STRATEGIE TERAPEUTICHE
ATTUALI E FUTURE
NEL MIELOMA MULTIPLO:

LA CHEMIOTERAPIA E GLI ANTICORPI MONOCLONALI

PRESIDENTE
Mario Boccadoro

RESPONSABILI SCIENTIFICI
Giulia Benevolo
Sara Bringhen

TORINO
31 marzo 2017
NH HOTEL PIAZZA CARLINA

OSPEDALE MAGGIORE DELLA CARITÀ
NOVARA

UPO
UNIVERSITÀ DEL PIEMONTE ORIENTALE

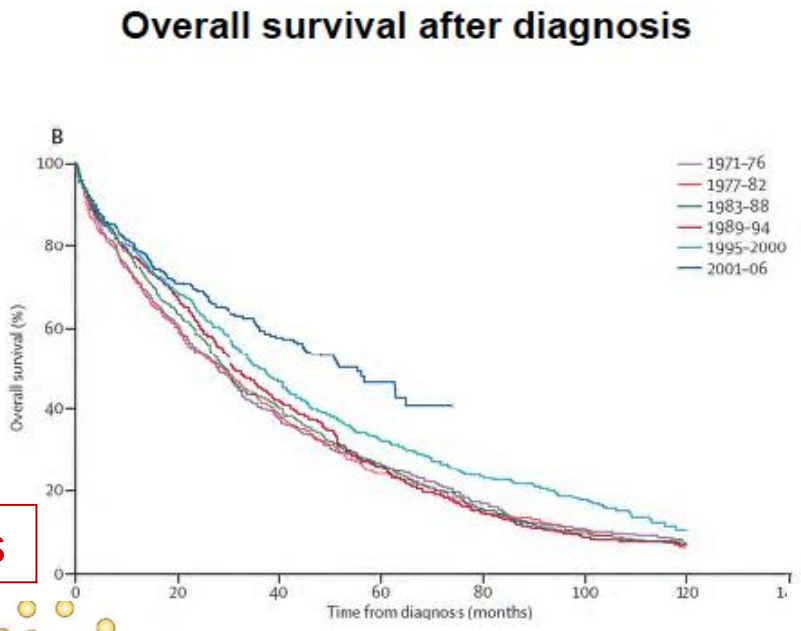
Anticorpi monoclonali: benefici clinici nella monoterapia

Lorenzo De Paoli, MD, PhD

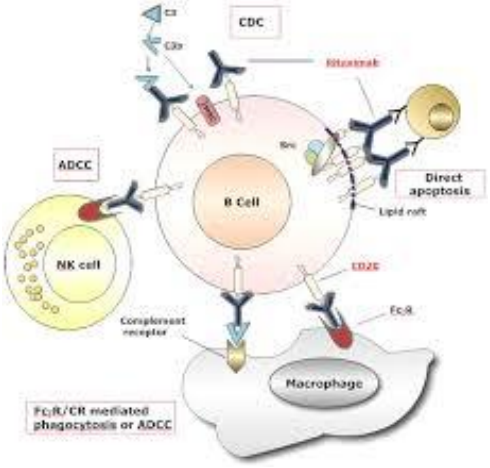
Divisione di Ematologia
Dipartimento di Medicina Traslazionale
Università del Piemonte Orientale
Amedeo Avogadro
Novara

MM outcome and treatment options

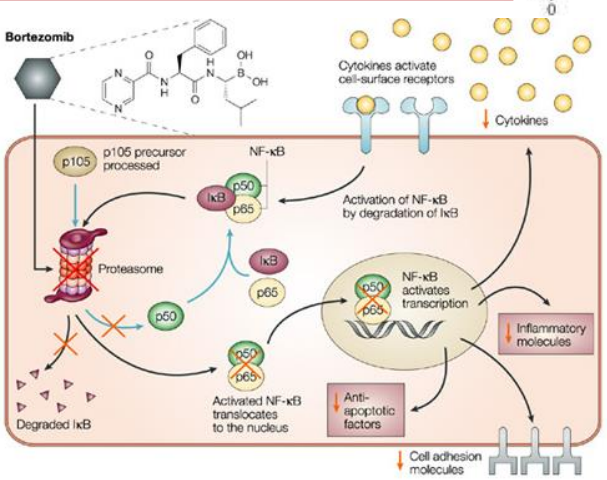
Chemotherapy



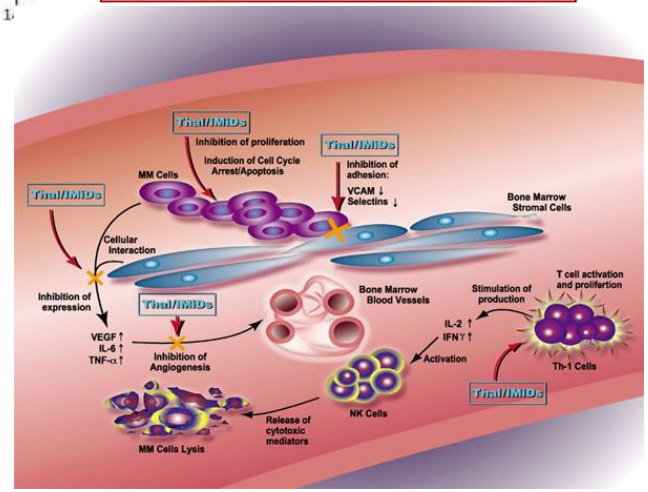
Monoclonal antibody



Proteasome inhibitors



Immunomodulators



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

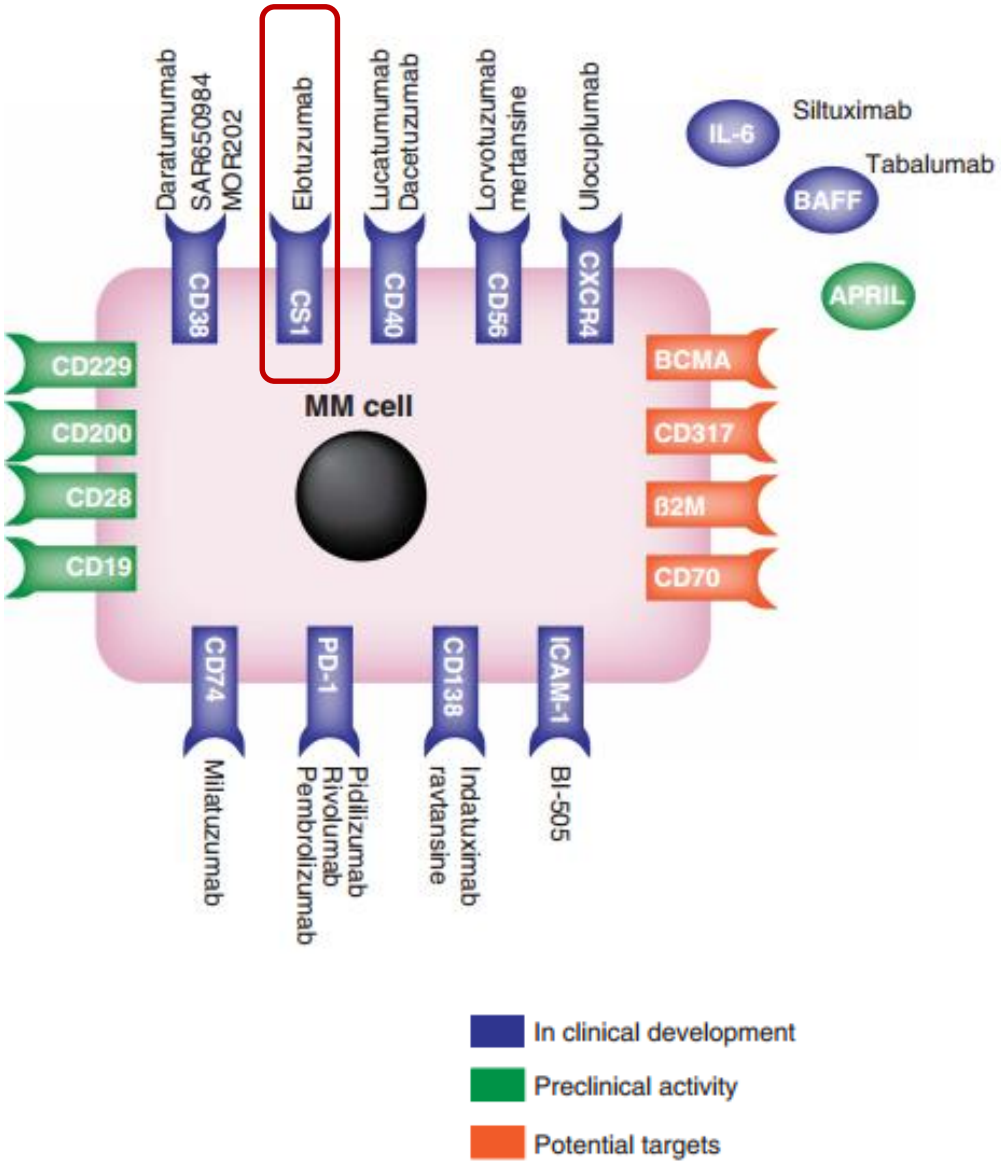
- ✓ New kind of treatment with distinct mode of action (CHT, IMIDS, PIs) to improve outcome in incurable disease

- ✓ 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

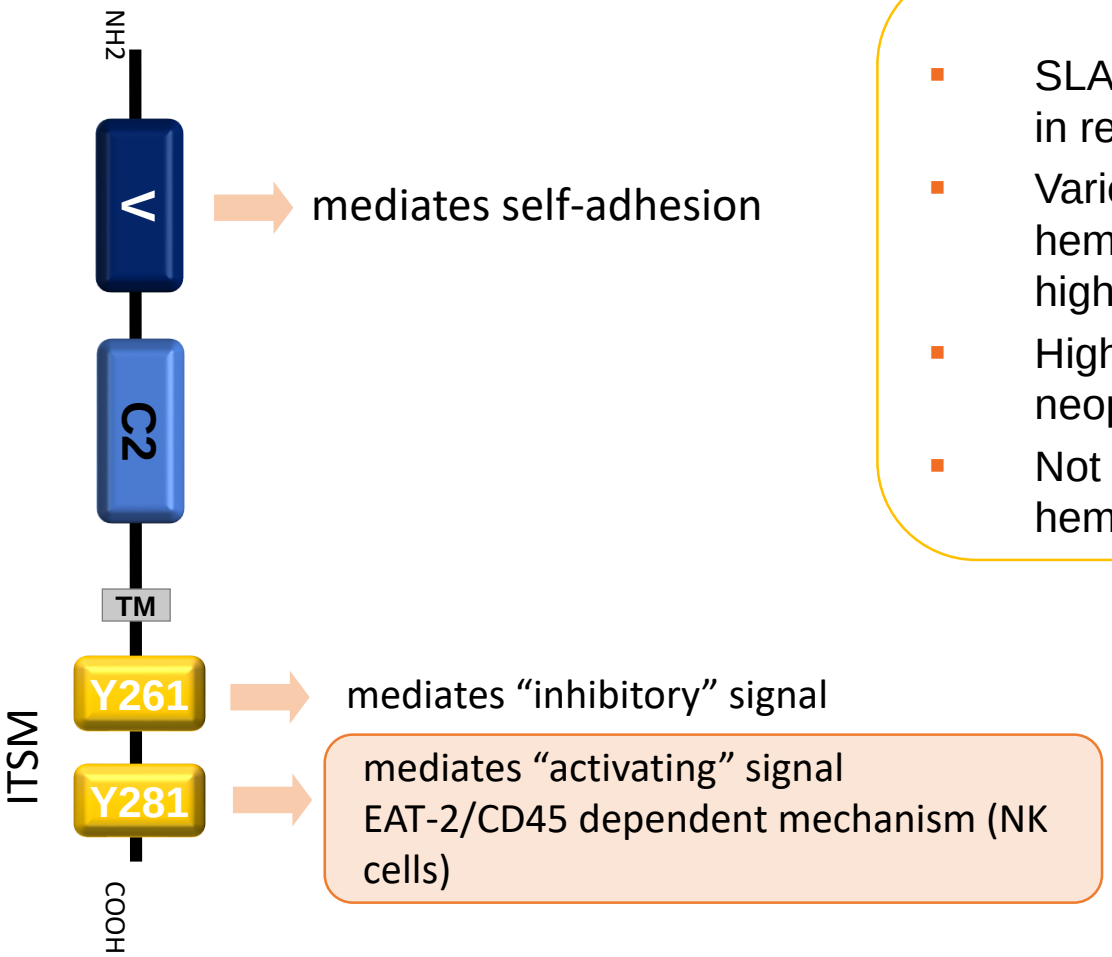
MM cells and its microenvironment: target molecules

