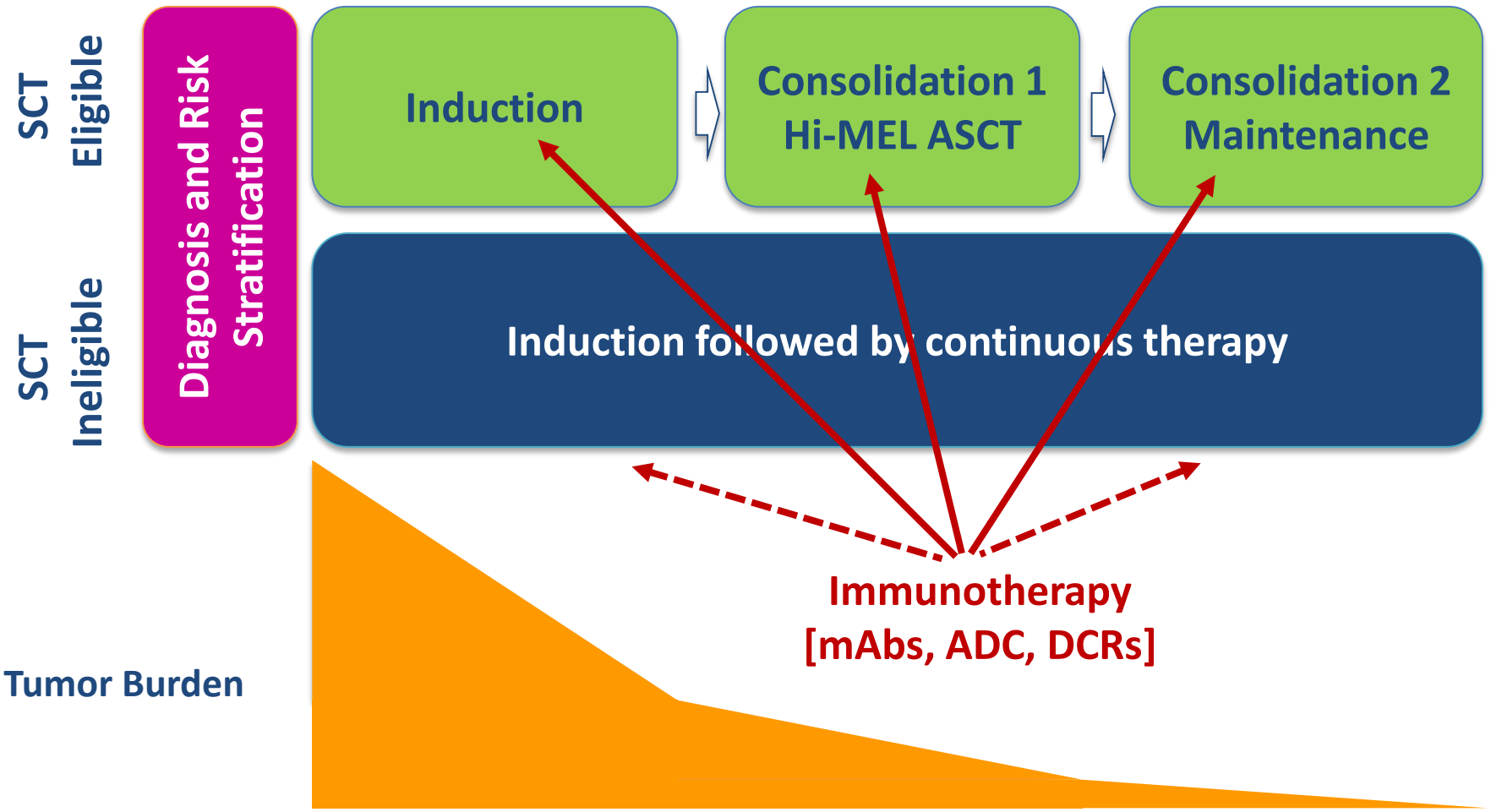
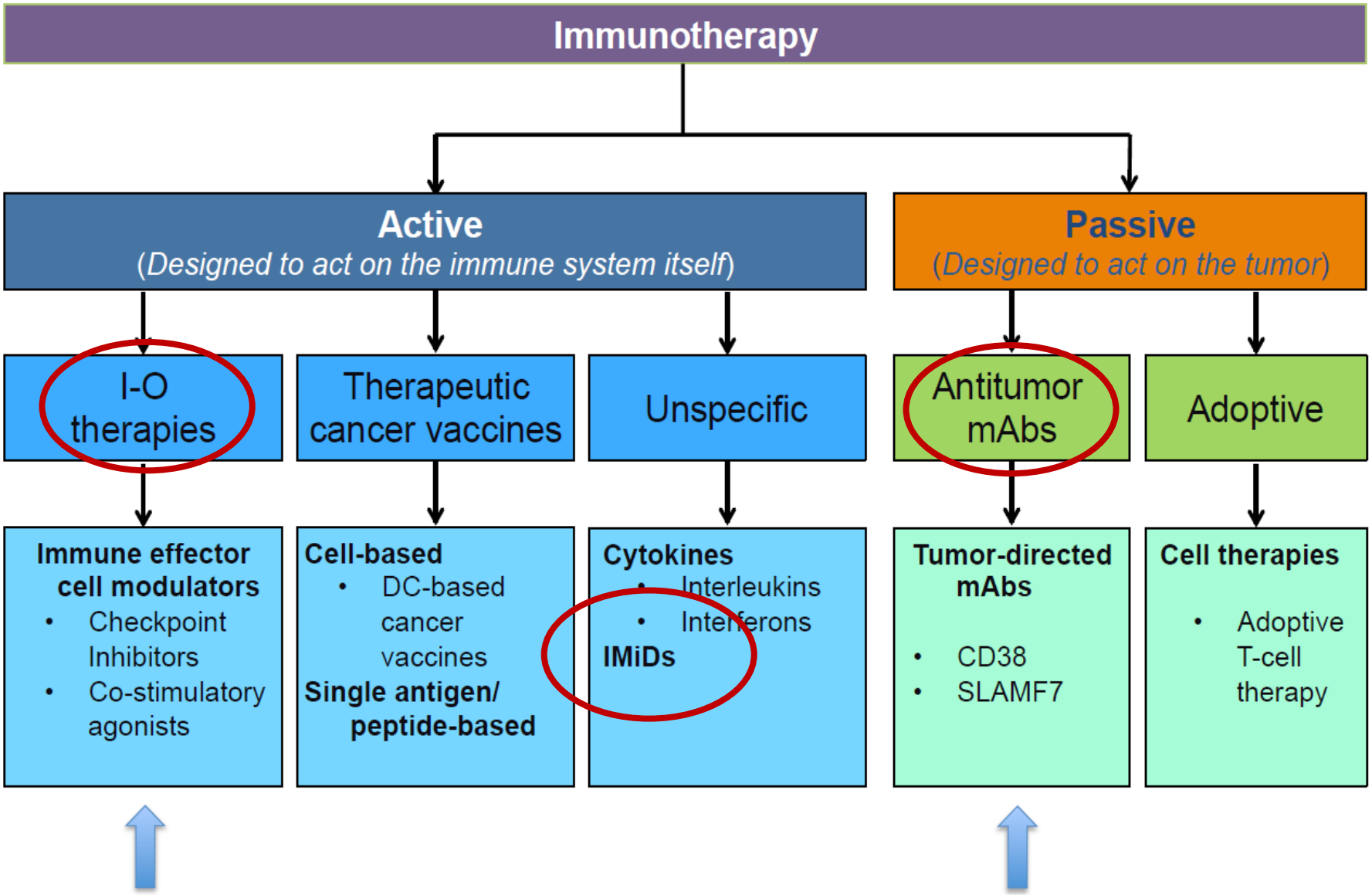
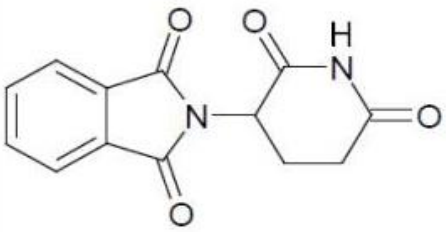
Myeloma Treatment Paradigm



