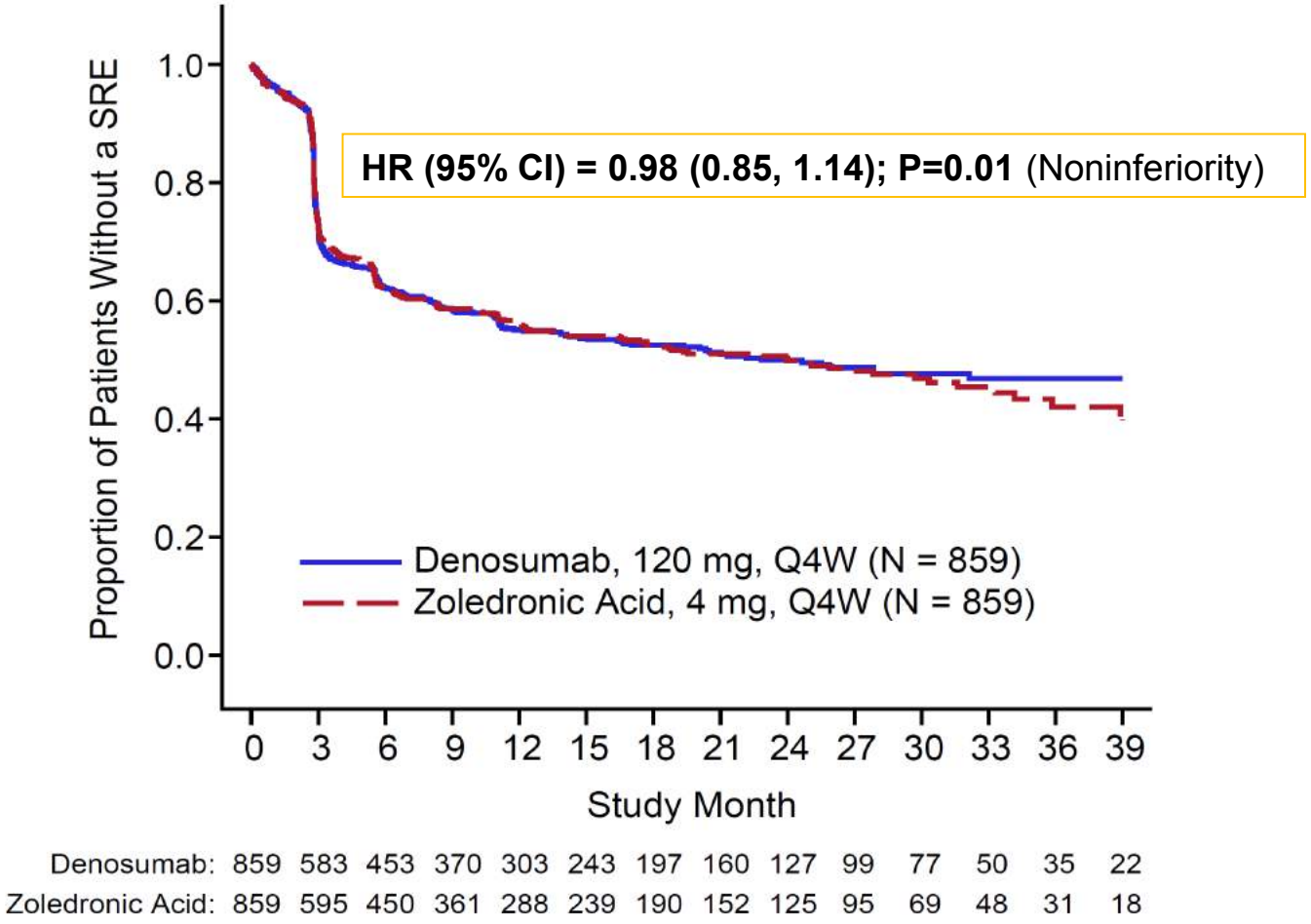
Study design

An International, Randomized, Double Blind Trial Comparing Denosumab With Zoledronic Acid for the Treatment of Bone Disease in Patients With Newly Diagnosed Multiple Myeloma