- ✓ 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

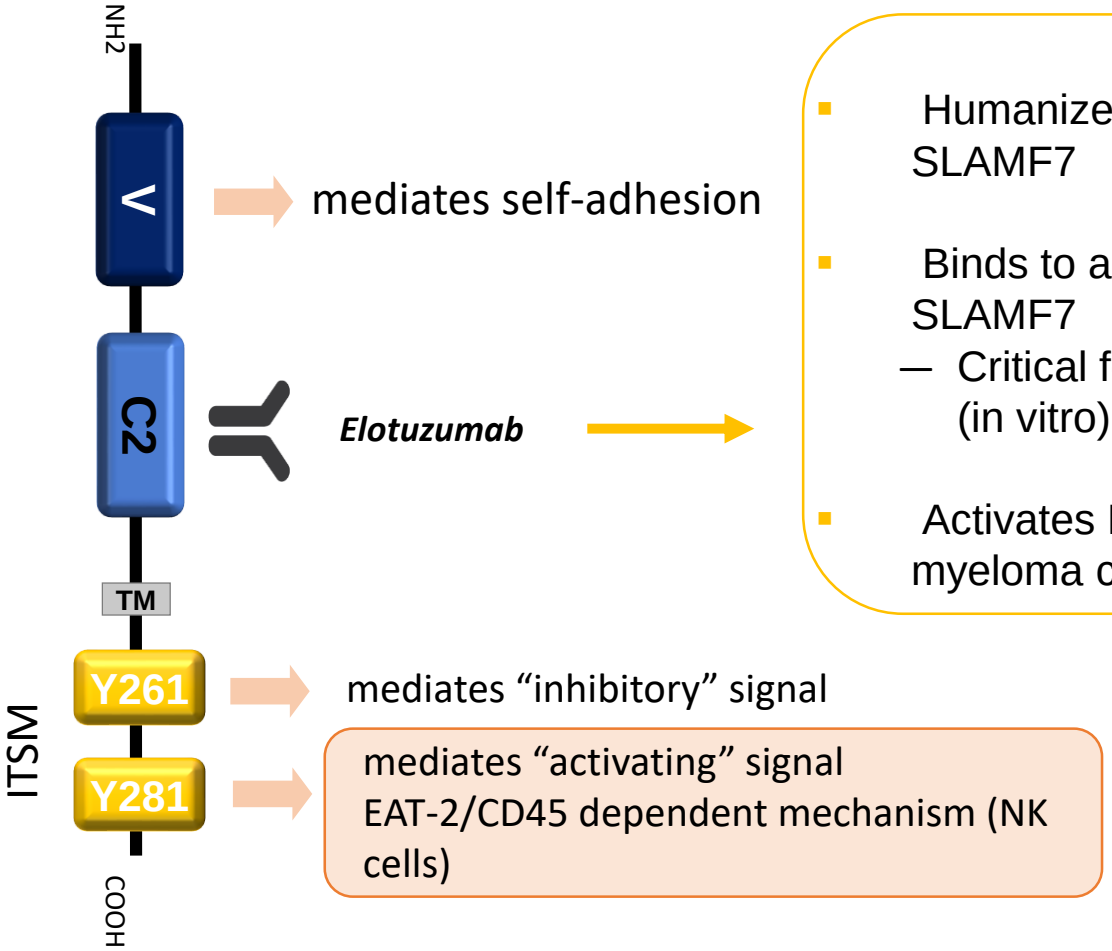


SLAMF7

- 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

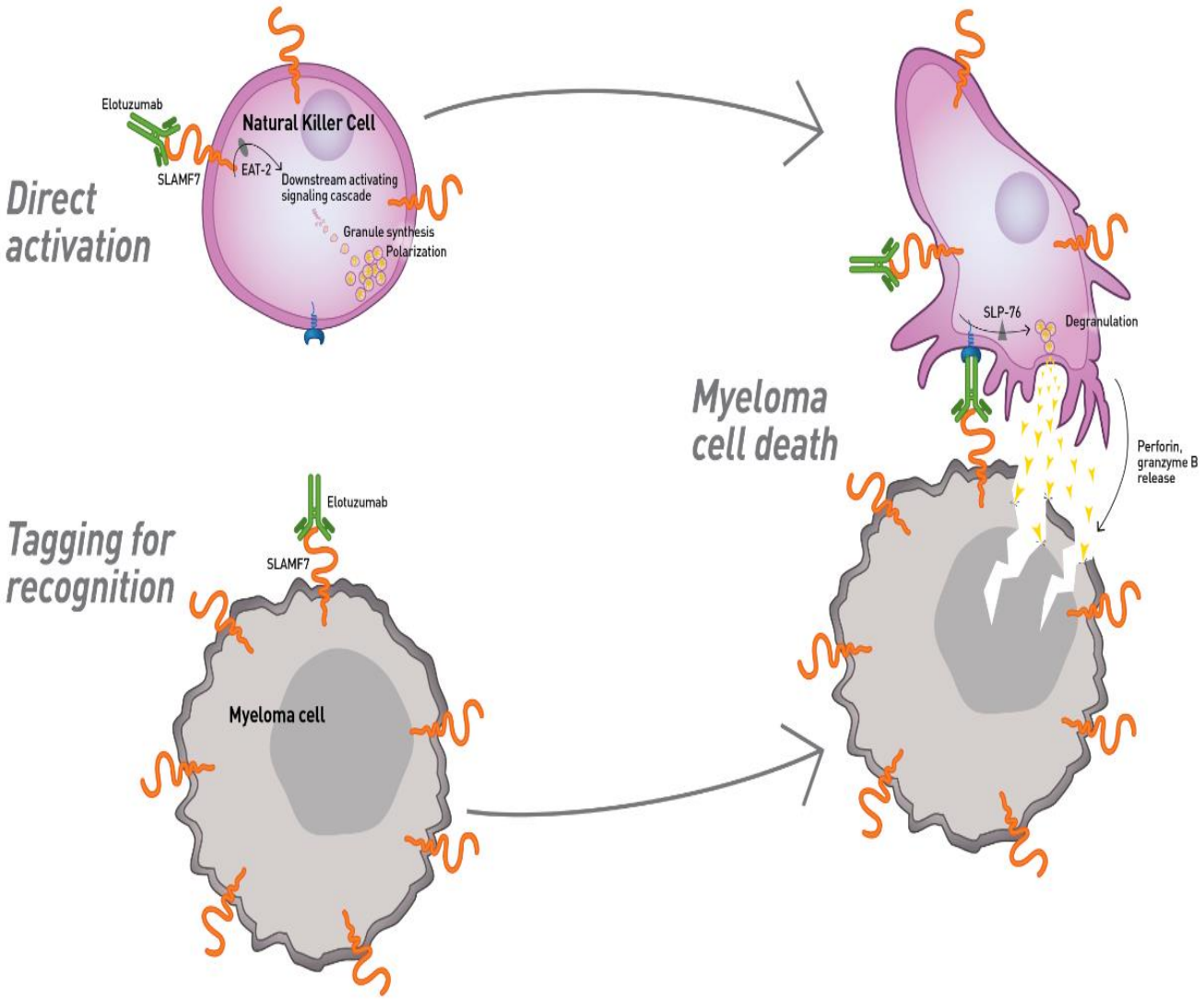


Elotuzumab

- Humanized, IgG1 mab specific for human SLAMF7
- Binds to a membrane-proximal motif of SLAMF7
  - Critical for mediating killing of target cells (in vitro)
- Activates NK cells (EAT-2 +), but not myeloma cells (EAT-2 -)

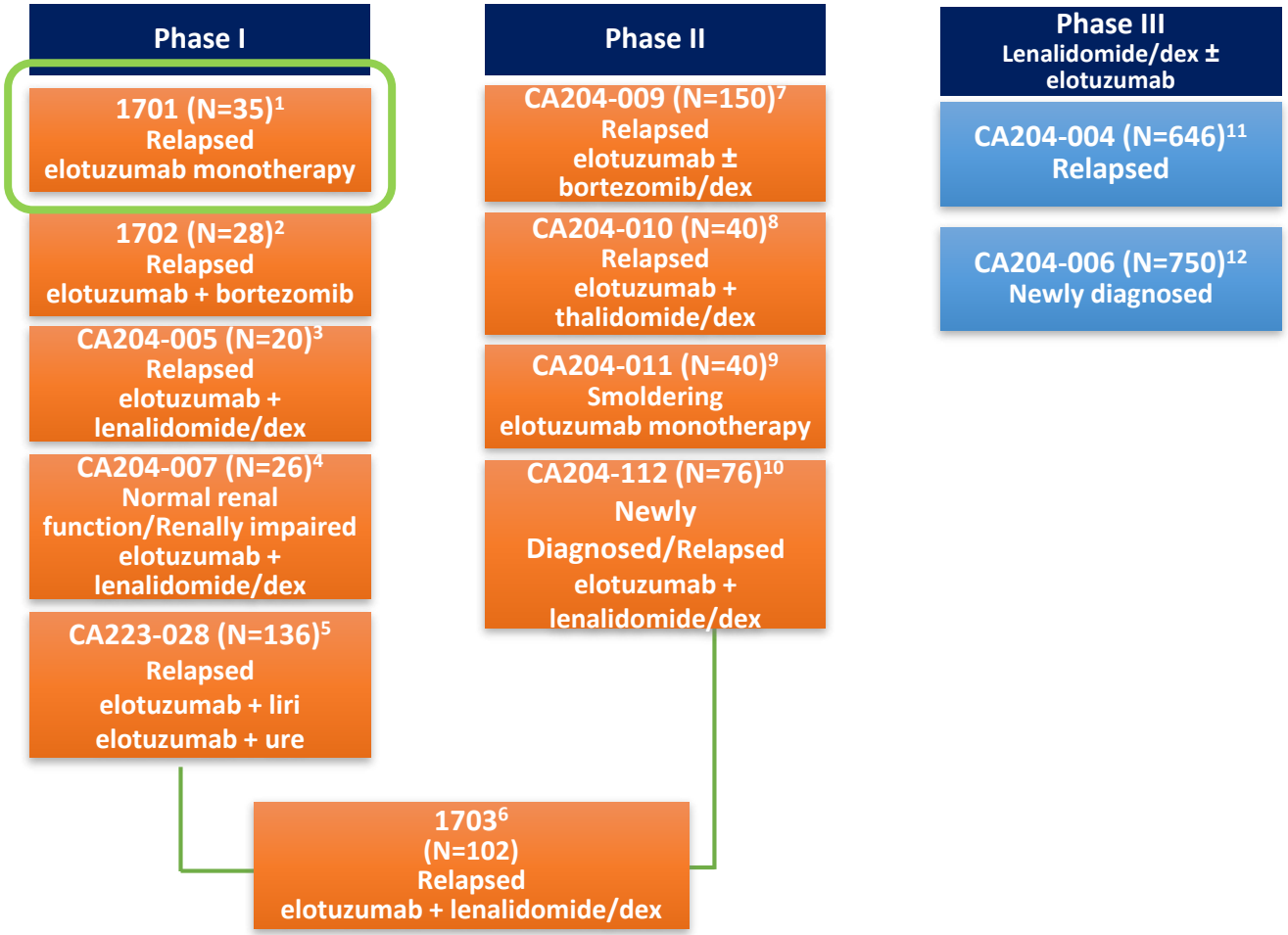
Veillette et al, Critical Reviews in Onc and Heme, 2013
Cruz-Munoz et al, Nature Immunology, 2009.

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 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%	-	NO EFFICACY
Jakuboviak JCO 2012 (1702)	1	BOR	28	2 (BOR refractory 2/3)	48	9.46	ORR in BOR combination with mild increase in PFS (9.7 vs 6.9 mos)
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	Good ORR and PFS in LEN combination Reccommended dose: 10 mg
Richardson Lancet Hematol2015 (1703)	2	LEN-DEX (ELO 10 mg vs 20 mg)	73	1-3	92 vs 76	33 vs 18.6	