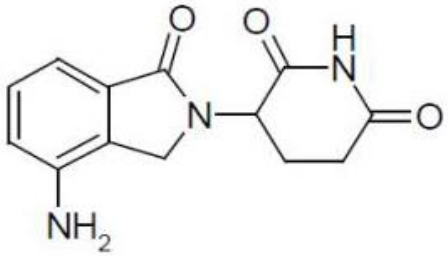
Immunotherapies under investigation for Multiple Myeloma



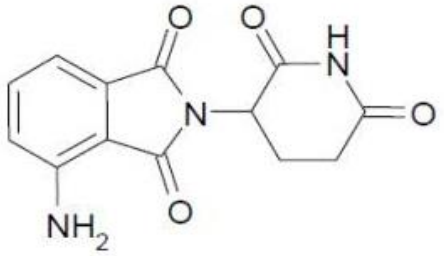
IMIDS: a growing family of antitumor Pleiotropic Pathway Modifiers



Thalidomide



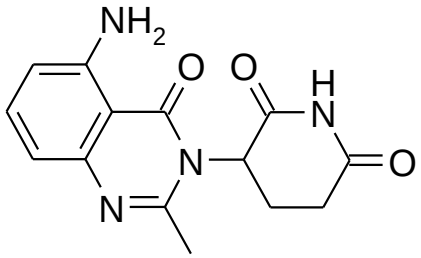
Lenalidomide



Pomalidomide

IMiDs

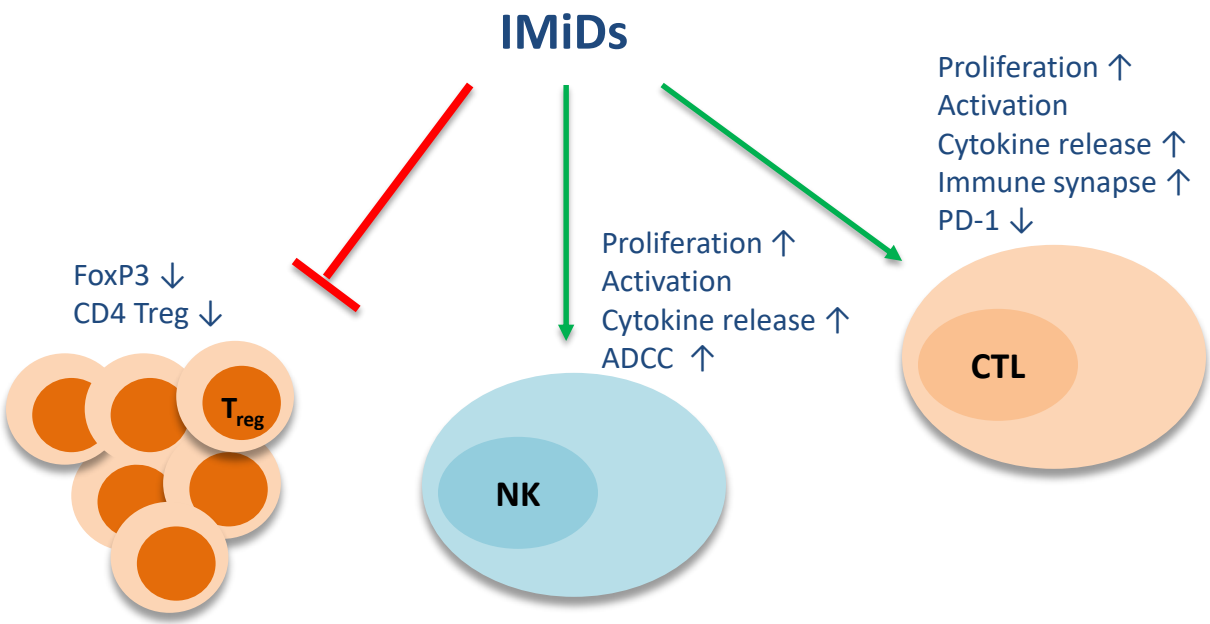
PPM

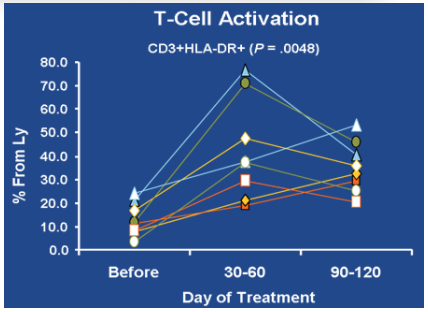


CC-122

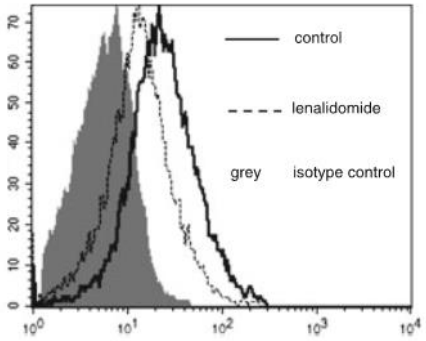
	Fold Activity		
	LEN	**POM**	**CC-122**
Immune modulation	**x**	**10x**	**10x**
Anti-proliferation (NHL, MM lines)	**x**	**10x**	**10x**
Anti-angiogenesis (HUVEC sprouting)	**x**	**5x**	**100x**

IMIDS: a growing family of antitumor Pleiotropic Pathway Modifiers

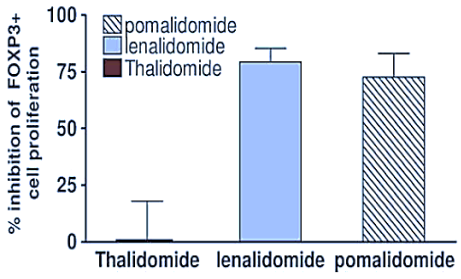




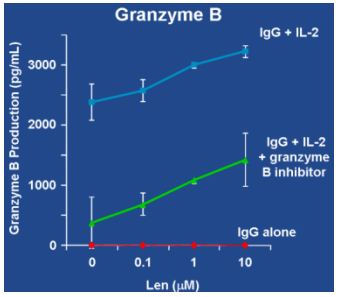