Raje N et al, SC-IT-AMG162-00010

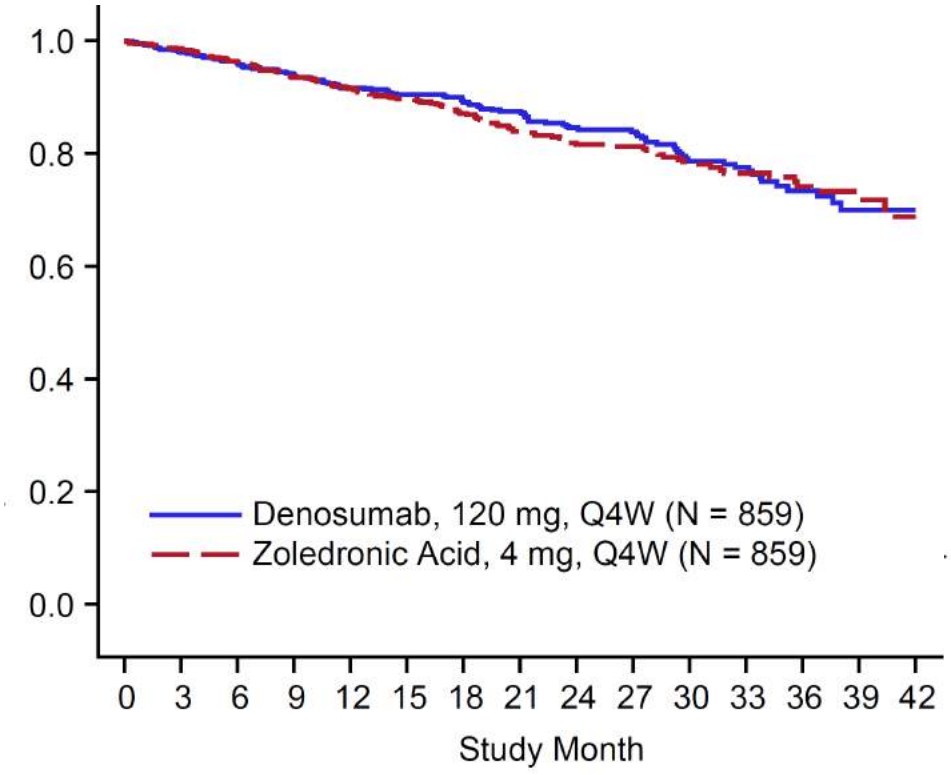
Results: non inferiority for time to first Skeletal related event