Summary

✓ Phase 1 study demonstrated no efficacy of Elotuzumab in monotherapy

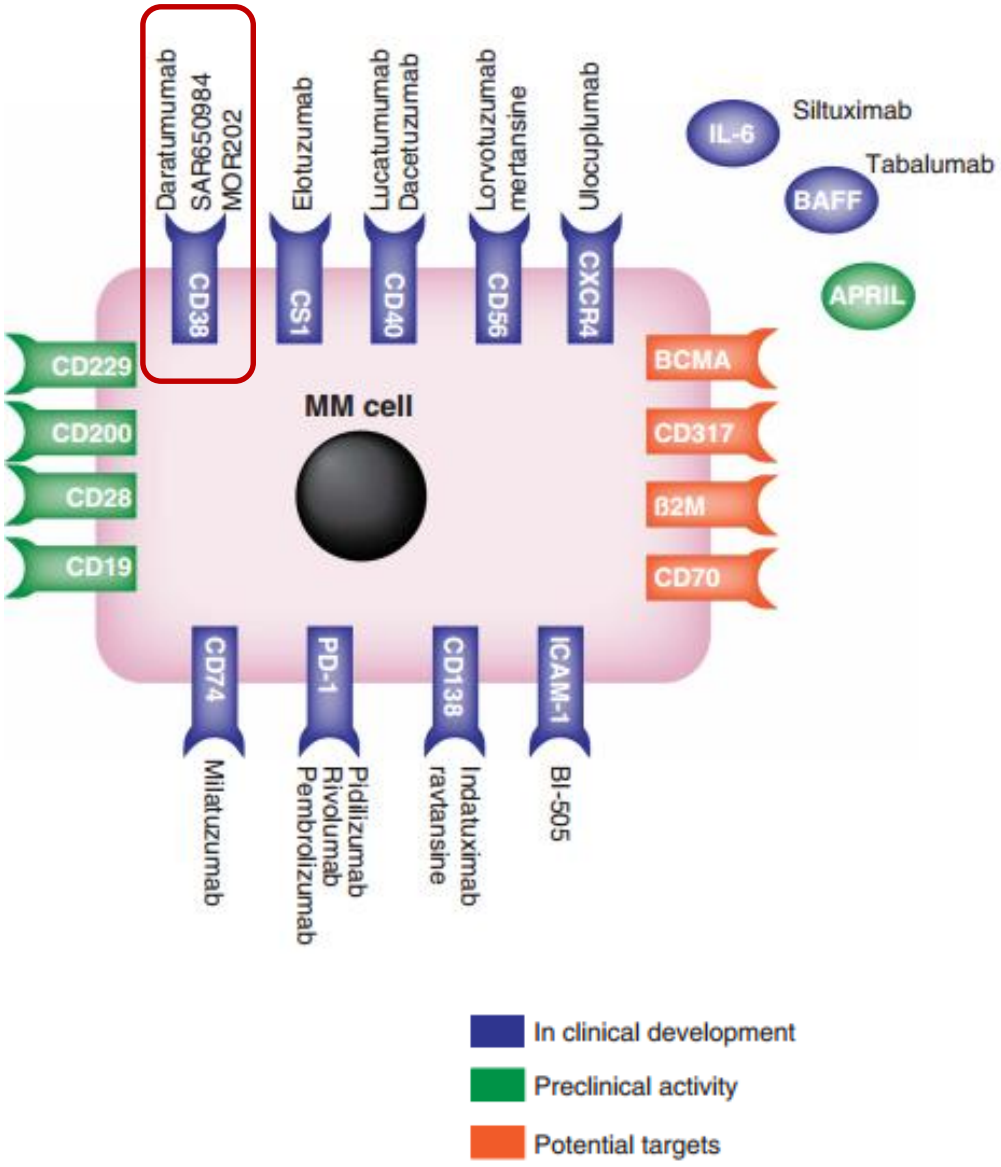
✓ Phase 1 and 2 studies demonstrated significant anti-tumor activity of Elotuzumab in combination with Lenalidomide and bortezomib in R/R MM setting

✓ 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

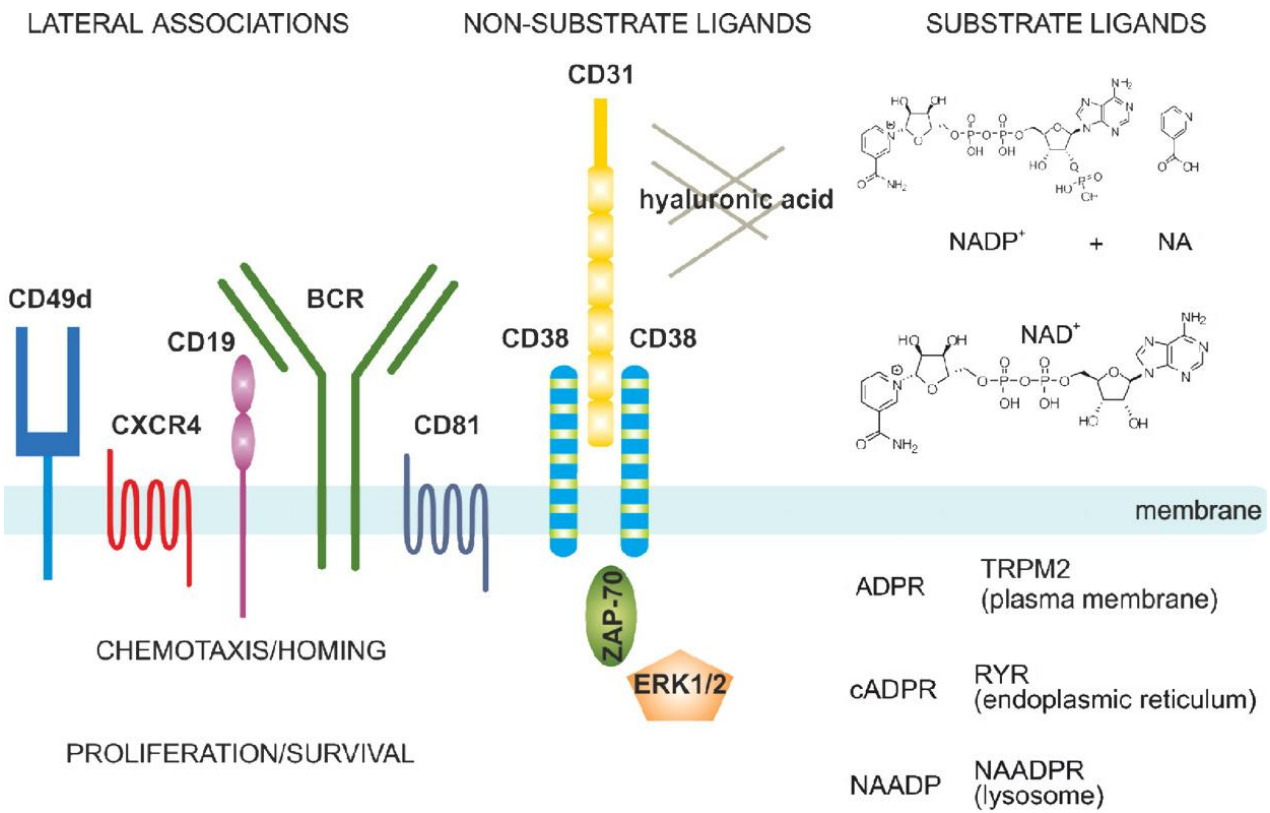
- ✓ Ab anti SLAMF7 or CS1
- ✓ Ab anti CD38
- ✓ Ab anti PD-1/PDL-1
- ✓ Denosumab
- ✓ Other Ab targets



Lonial S, Leukemia 2016

CD38

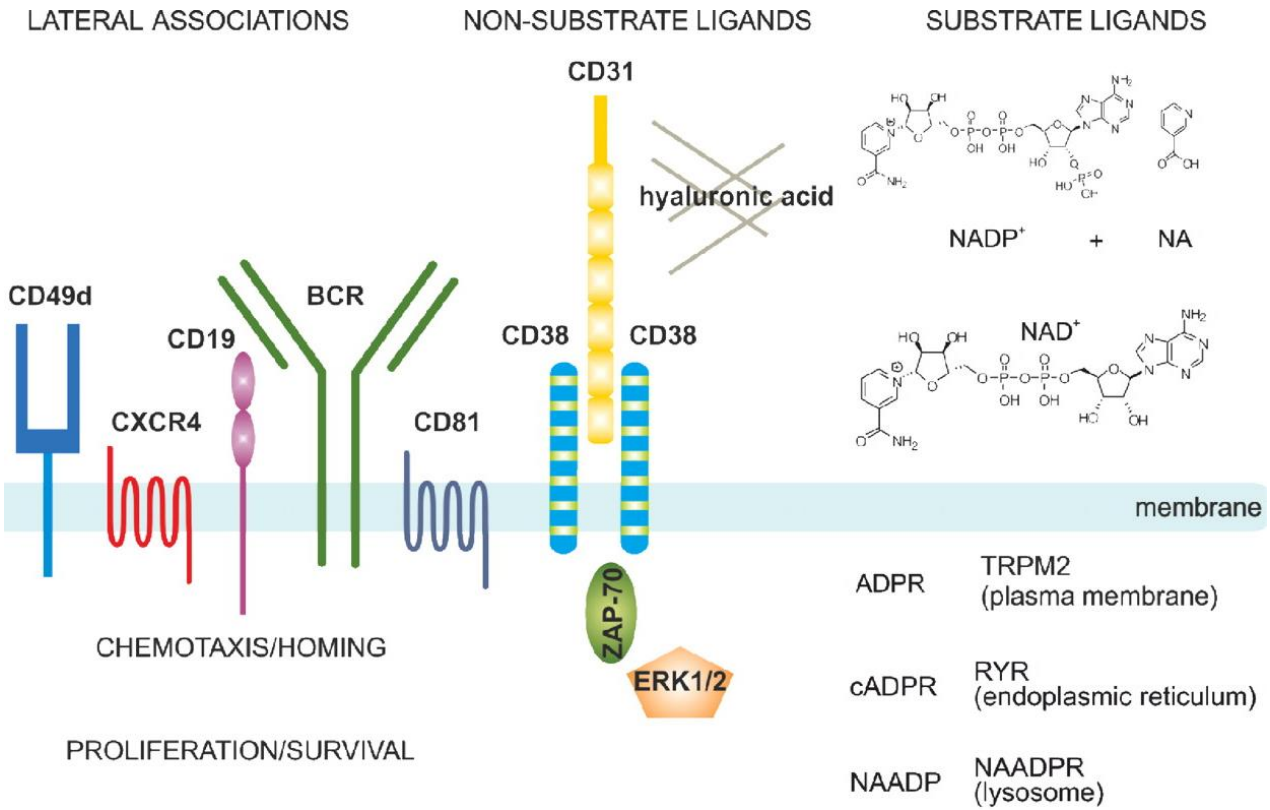
- Cell surface receptor close to BCR complex that regulates T cells activation/proliferation
- Ectoenzyme involved in calcium signaling
- low expression in hematopoietic cells (NK B and T cells) and non –hematopoietic cells
- High expression in MM cells



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

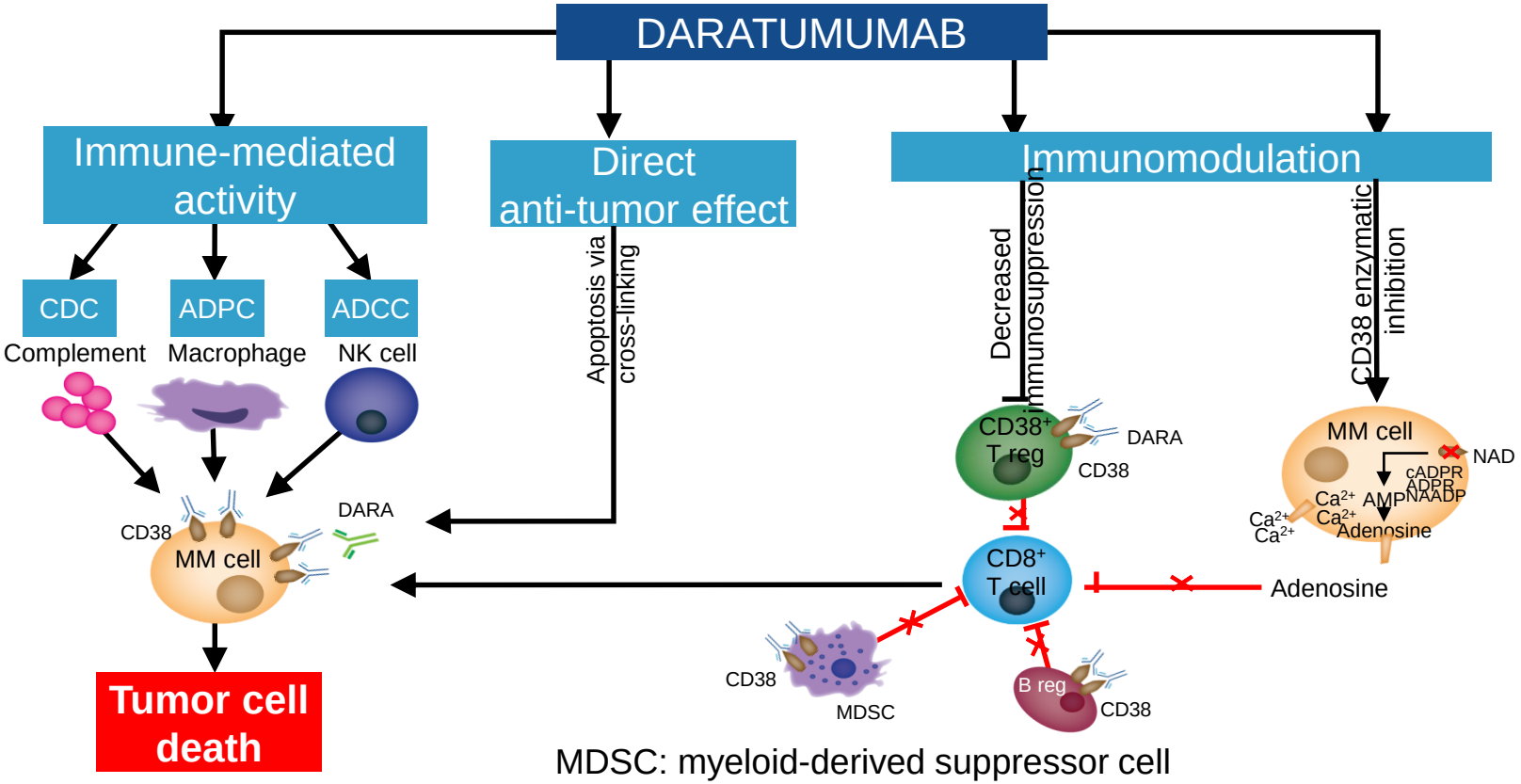
- ✓ Daratumumab
- ✓ SAR650984 (isatuximab)
- ✓ MOR202