Lioznov M, et al. *Bone Marrow Transplant.* 2010



Luptakova K, et al. *Cancer Immunol Immunother*. 2013



Galustian *C, et al. Cancer Immunol Immunother*. 2009



Wu L, et al. *Clin Cancer Res*. 2008

Mean Cytokine Secretion From Stimulated CD8+ T Cells Isolated From 9 MM Patients With CR or VGPR Following ASCT

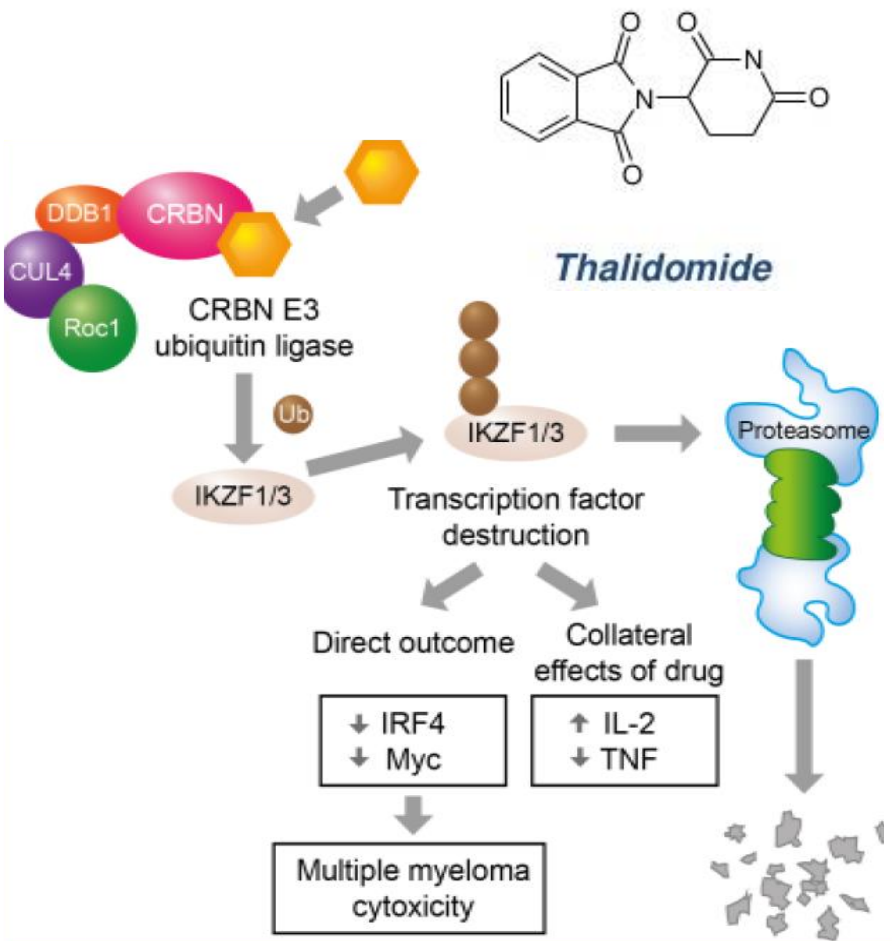
Cytokine Secretion (ng/mL)			
	Control	Lenalidomide	Pomalidomide
IFNγ	66.4 ± 21.0	217.5 ± 62.1*	437.1 ± 137.1*
TNFα	4.9 ± 1.7	21.4 ± 5.4**	44.9 ± 9.4**
IL2	1.9 ± 1.7	5.3 ± 2.7	12.7 ± 6.6

*P<0.01
**P<0.001

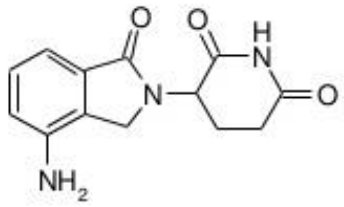
CD8+ T cells were stimulated with anti-CD3 and anti-CD28 antibodies for 144 h
Values represent mean ± standard error

Fostier K, et al. *Blood*. 2013;122(Abstr 3214).