Raje N et al, SC-IT-AMG162-00010

Results: overall survival and progression free survival

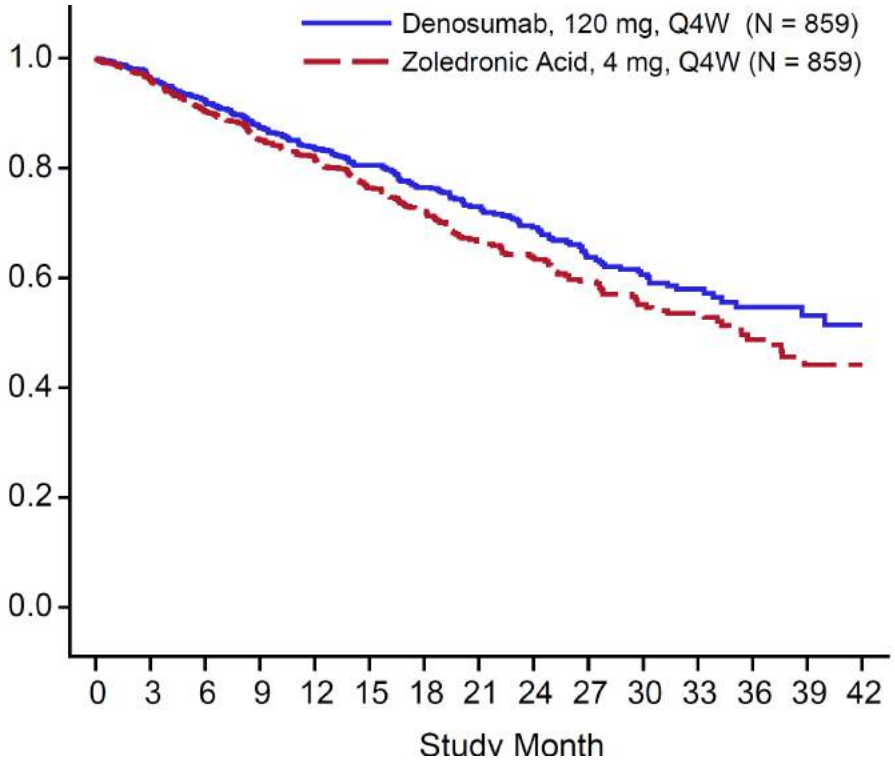
Overall survival



HR (95% CI) = 0.90 (0.70, 1.16); P = 0.41

Denosumab	121 Deaths (14.1%)
Zoledronic Acid	129 Deaths (15.0%)

Progression free survival



HR (95% CI) = 0.82 (0.68, 0.99); P = 0.036 (Descriptive)

	Median Duration (95% CI), Months
Denosumab	46.09 (34.30, Not Estimable)
Zoledronic Acid	35.38 (30.19, Not Estimable)

Raje N et al, SC-IT-AMG162-00010

Results: Adverse Events of interest

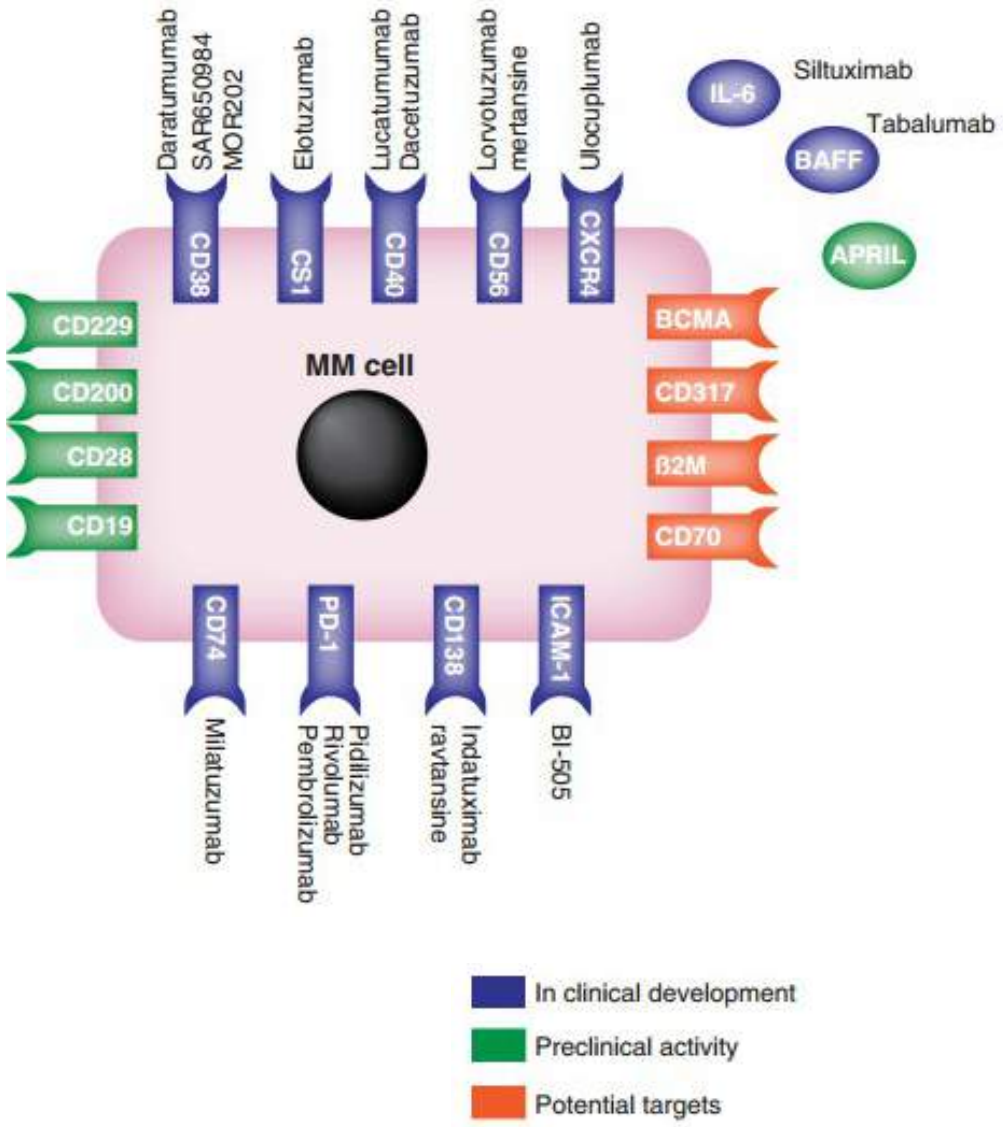
	Denosumab N = 850, n (%)	Zoledronic Acid N = 852, n (%)
Hypocalcemia	144 (16.9)	106 (12.4)
Serious AEs of Hypocalcemia	8 (0.9)	2 (0.2)
Adjudicated Positive Osteonecrosis of the Jaw	35 (4.1)	24 (2.8)
Adjudicated Positive Atypical Femur Fracture	0	0
AEs Potentially Associated With Hypersensitivity	219 (25.8)	189 (22.2)
Serious AEs Potentially Associated With Hypersensitivity	5 (0.6)	9 (1.1)
Musculoskeletal Pain	407 (47.9)	425 (49.9)
Infections and Infestations	537 (63.2)	500 (58.7)
Serious AEs of Infections and Infestations	165 (19.4)	163 (19.1)
New Primary Malignancy	22 (2.6)	12 (1.4)
AEs Potentially Associated with Renal Toxicity	85 (10.0)	146 (17.1)
Acute Phase Reactions	46 (5.4)	74 (8.7)