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

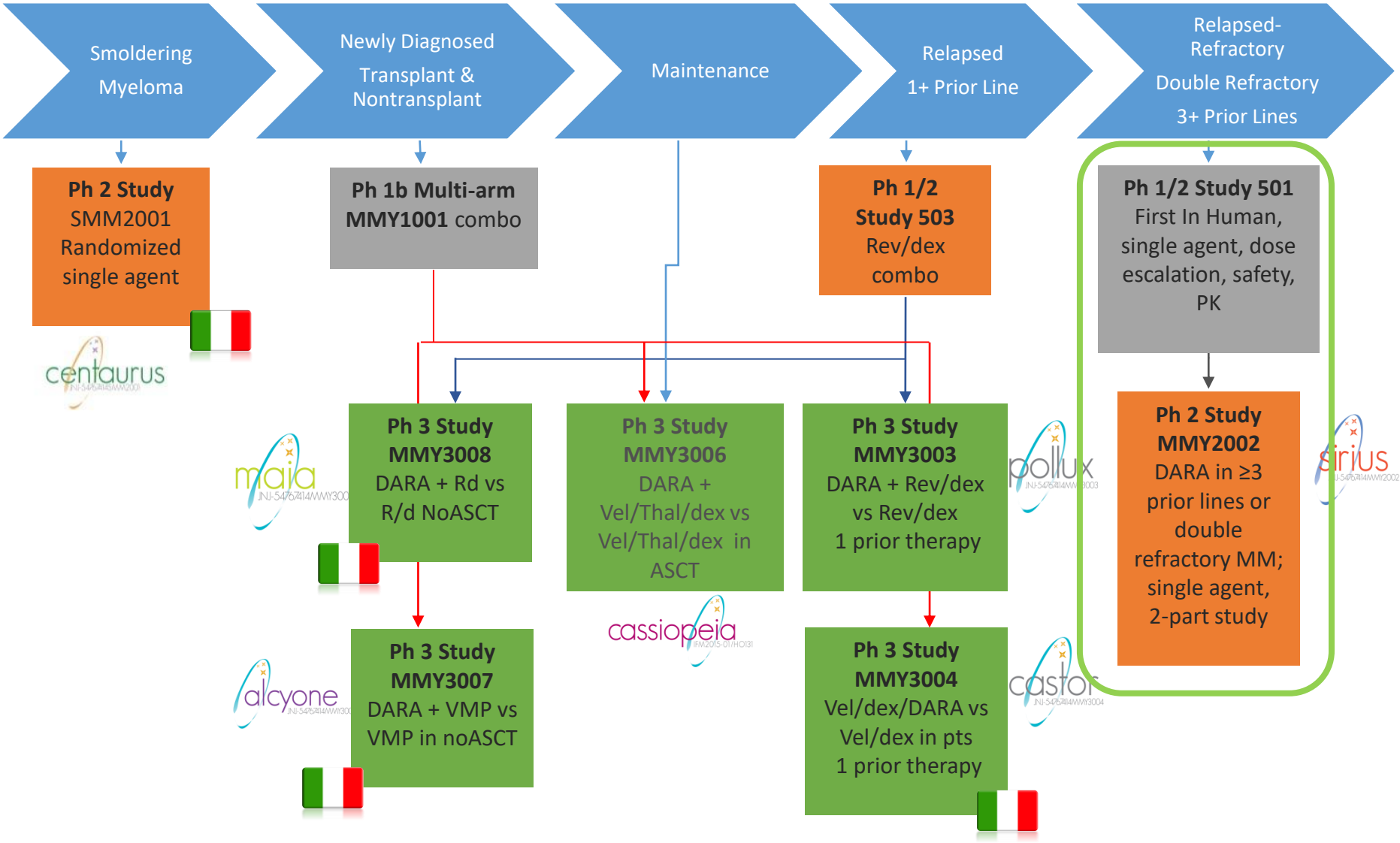
- Complement-dependent cytotoxicity (CDC)
- Antibody-dependent cell-mediated phagocytosis (ADCP)
- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Induction of apoptosis
- Modulation of cellular enzymatic activities associated with calcium mobilization and signaling



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

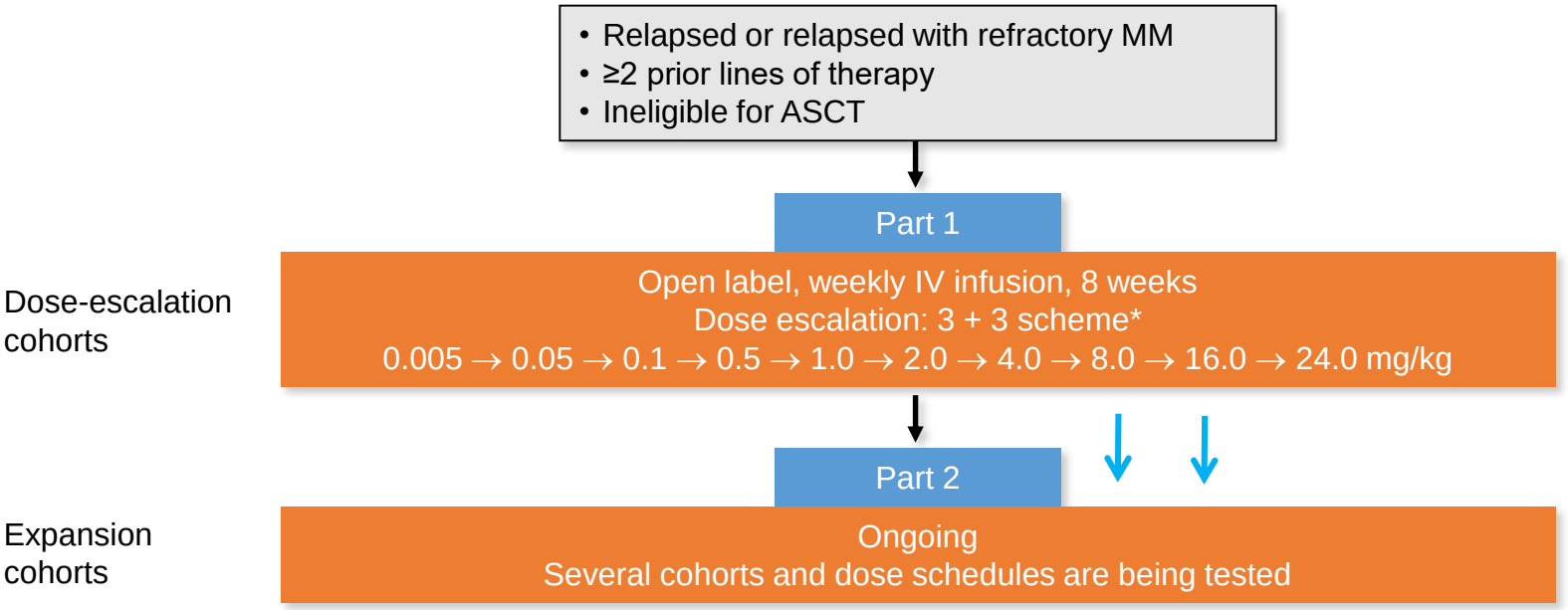
Pooled analysis Studies GEN501 and MMY2002 (Sirius)

Median follow-up: 14.8 months

Usmani et al Abs #29 Orlando, ASH 2015

Daratumumab single agent: GEN501

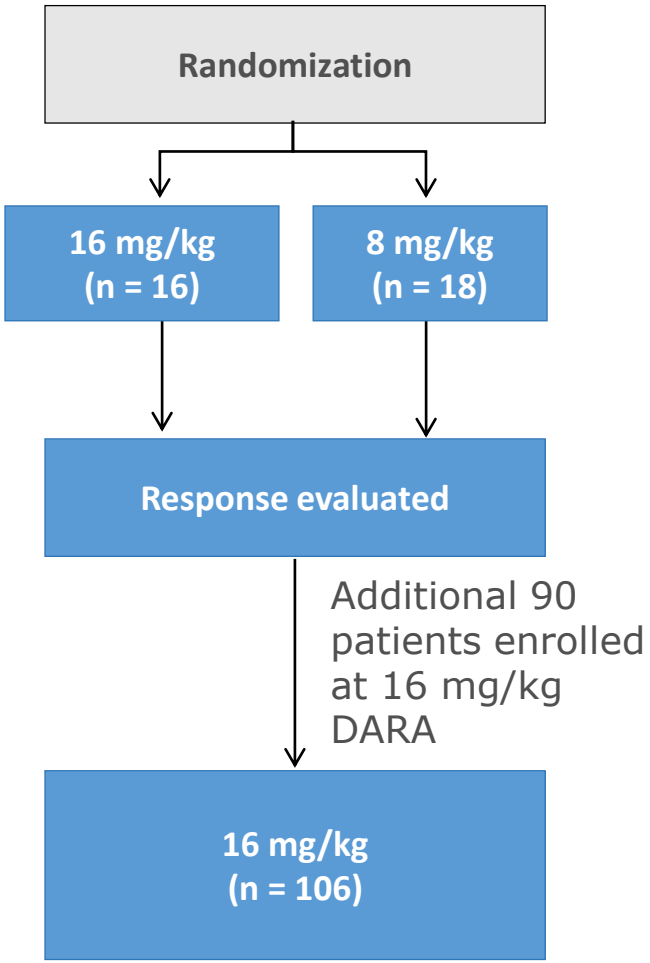
Phase I/II Study Design



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

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: baseline characteristics

	16 mg/kg		
	GEN501, Part 2 n = 42	SIRIUS n = 106	Combined N = 148
Median (range) age, y	64.0 (44-76)	63.5 (31-84)	64 (31-84)
≥65 years of age, n (%)	20 (48)	48 (45)	68 (46)
Female/male sex, %	36/64	51/49	53/47
ECOG score, n (%)			
0	12 (29)	29 (27)	41 (28)
1	28 (67)	69 (65)	97 (66)
2	2 (5)	8 (8)	10 (7)
Median (range) time since diagnosis, y	5.8 (0.8-23.7)	4.8 (1.1-23.8)	5.1 (0.8-23.8)
Median (range) number of prior lines of therapy	4 (2-12)	5 (2-14)	5 (2-14)
>3 prior lines of therapy, n (%)	26 (62)	87 (82)	113 (76)
Prior ASCT, n (%)	31 (74)	85 (80)	116 (78)
Prior PI, n (%)	42 (100)	106 (100)	148 (100)
Bortezomib	42 (100)	105 (99)	147 (99)
Carfilzomib	8 (19)	53 (50)	61 (41)
Prior IMiD, n (%)	40 (95)	106 (100)	146 (99)
Lenalidomide	40 (95)	105 (99)	145 (98)
Pomalidomide	15 (36)	67 (63)	82 (55)
Thalidomide	19 (45)	47 (44)	66 (45)

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

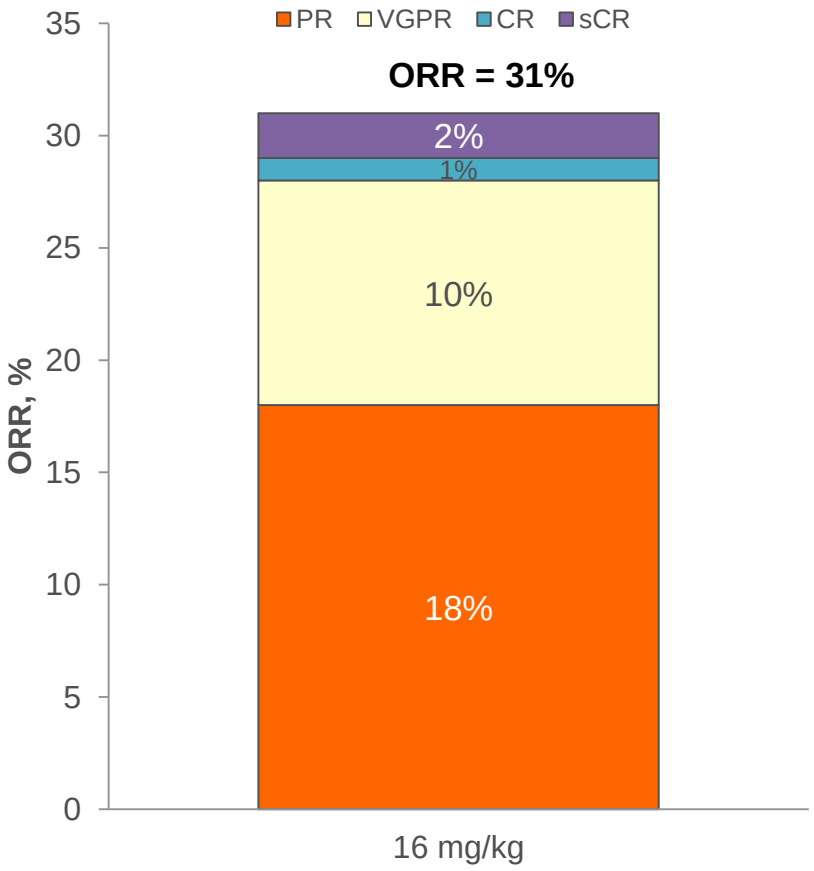
Daratumumab: baseline refractory status

Refractory to, n (%)	16 mg/kg GEN501, Part 2 n = 42	16 mg/kg SIRIUS n = 106	Combined N = 148
Last line of therapy	32 (76)	103 (97)	135 (91)
Both PI and IMiD	27 (64)	101 (95)	128 (86)
PI only	3 (7)	3 (3)	6 (4)
IMiD only	4 (10)	1 (1)	5 (3)
PI + IMiD + alkylating agent	21 (50)	79 (75)	100 (68)
Bortezomib	30 (71)	95 (90)	125 (84)
Carfilzomib	**7 (17)**	**51 (48)**	**58 (39)**
Lenalidomide	31 (74)	93 (88)	124 (84)
Pomalidomide	**15 (36)**	**67 (63)**	**82 (55)**
Thalidomide	12 (29)	29 (27)	41 (28)
Alkylating agent only	25 (60)	82 (77)	107 (72)