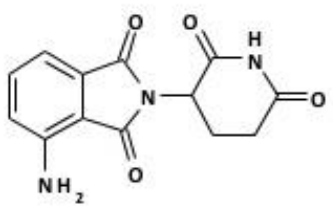
Pleiotropic effects of IMIDs



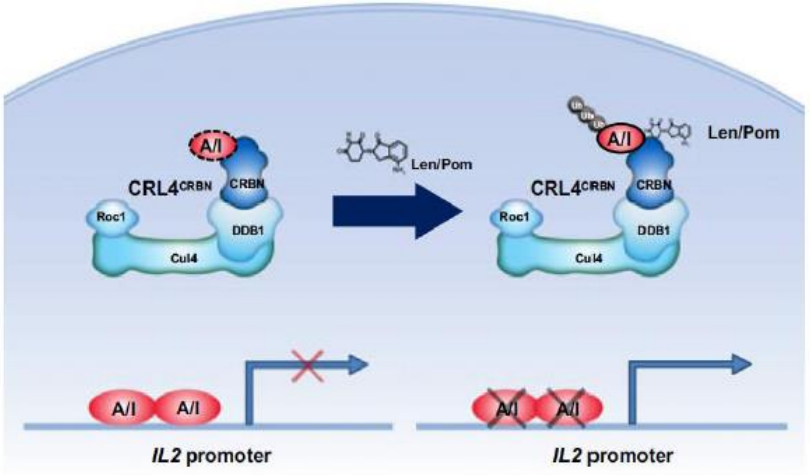
Thalidomide



Lenalidomide



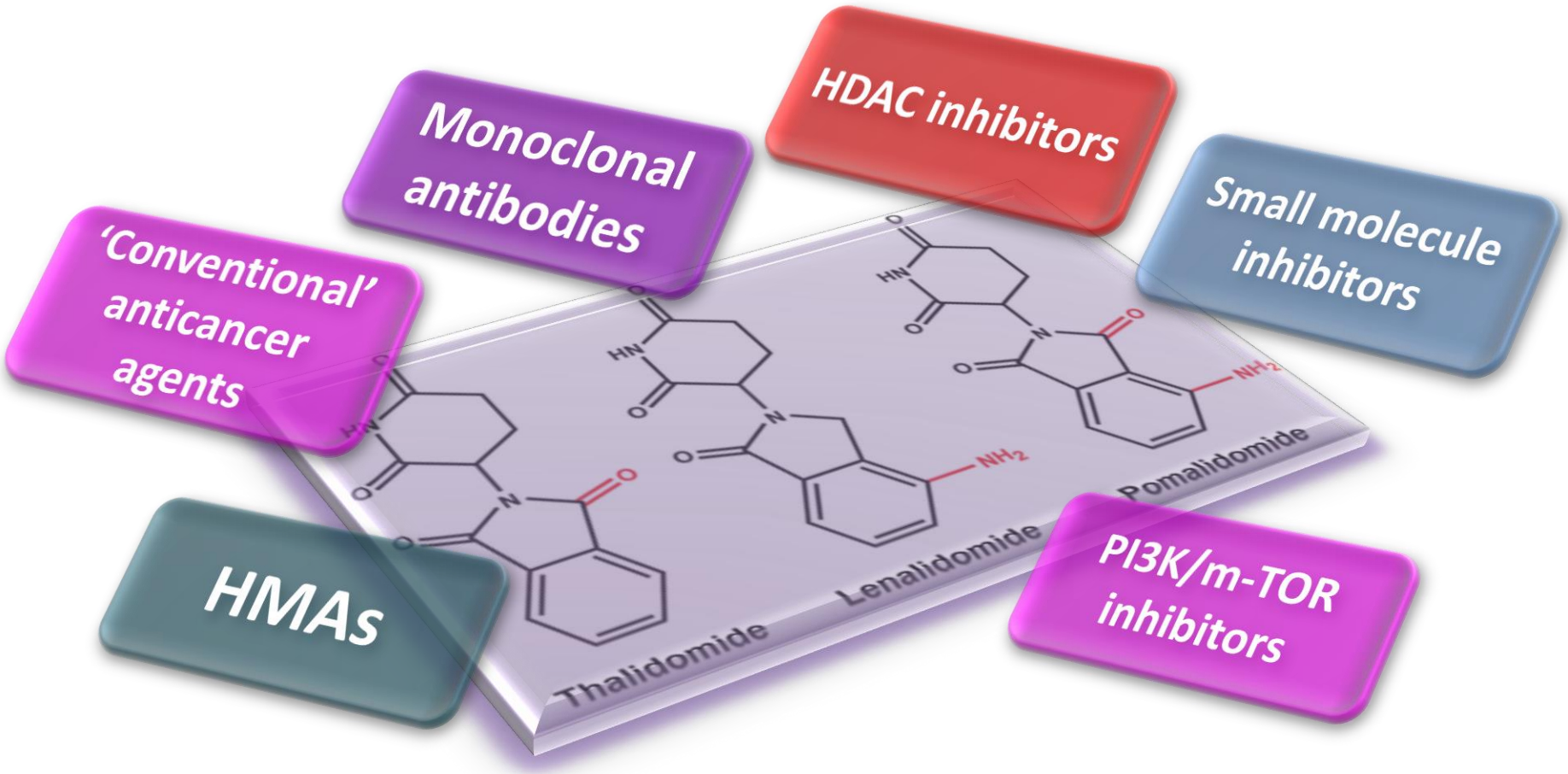
Pomalidomide



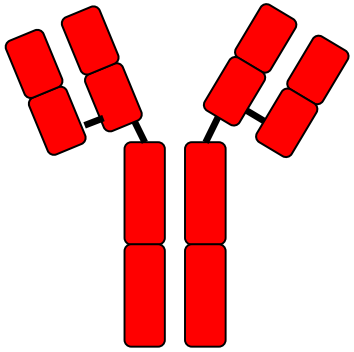
Aiolos and Ikaros repress IL2 expression

IMiDs promote the degradation of Aiolos and Ikaros, leading to IL2 expression

Imids® as a core platform to implement novel therapeutic strategies in hemopoietic malignancies