- ✓ There were significantly lower incidences of adverse events potentially related to renal toxicity with denosumab therapy compared to zoledronic acid,10% vs 17.1%, P<0.001, particularly in those patients with baseline CrCl≤60mL/minute, 12.9% vs 26.4%, respectively
- ✓ The incidence of hypocalcemia events was 144 (16.9%) for denosumab and 106 (12.4%) for zoledronic acid, with the majority of events grade 1 or 2; there were no grade 5 events

Raje N et al, SC-IT-AMG162-00010

MM cells and its microenvironment: target molecules

- ✓ Ab anti SLAMF7 or CS1
- ✓ Ab anti CD38
- ✓ Ab anti PD-1/PDL-1
- ✓ Denosumab
- ✓ Other Ab targets



Lonial S, Leukemia 2016

Trials of investigational agents

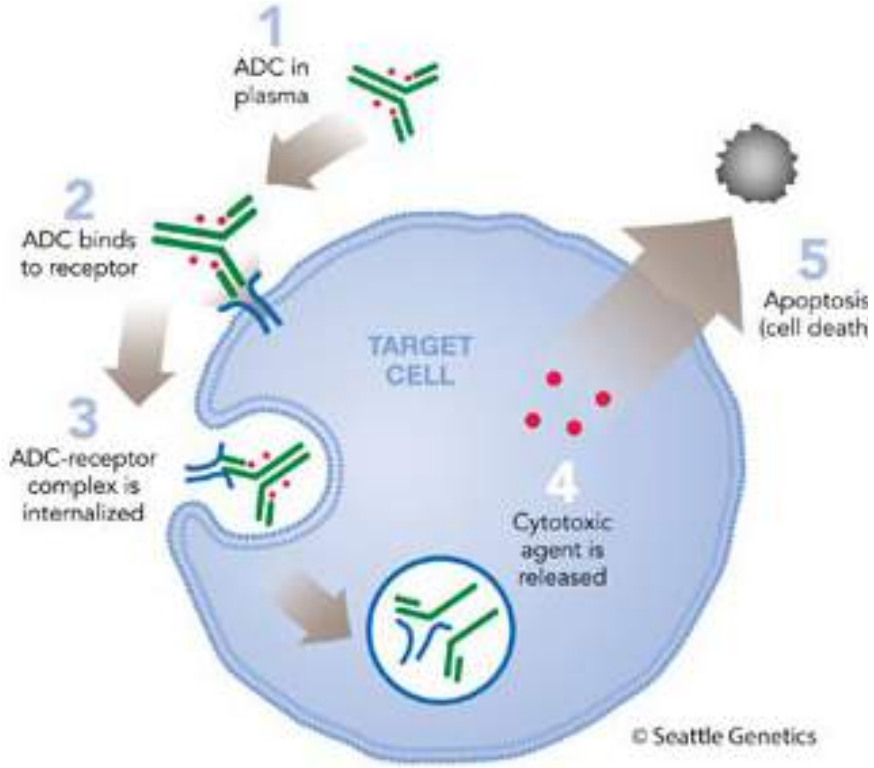
mAb	Target	Phase	Number of pts	Response rate %	Author
Siltuximab	IL-6	1, RRMM	14	0%	Voorhees, Br J Hem 2013
Dacetuzumab	CD40	1, RRMM	44	20% SD	Hussein, Haematologica 2010
Lucatumumab	CD40	1, RRMM	28	43% SD, 4%PR	Besinger, Br J Hematol 2012
DAT-SM6	GRP78	1, RRMM	12	33% SD	Rasche, Haematologica 2015
Figitumumab	IGF-IR	1, RRMM	27	33%	Lacy, J Clin Oncol 2008
BI-505	CD54	1, RRMM	35	20%	Hansson, Clin Cancer Res 2015
Indatuximab LEN DEX	CD138	2, RRMM	36	78% (73% prior exposure to LEN)	Kelly, ASH 2014
Tabalumab BOR DEX	BAFF	1, RRMM	48	46%	Raje, ASH 2012