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

Daratumumab efficacy: ORR in combined analysis

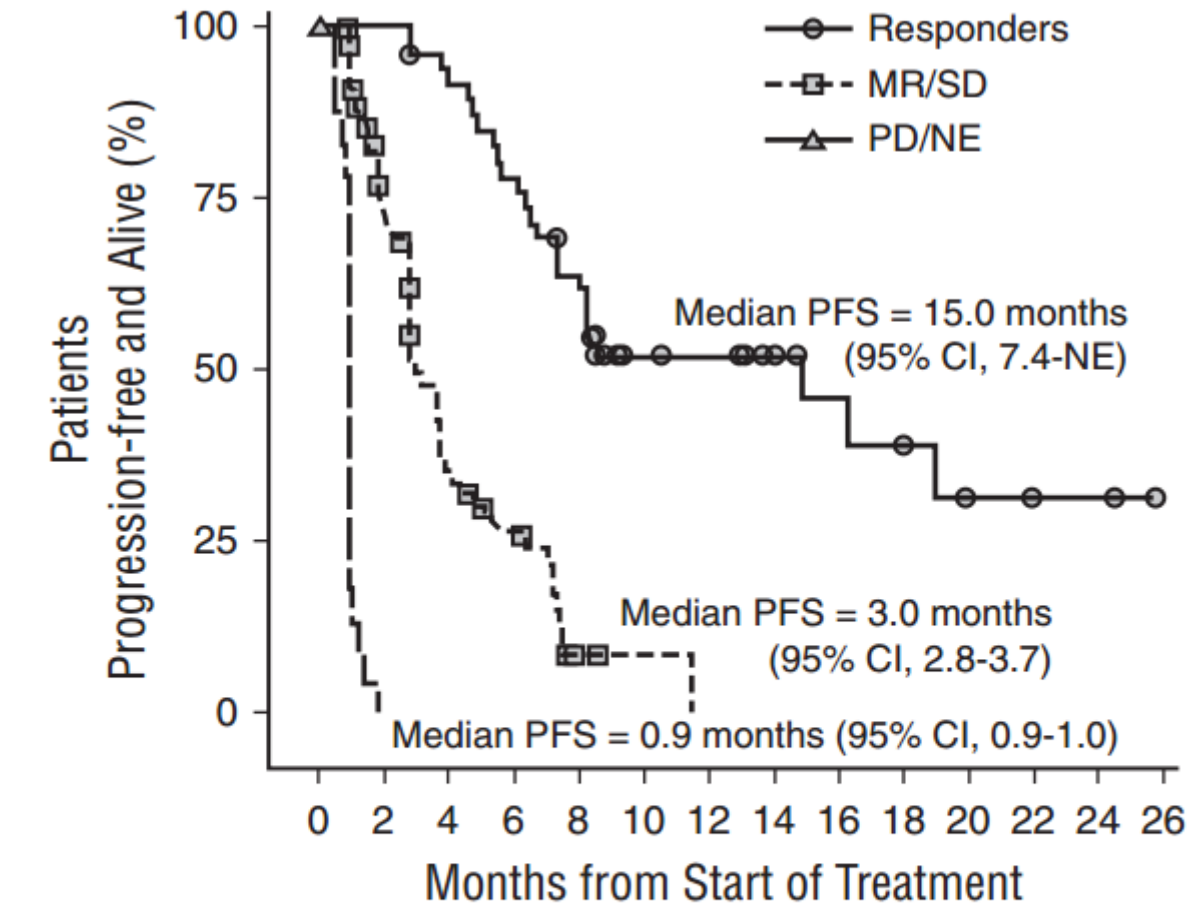
	16 mg/kg (N = 148)	
	n (%)	95% CI
ORR (sCR+CR+VGPR+PR)	**46 (31)**	**23.7-39.2**
Best response		
sCR	3 (2)	0.4-5.8
CR	2 (1)	0.2-4.8
VGPR	14 (10)	5.3-15.4
PR	27 (18)	12.4-25.4
MR	9 (6)	2.8-11.2
SD	68 (46)	37.7-54.3
PD	18 (12)	7.4-18.5
NE	7 (5)	1.9-9.5
VGPR or better (sCR+CR+VGPR)	19 (13)	7.9-19.3
CR or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

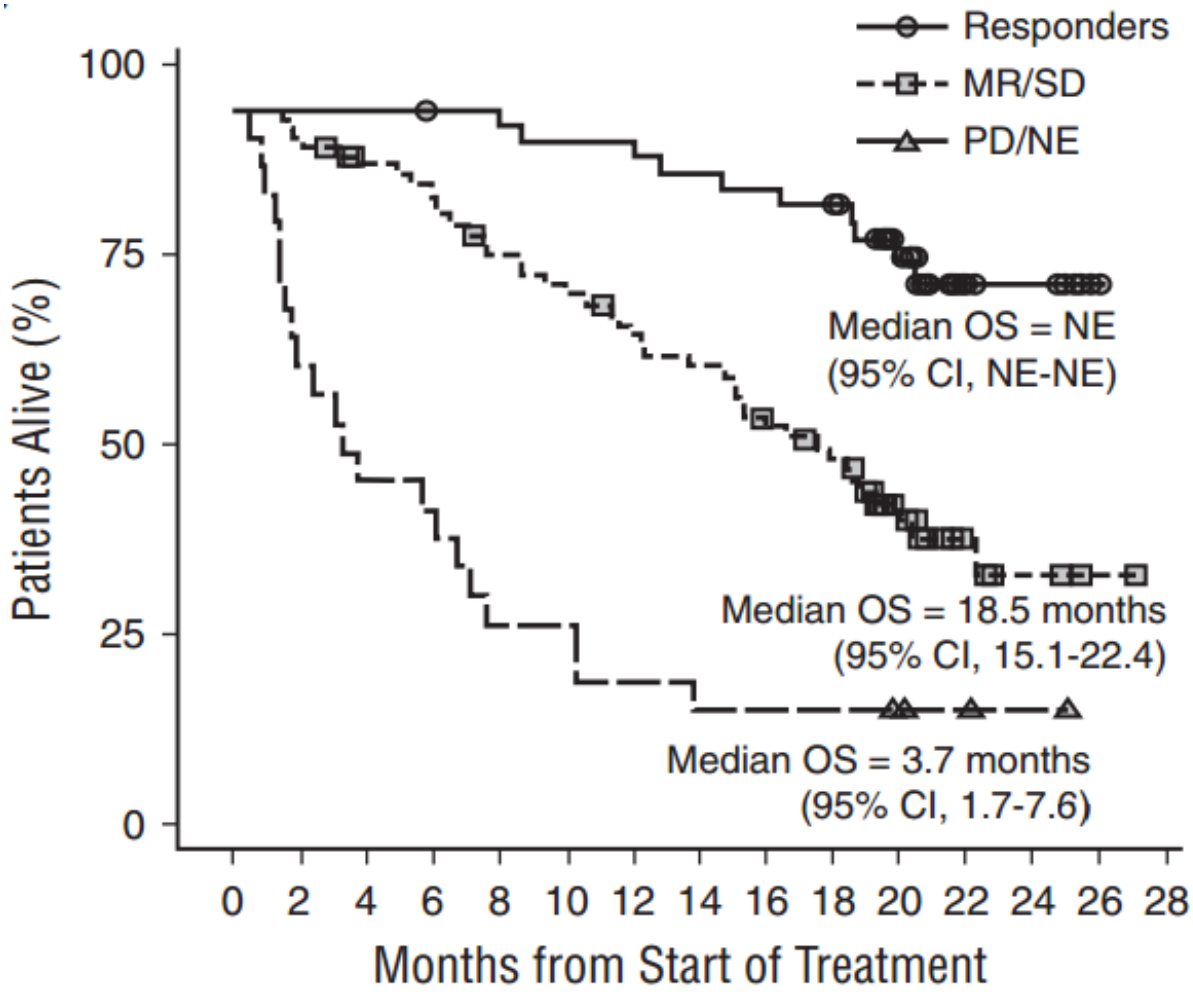


Patients at risk

Responders	46	46	41	35	27	14	13	10	7	6	4	3	2	0
MR/SD	77	45	20	13	2	1	0	0	0	0	0	0	0	0
PD/NE	25	0	0	0	0	0	0	0	0	0	0	0	0	0

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

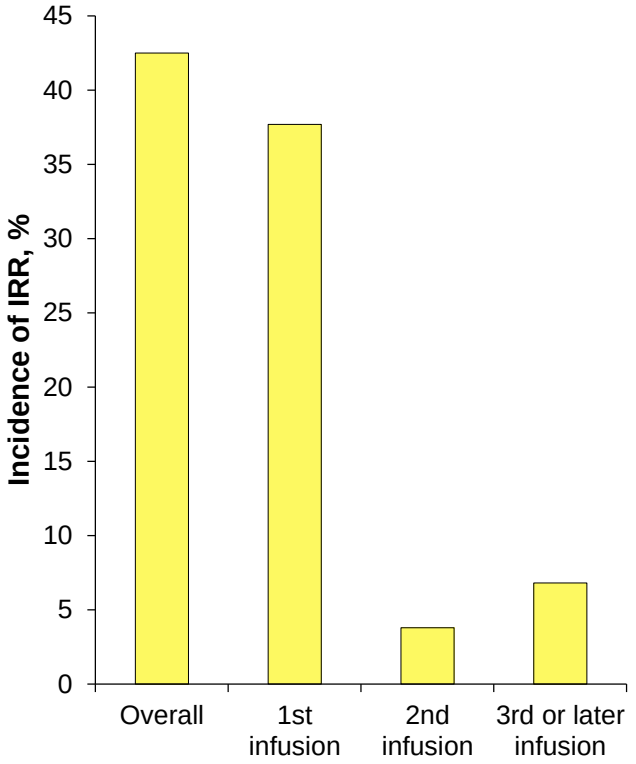
TEAE, n (%)	Any grade N = 148	Grade ≥3 N = 148
Fatigue	61 (41)	3 (2)
Nausea	42 (28)	0
Anemia	41 (28)	26 (18)
Back pain	36 (24)	3 (2)
Cough	33 (22)	0
Neutropenia	30 (20)	15 (10)
Thrombocytopenia	30 (20)	21 (14)
Upper respiratory tract infection	30 (20)	1 (<1)

- 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

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 (phase 3 trials ongoing)

Daratumumab: regulatory update

UNIVERSITÀ DEL PIEMONTE ORIENTALE

- ✓ **16 NOV 2015: FDA approval**

*"Darzalex is indicated for the treatment of patients with multiple myeloma who have received **at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory** to a PI and an immunomodulatory agent."*

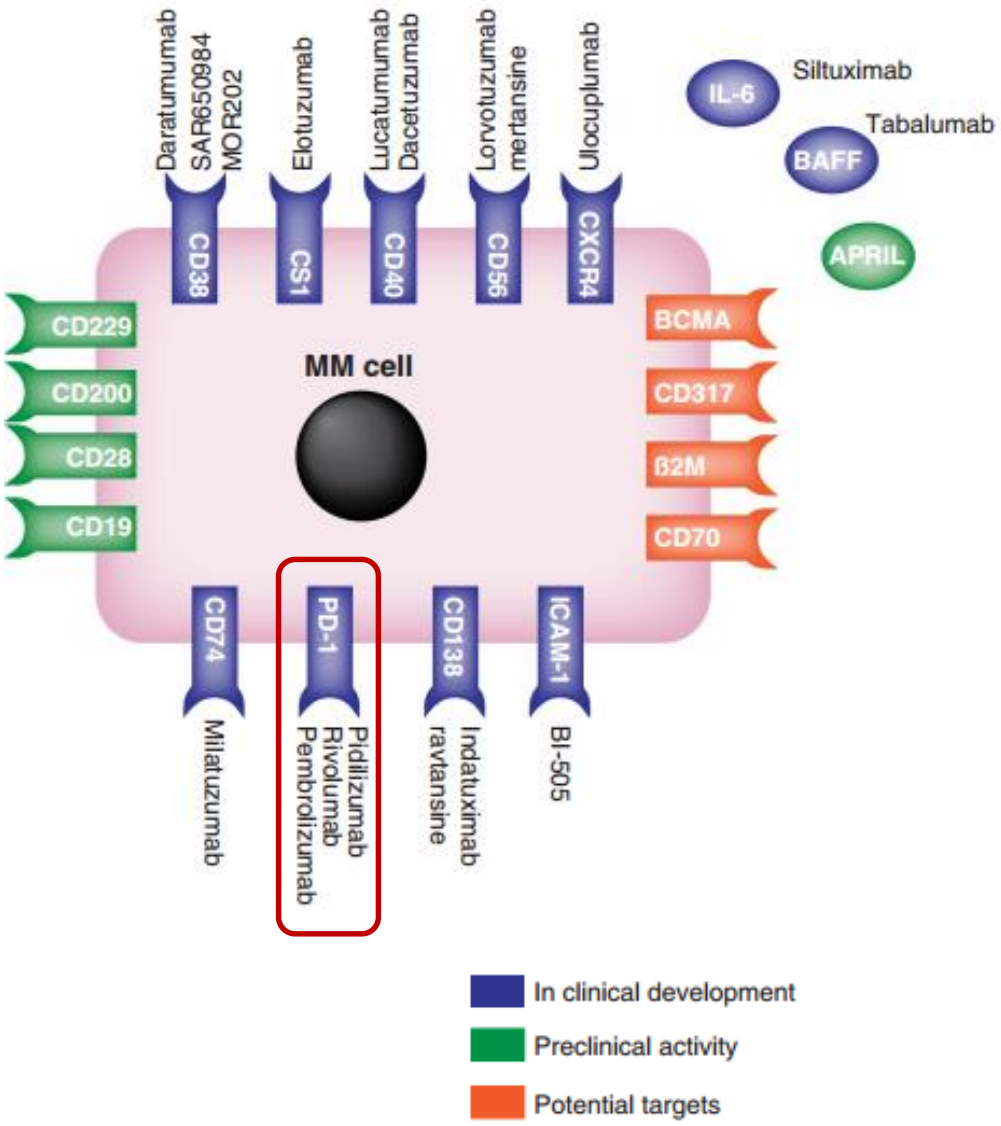
- ✓ **01 APR 2016: CHMP positive opinion**