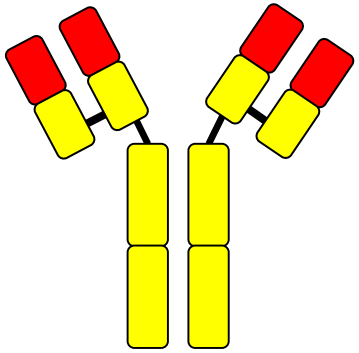


Therapeutic Mabs



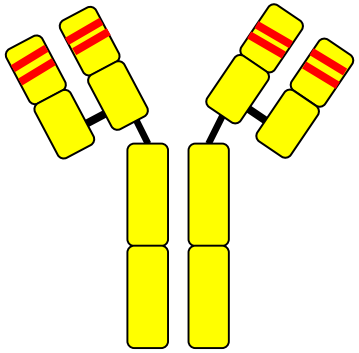
Mouse

'momab'
= fully murine
(Tositumomab)



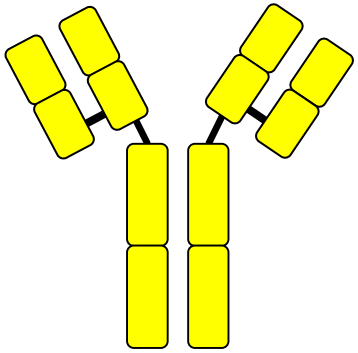
Chimeric

'ximab'
= chimeric
mouse or rat Ig variable regions; human constant regions
(Rituximab)



Humanized

'zumab'
= humanized chimeric mAb with only complementarity determining regions being mouse origin
(Bevacizumab)



Human

'umab'
= fully human
(**Daratumumab**)

\+ -

Immunogenicity

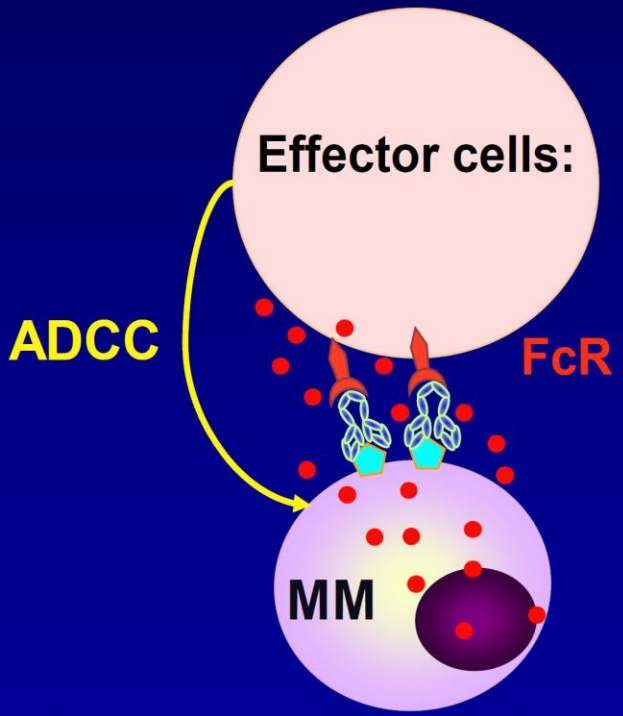
Daratumumab
SAR650984
MOR202
CD38
Elotuzumab
CS1
Lucatumumab
Dacetuzumab
CD40
Lorvotuzumab
mertansine
CD56
Ulocuplumab
CXCR4
IL-6
Siltuximab
Tabalumab
BAFF
APRIL
CD229
CD200
CD28
CD19
MM cell
BCMA
CD317
ß2M
CD70
CD47
CD74
Milatuzumab
PD-1
Pidilizumab
Rivolumab
Pembrolizumab
CD138
Indatuximab
ravtansine
ICAM-1
BI-505
In clinical development
Preclinical activity
Potential targets
Newcomers

Anticorpi monoclonali nel Mieloma Multiplo

Bersaglio	mAb			Stadio dello sviluppo
Molecole di superficie				
SLAMF7 (CS1) [(Signaling Lymphocytic Activation Molecule Family 7 (Cell Surface 1)]	Elotuzumab	approvato da FDA & EMA	Umanizzato	Fase 1/2/3
CD38 (Cluster of Differentiation 38)	Daratumumab Isatuximab (SAR650984) MOR202	approvato da FDA & EMA	Totalmente umano Chimerico Totalmente umano	Fase 1/2/3/4 Fase 1/2 Fase 1/2
CD138 (Cluster of Differentiation 138)	Indatuximab ravtansine (BT062)			Fase 1/2
BCMA (B-Cell Maturation Antigen)	J6M0-mcMMAF (GSK2857916)			Fase 1
Molecole segnale				
IL-6 (Interleukin-6)	Siltuximab			Fase 2
RANKL (RANK Ligand)	Denosumab			Fase 3
VEGF (Vascular Endothelial Growth Factor)	Bevacizumab			Fase 2
DKK1 (Dickkopf 1)	BHQ880			Fase 2
Inibitori del checkpoint immunitario				
PD-1 (Programmed Cell Death-1)	Pembrolizumab Nivolumab Pidilizumab			Fase 1/2/3 Fase 1/2 Fase 1/2
PD-L1 (Programmed Cell Death-Ligand 1)	Durvalumab			Fase 1
CTLA4 (Cytotoxic T-Lymphocyte Antigen 4)	Ipilimumab			Fase 1/2
KIR (Killer Inhibiting Receptor)	Lirilumab			Fase 1

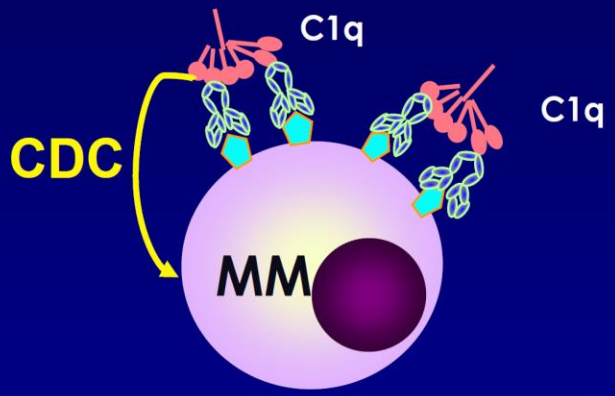
MAb-Based Therapeutic Targeting of Myeloma