Limitated efficacy as a single agent

Promising efficacy in combination regimens

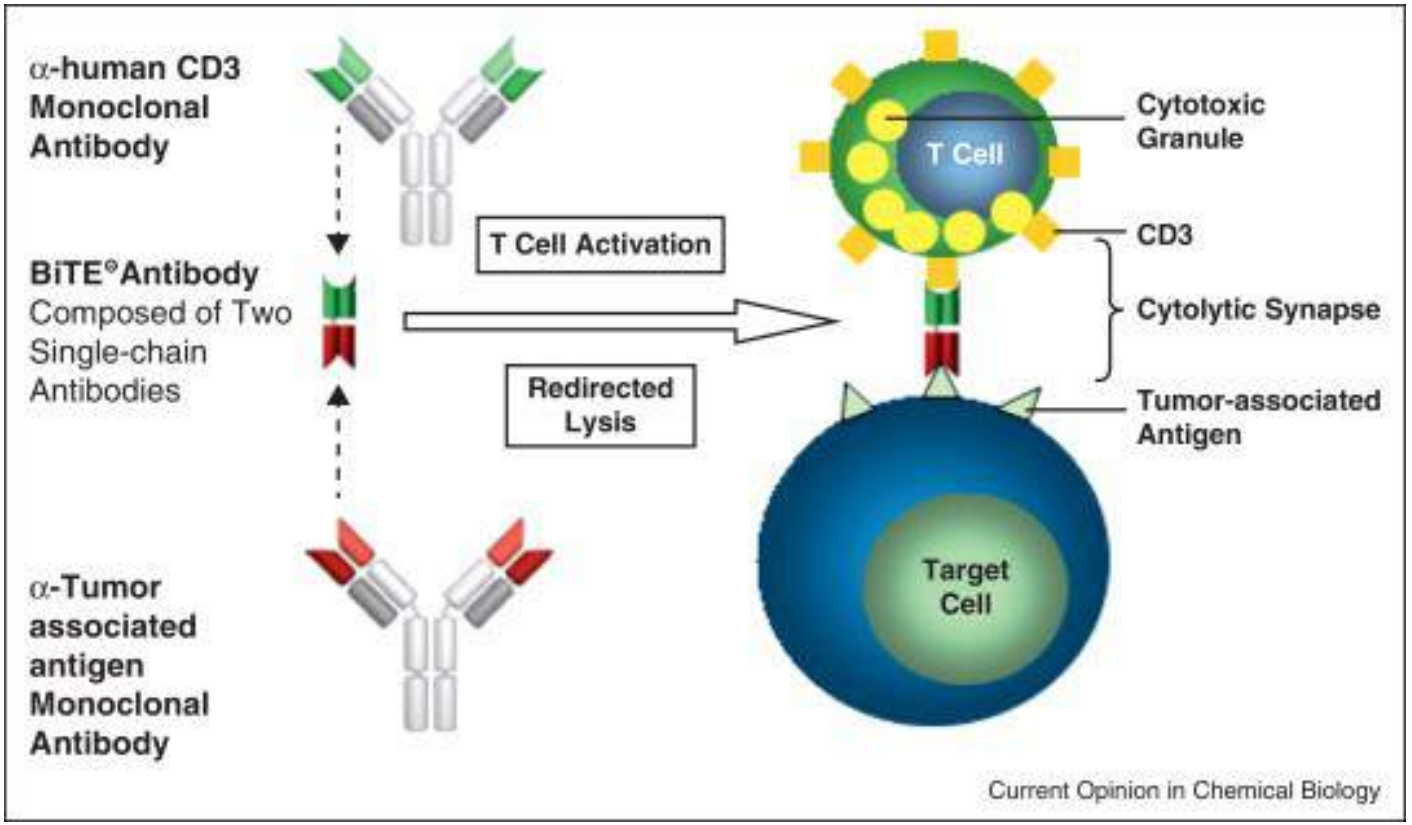
Monoclonal Ab drug conjugate

- ✓ Toxins or radioactive isotopes are bound to the costant region of the Mabs
- ✓ When Mab binds to the surface of tumor cells the toxin will kill cancer cells and cell within a certain radius (killing zone)



mAb	Target	Phase	Number of pts	Response rate %	Author
Milatuzumab-doxorubicin	CD74	1, RRMM	-	Ongoing	-
Anti-BCMA auristatin	BCMA	1, RRMM	24	ongoing	Cohen, Am Soc Hematol abstract 2016
Indatuximab-ravtansine	CD138	1, RRMM	23	52% SD+ PR for > 3 months	Kelly, ASH abstract 2014

Bispecific T-cell Engager Ab (BiTE)