*"Darzalex as **monotherapy** is indicated for the treatment of adult patients with **relapsed and refractory** multiple myeloma, whose **prior therapy included a proteasome inhibitor and an immunomodulatory** agent and who have demonstrated **disease progression on the last therapy**."*

- ✓ **23 APR 2016: EMA approval**

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

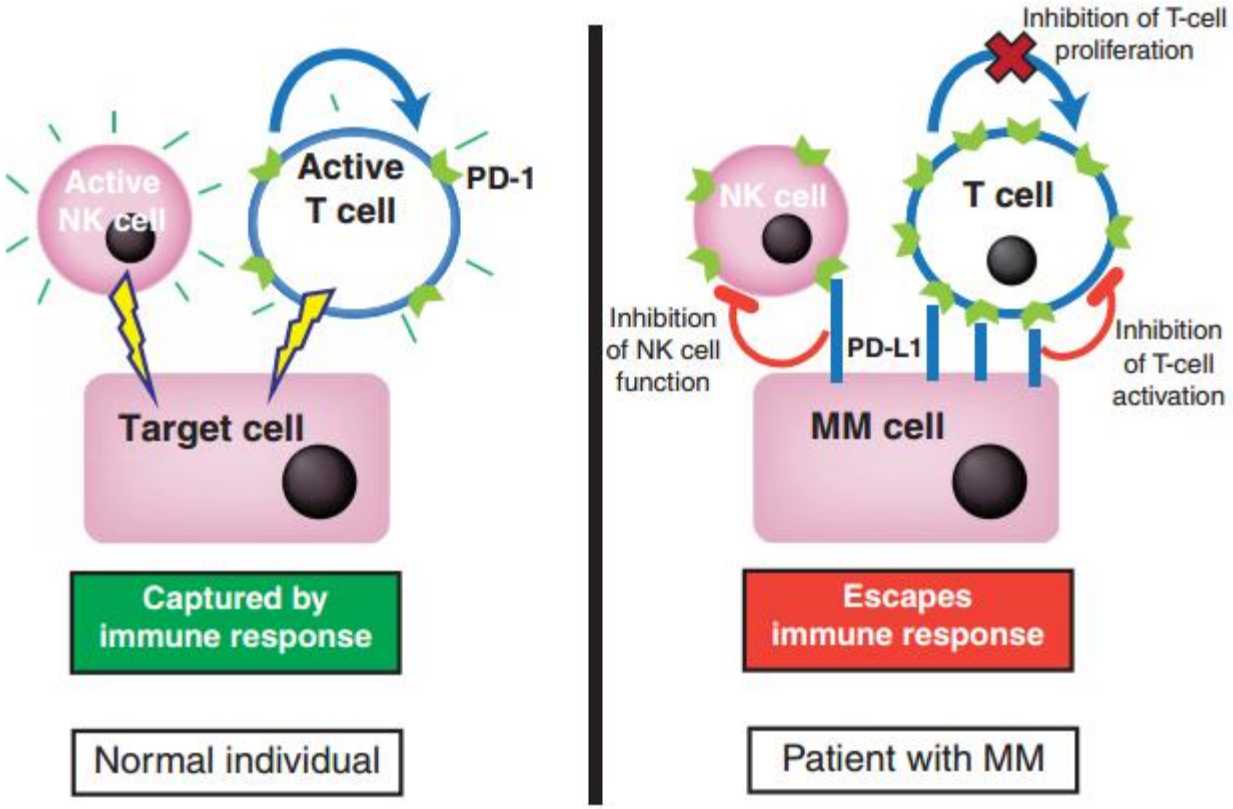


Lonial S, Leukemia 2016

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

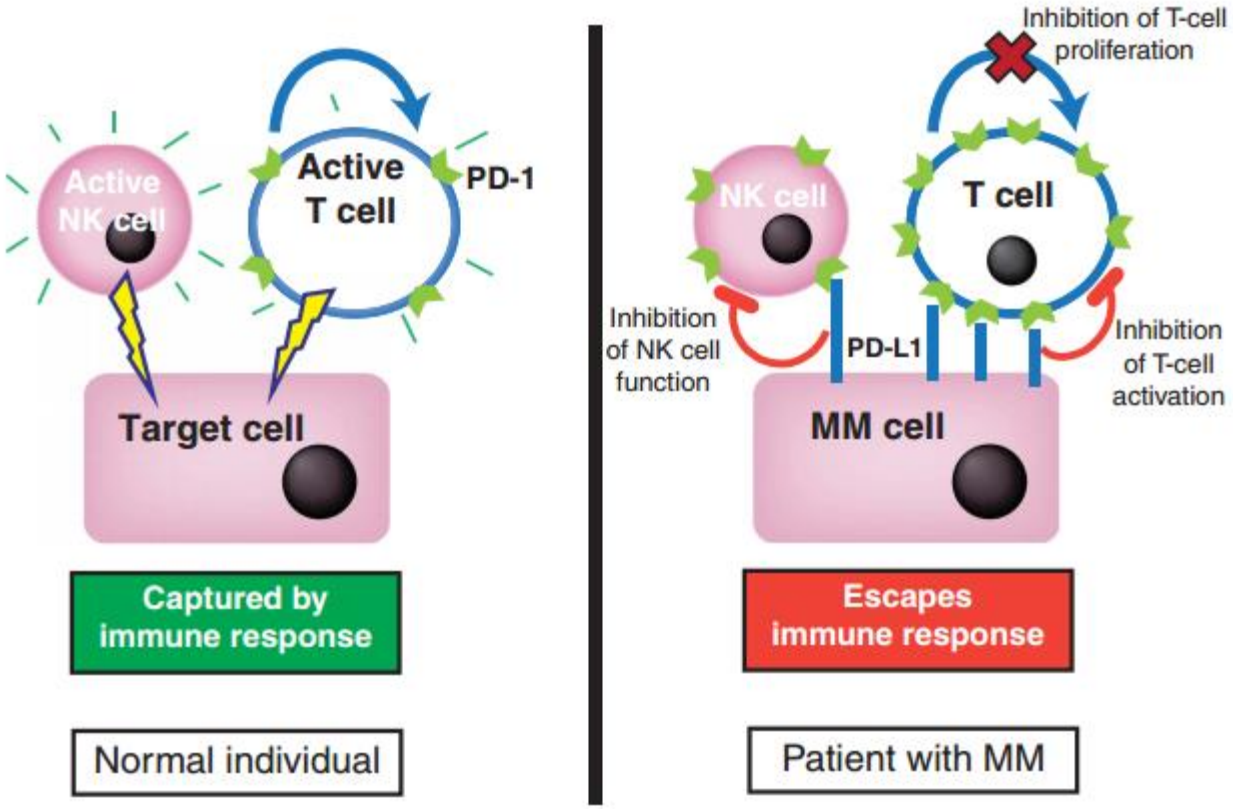


Topalian SL, Curr Opin Immunol 2012; Chen DS, Clin Cancer Res 2012

PD-1, PD-L1 and mAbs

- ✓ 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



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

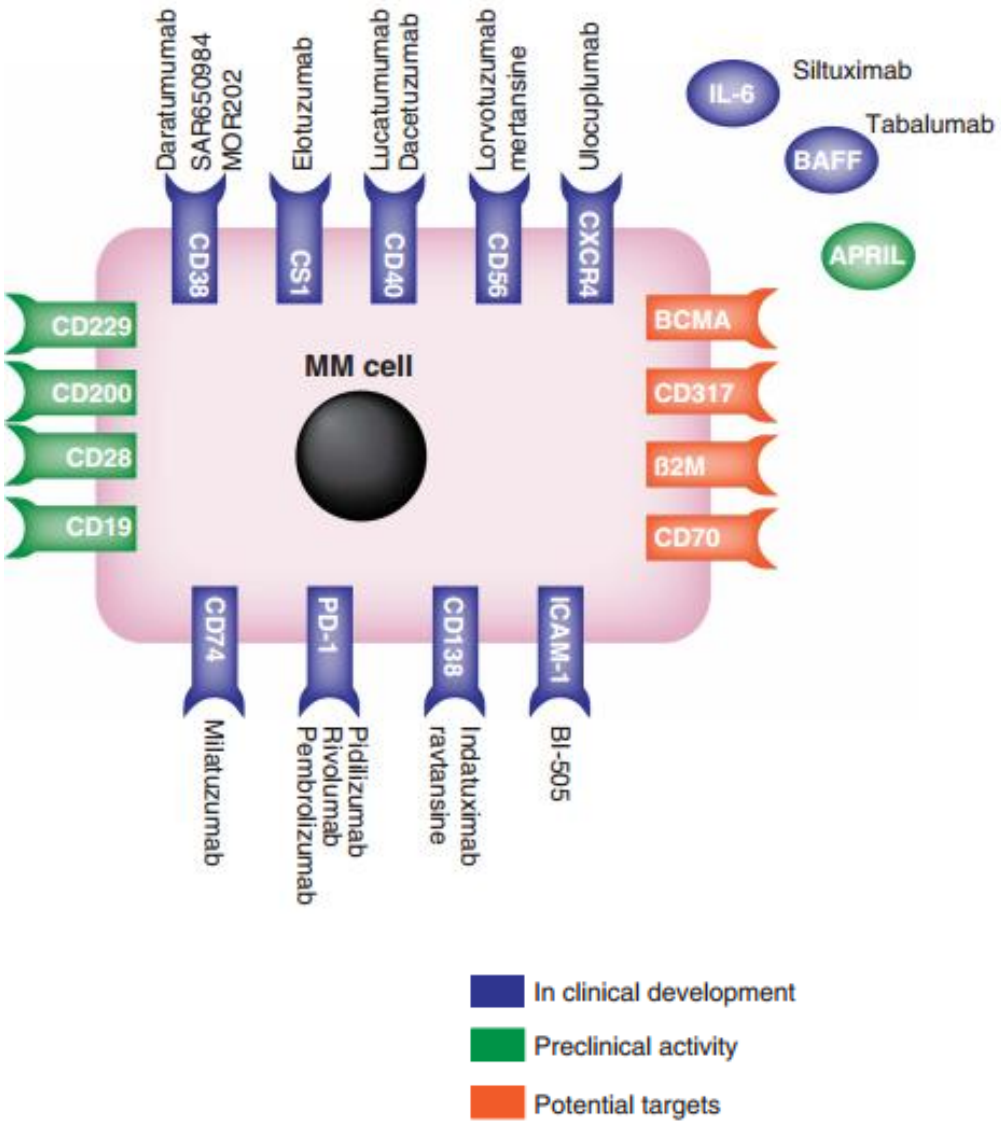
Author	Phase study	Combination	Number of pts	Median n. of prior Th	Response rate % (≥ PR)	PFS (months)
Lesokhin, 2016 J Clin Oncol (nivolumab)	1b	NIVOLUMAB alone	27	78% ≥ 3	63% SD, 4% CR	-
SanMiguel, 2015 Blood (pembrolizumab)	1	PEMBROLIZUMAB LEN-DEX	50	3	76% (76% LEN refractory)	Short follow-up
Badros,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