Antibody-dependent Cellular cytotoxicity (ADCC)



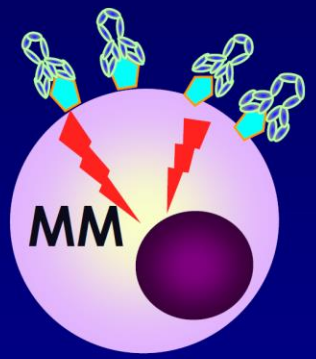
- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (CS1; SLAMF7)
- Daratumumab, SAR650984, MOR 202 (CD38)
- XmAb®5592 (HM1.24)

Complement-dependent Cytotoxicity (CDC)



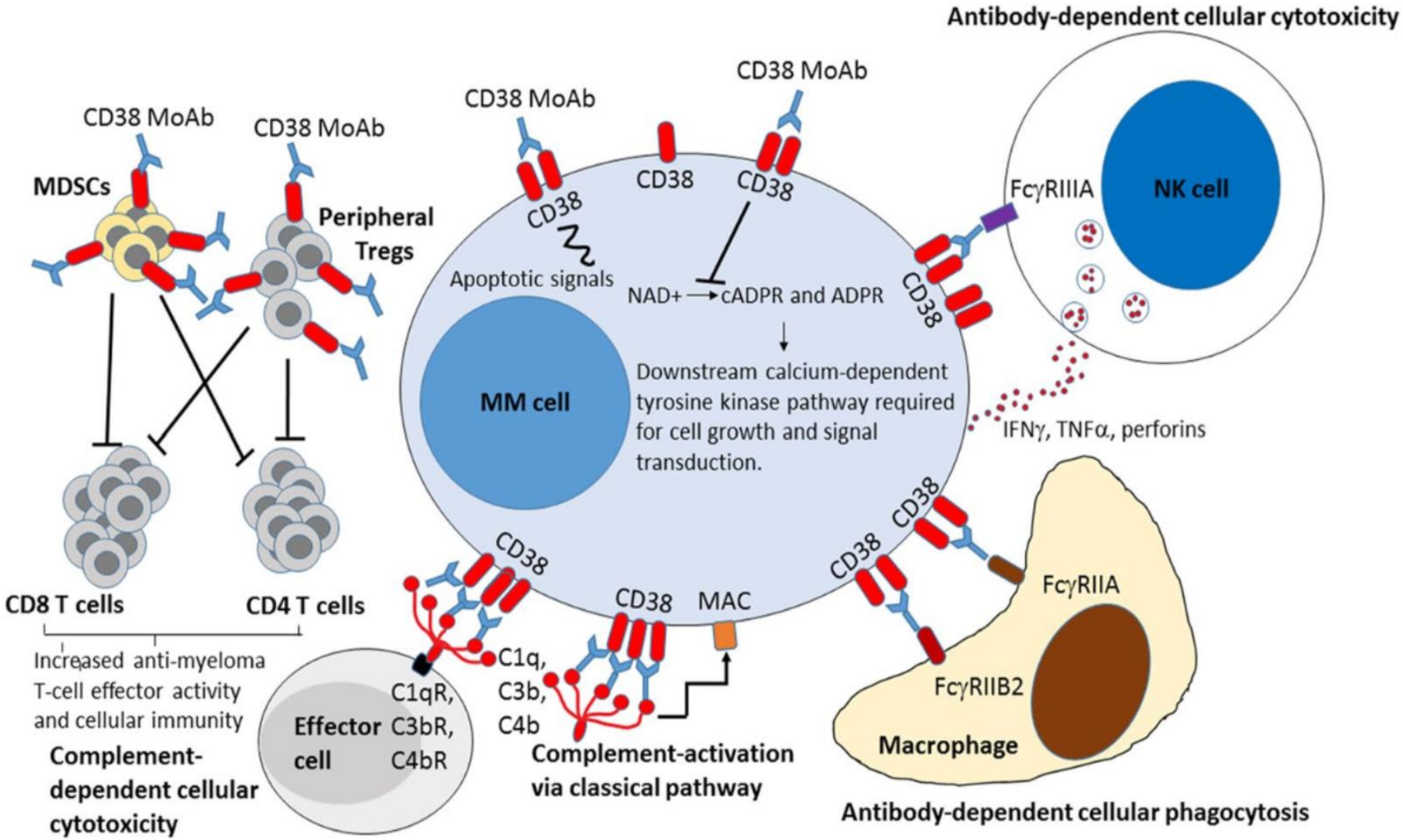
- Daratumumab
- SAR650984 (CD38)

Apoptosis/growth arrest via targeting signaling pathways



- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)
- Siltuximab (1339) (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab, SAR650984, MOR 202 (CD38)

Multi-faceted properties of CD38 MoAbs.



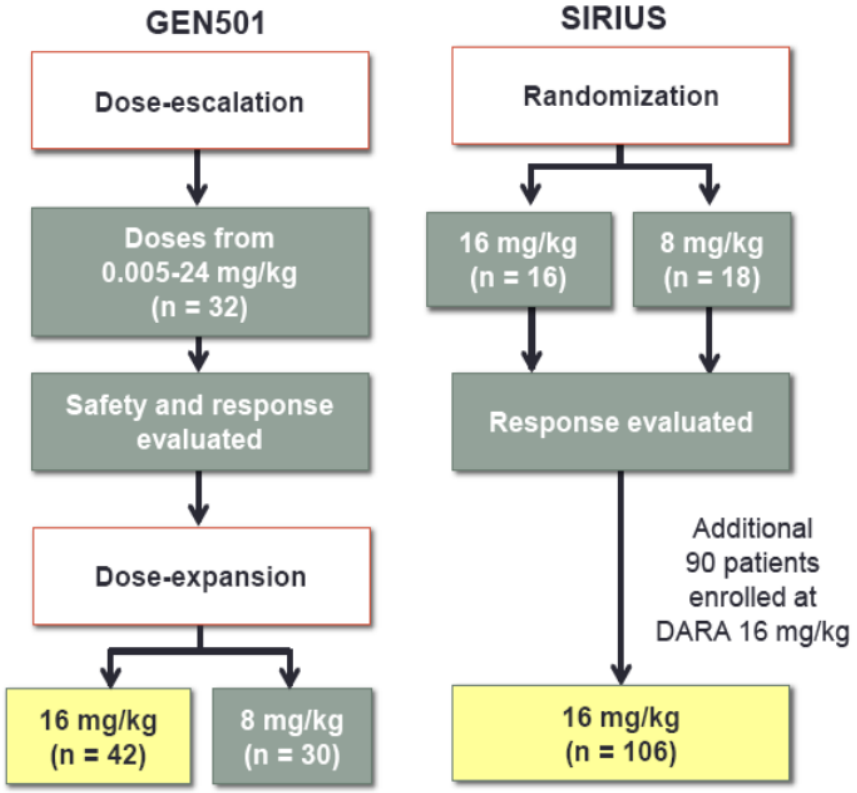
Shallis RM, Terry CM, Lim AH,Cancer Immunol Immunother. 2017