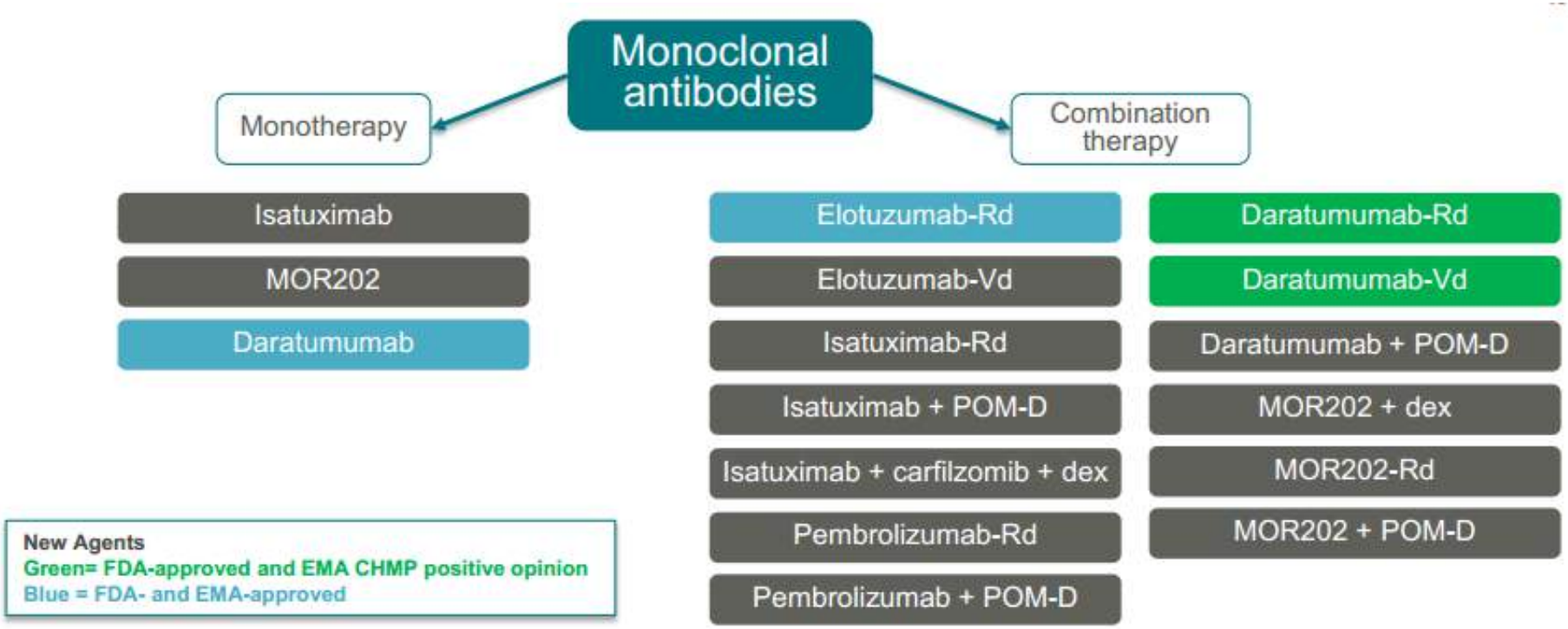


BiTE in RR multiple myeloma

✓Bispecific CD3/CD138 mAb (preclinical activity)

✓Bispecific CD3/BCMA mAb (BI 836909) (phase 1 ongoing)

Summary: potential for mAb in RRMM



ASCT, autologous stem cell transplant;
PFS, progression-free survival;
RIC, reduced-intensity conditioning