MM cells and its microenvironment: target molecules

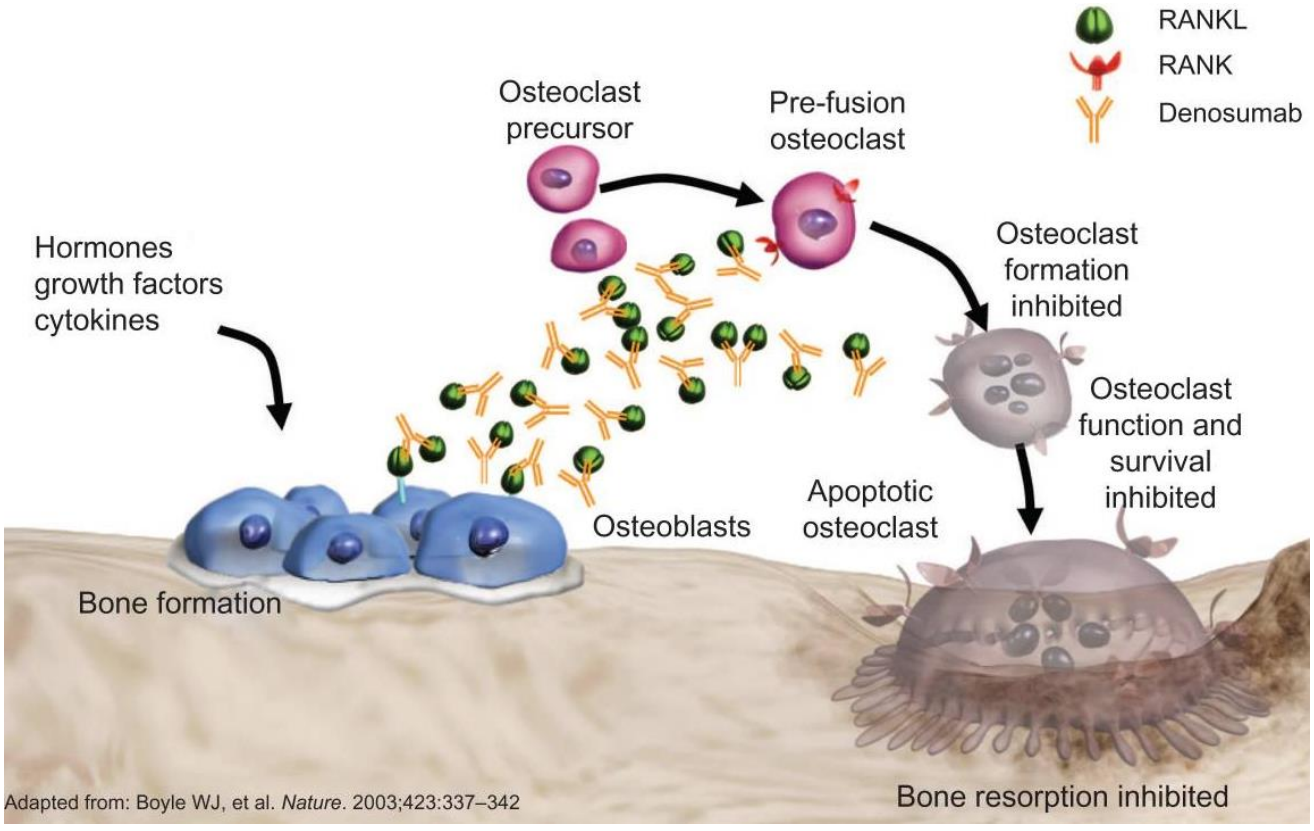
- ✓ Ab anti SLAMF7 or CS1
- ✓ Ab anti CD38
- ✓ Ab anti PD-1/PDL-1
- ✓ Denosumab
- ✓ Other Ab targets



Lonial S, Leukemia 2016

Denosumab: a future option?

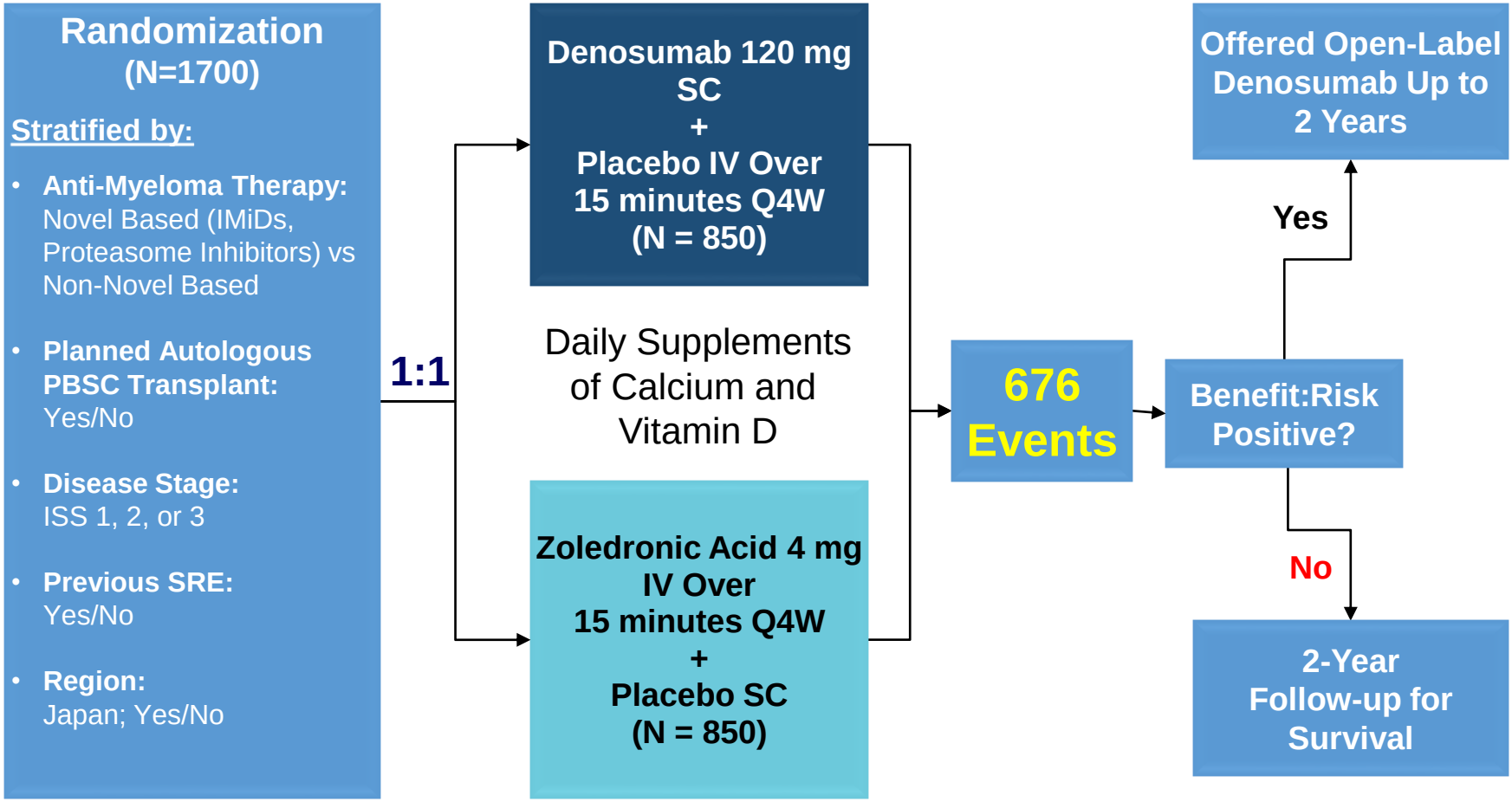
- ✓ RANK ligand (RANKL) is a key driver of osteoclast-mediated osteolysis, increasing the risk of skeletal-related events and impacting morbidity, mortality and quality of life in MM pts
- ✓ Denosumab, a human monoclonal antibody that binds with high specificity and affinity to RANKL, may directly inhibit 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

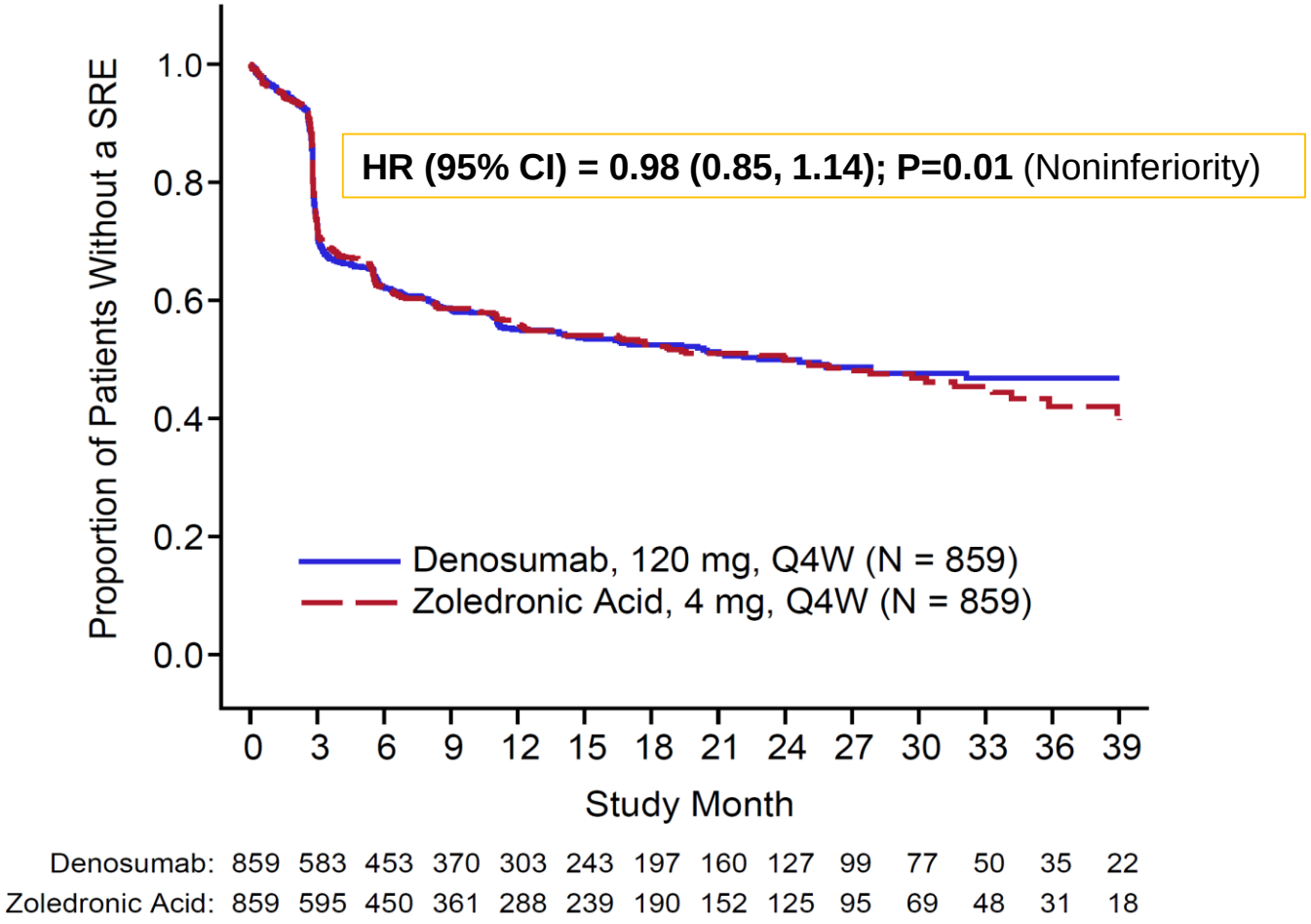
Study design

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

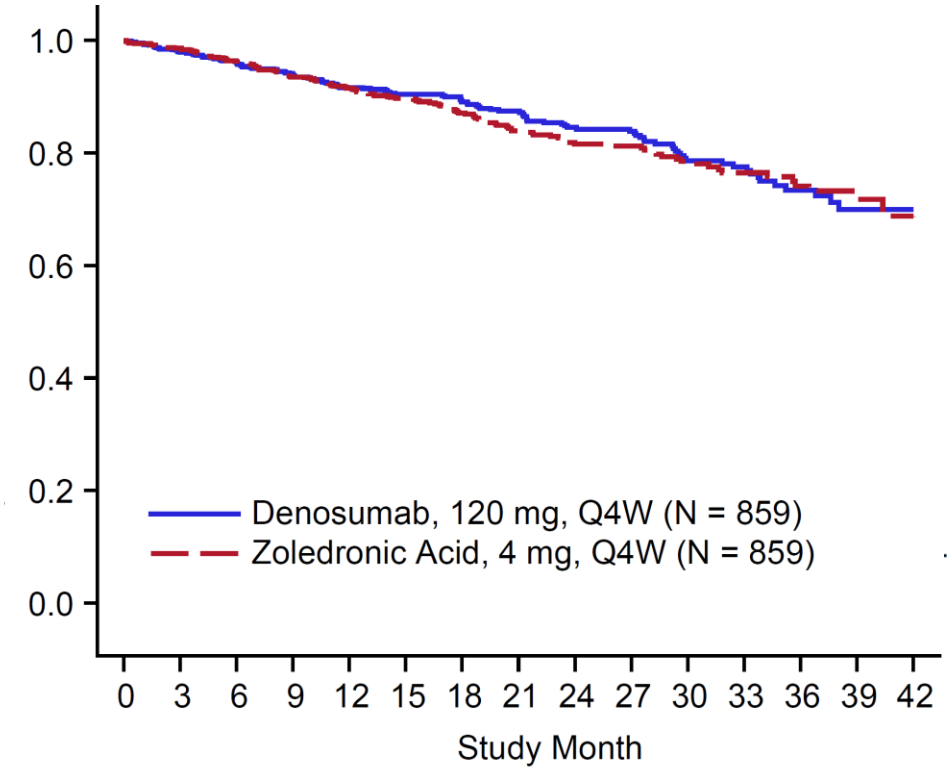
Results: non inferiority for time to first Skeletal related event