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

Pooled analysis Studies GEN501 and MMY2002 (Sirius)

Median number of previous lines of therapy: 5 (2-14), including pomalidomide (55%) and carfilzomib (39%)

- ≥18 years of age, ECOG status ≤2[1,2]
- GEN501[1]
  - Open-label, multicenter, phase 1/2, dose-escalation and dose-expansion study
  - Relapsed from or refractory to ≥2 prior lines of therapy including PIs and IMiDs
- SIRIUS[2]
  - Open-label, multicenter, phase 2 study
  - Patients had received ≥3 prior lines of therapy, including a PI and an IMiD, or were double refractory to a PI and an IMID
- DARA was approved by the FDA on November 16, 2015, based on these studies



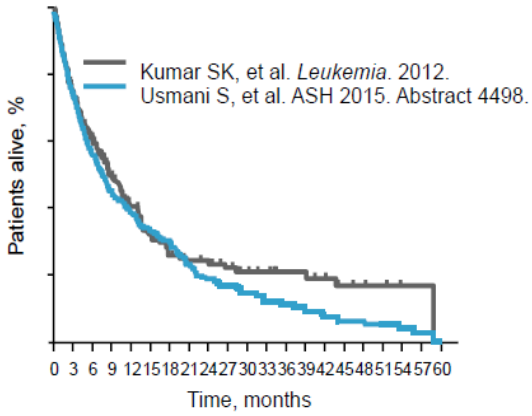
16 mg/kg
N = 148

Median follow-up of 20.7 months

1. Lokhorst HM, *N Engl J Med*. 2015;373(13):1207-1219
2. Lonial S. *Lancet*. 2016;387(10027):1551-1560.

Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

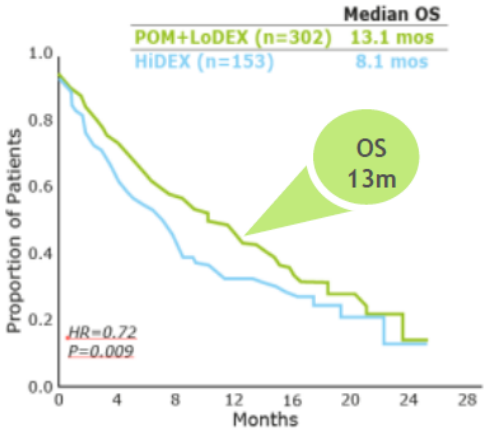
The Breakthrough (BT) population outcome



RRMM:

Median OS 5-9 months in patients relapsed or refractory MM after ≥3 prior lines of therapy, including IMID and PI

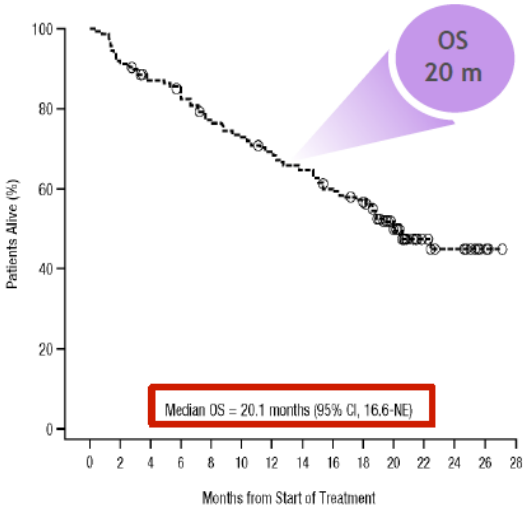
1. Kumar SK, et al. Leukemia. 2012;26(1):149-157.
2. Usmani S, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 4498.



Pomalidomide:

Median OS 13,1months in patients relapsed or refractory MM after ≥2 prior lines of therapy, including IMID and PI

San Miguel J et al. Lancet Oncol 2013; 14: 1055–66



Daratumumab – Single Agent:

Median OS of 20 months in patients with relapsed or refractory, double refractory or relapsed after ≥3 lines of therapy, including pomalidomide and carfilzomib

Usmani S et al. Blood. 2016;128(1):37-44

Daratumumab
Regulatory Update

November 2015: FDA

"Daratumumab 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."*

April 2016: EMA

"Daratumumab 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 immunomodulator****y agent and who have demonstrated* ***disease progression on the last therapy****."*

CASTOR MMY3004 DaraVd vs Vd

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

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
Every 4 weeks - Cycles 9+ (until PD or safety)

Vel: 1.3 mg/m² SC, Days 1,4,8,11 - Cycles 1-8
dex: 20 mg PO-IV, Days 1,2,4,5,8,9,11,12 - Cycles 1-8

Vd (n = 247)

Vel: 1.3 mg/m² SC, Days 1,4,8,11 - Cycles 1-8
dex: 20 mg PO-IV, Days 1,2,4,5,8,9,11,12 - Cycles 1-8