Empliciti US Prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761035s000lbl.pdf; Empliciti EU SmPC: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003967/WC500206673.pdf
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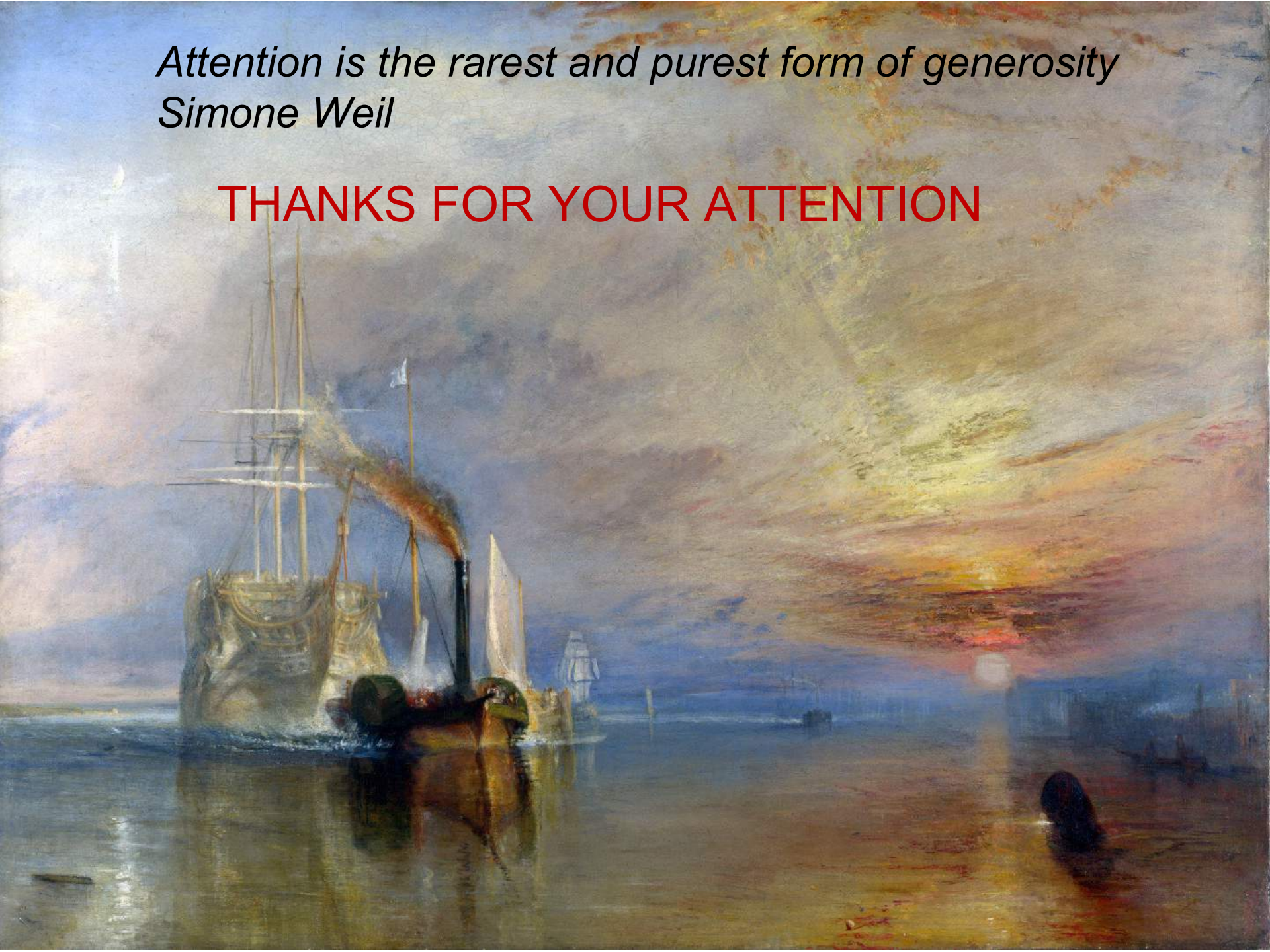
http://www.businesswire.com/news/home/20170224005351/en/DARZALEX%C2%AE%E2%96%BC-daratumumab-Receives-Positive-CHMP-Opinion-Treatment

Conclusions

- ✓ In RRMM setting daratumumab has shown robust single-agent activity, which has been enhanced in combination with other drugs (IMIDs and PIs), whereas the activity of other mAbs appears restricted to combination regimens
- ✓ mAbs are generally well tolerated with a favorable safety profile
- ✓ Combination with lenalidomide is probably the best option considering the positive effects of immune response of IMIDs
- ✓ Potential benefit of mAbs combinations themselves is under clinical testing
- ✓ mAbs may also have a role in early line of treatment or in smoldering myeloma suggesting, respecttively, a deeper response/PFS and a delay of symptomatic evolution of disease
- ✓ Denosumab is promising in setting of renal impairment (and improvement of PFS?)
- ✓ Further studies are needed to reveal the real impact of these agents in long-term survival and quality of life in patients with MM


Attention is the rarest and purest form of generosity
Simone Weil
THANKS FOR YOUR ATTENTION