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

Results: overall survival and progression free survival

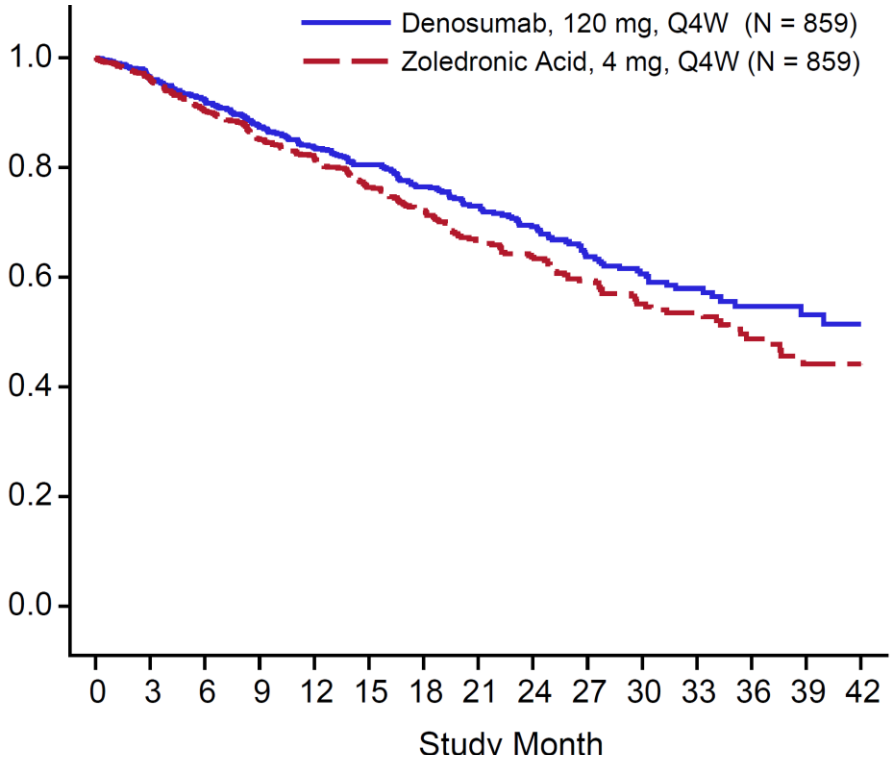
Overall survival



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

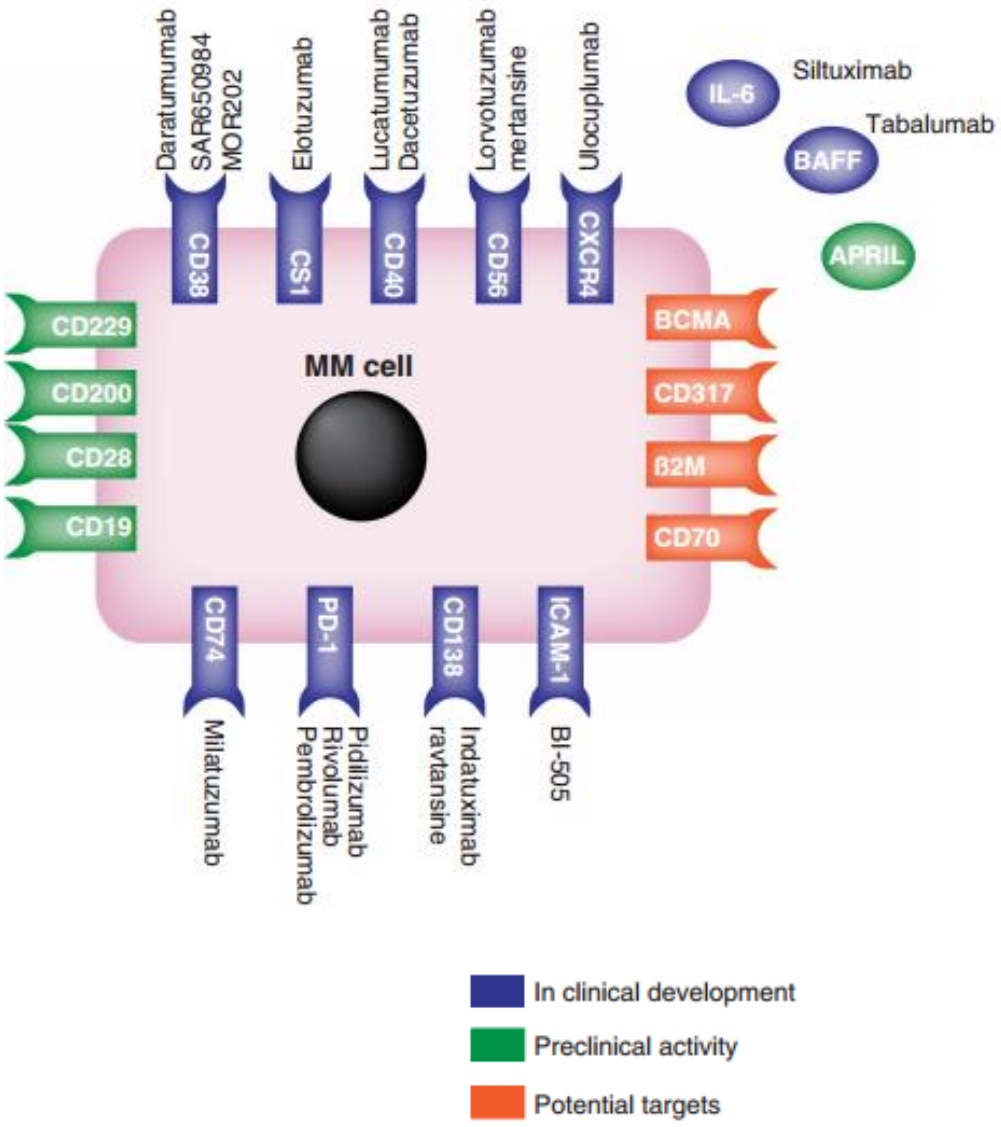
	Denosumab N = 850, n (%)	Zoledronic Acid N = 852, n (%)
Hypocalcemia	144 (16.9)	106 (12.4)
Serious AEs of Hypocalcemia	8 (0.9)	2 (0.2)
Adjudicated Positive Osteonecrosis of the Jaw	35 (4.1)	24 (2.8)
Adjudicated Positive Atypical Femur Fracture	0	0
AEs Potentially Associated With Hypersensitivity	219 (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



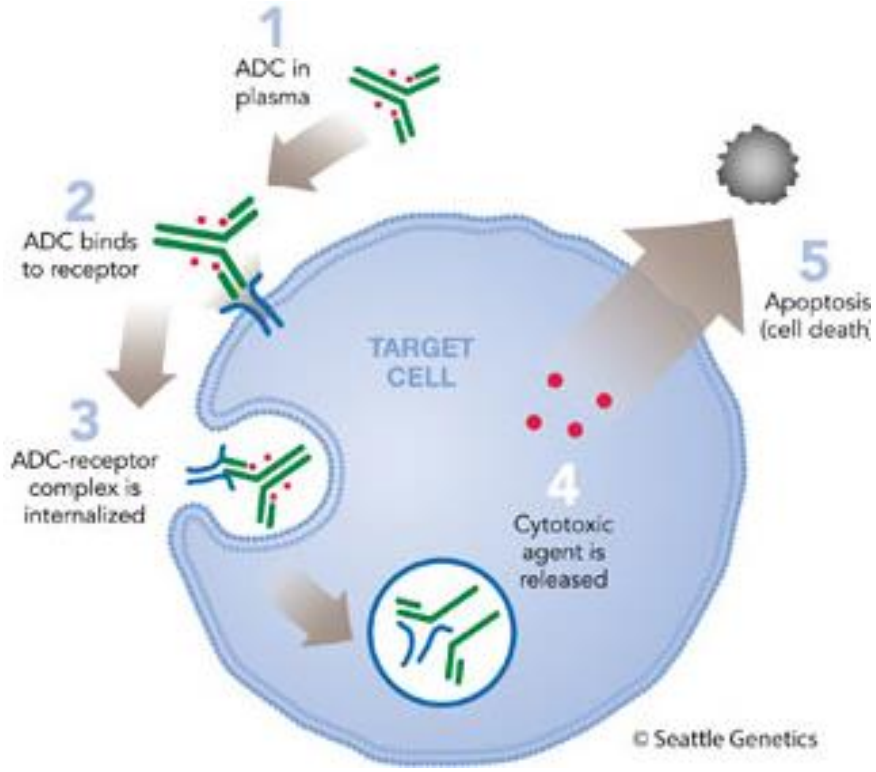
Lonial S, Leukemia 2016

Trials of investigational agents as single agent

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	35	20%	Hansson, Clin Cancer Res 2015

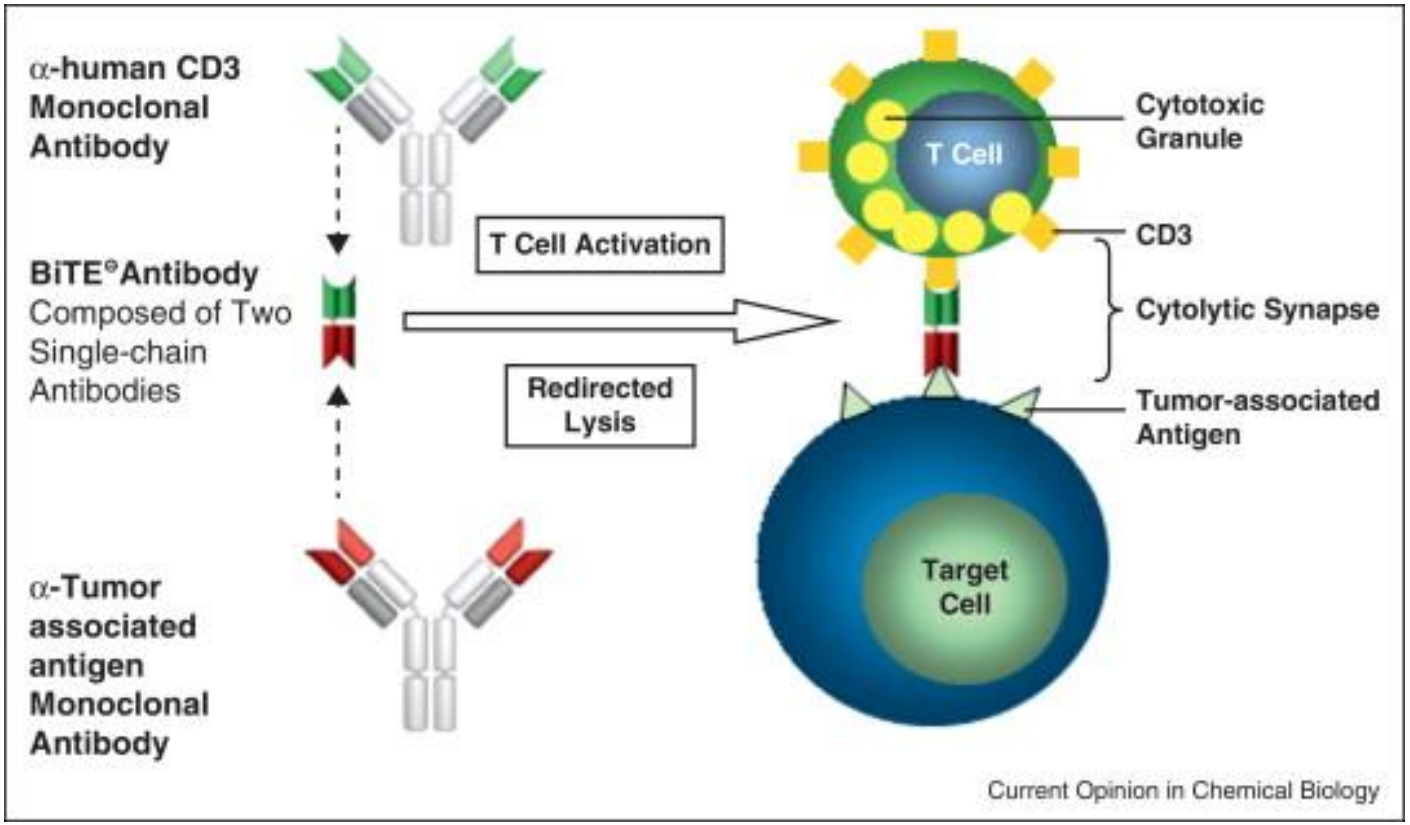
Monoclonal Ab drug conjugate

- ✓ 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)

Conclusions

- ✓ In RRMM setting daratumumab has shown robust single-agent activity, whereas the activity of other mAbs appears restricted to combination regimens
- ✓ mAbs are generally well tolerated with a favorable safety profile
- ✓ 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