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

Primary Endpoint

- PFS

Secondary Endpoints

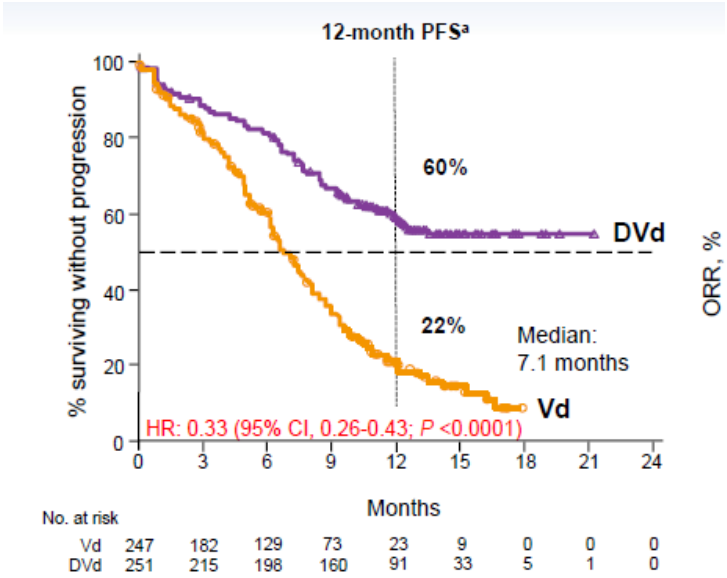
- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

Statistical analyses

- 295 PFS events: 85% power for 4.3-month PFS improvement
- Interim analysis: ~177 PFS events

Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/hour permitted

RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; Vel, bortezomib; SC, subcutaneous; dex, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; VGPR, very good partial response; CR, complete response;



- Median (range) follow-up: 13.0 (0-21.3) months

POLLUX MMY3003 Dara-Rd vs Rd

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

Key eligibility criteria

- RRMM
- ≥1 prior line of therapy
- Prior lenalidomide exposure, but not refractory
- Patients with creatinine clearance ≥30 mL/min

Stratification factors

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

RANDOMIZE 1:1

DRd (n = 286)

Daratumumab 16 mg/kg IV
- qw in Cycles 1-2, q2w in Cycles 3-6, then q4w until PD

R 25 mg PO
- Days 1-21 of each cycle until PD

d 40 mg PO
- 40 mg weekly until PD

Rd (n = 283)

R 25 mg PO
- Days 1-21 of each cycle until PD

d 40 mg PO
- 40 mg weekly until PD

Cycles: 28 days

Primary endpoint

- PFS

Secondary endpoints

- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

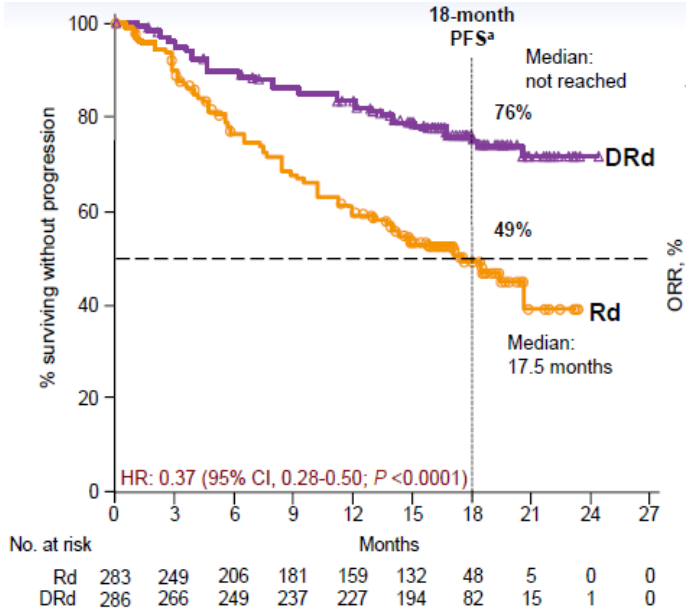
Statistical analyses

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

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

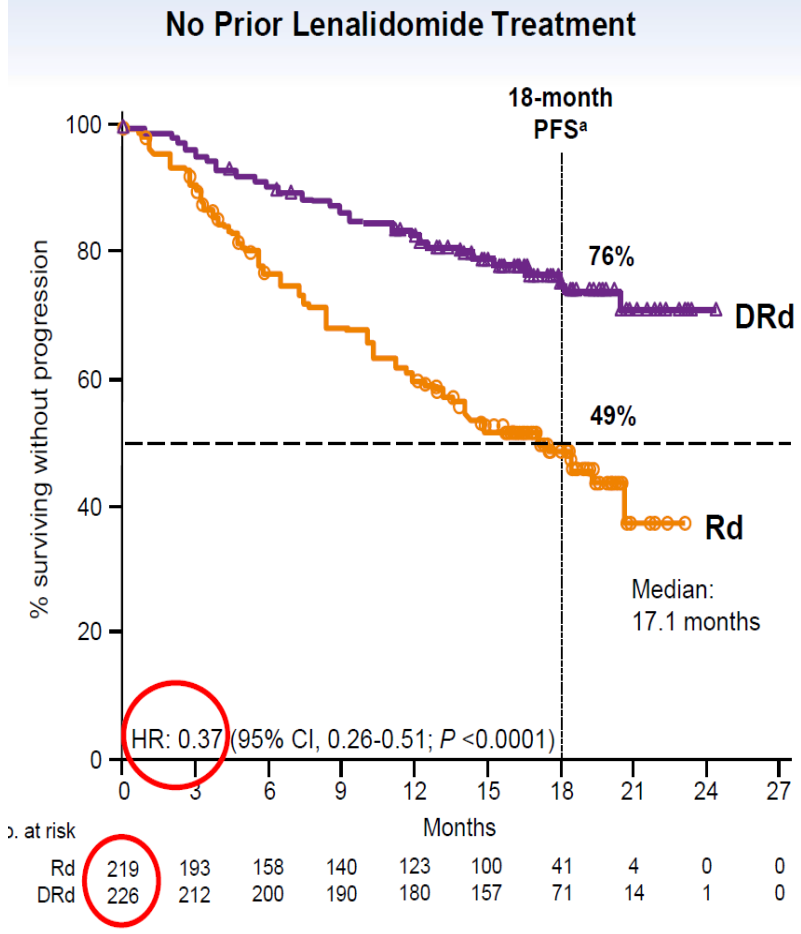
[a]On daratumumab dosing days, dexamethasone was administered 20 mg premedication on Day 1 and 20 mg on Day 2.
ISS, International Staging System; R, lenalidomide; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PO, oral; d, dexamethasone; TTP, time to progression; MRD, minimal residual disease.

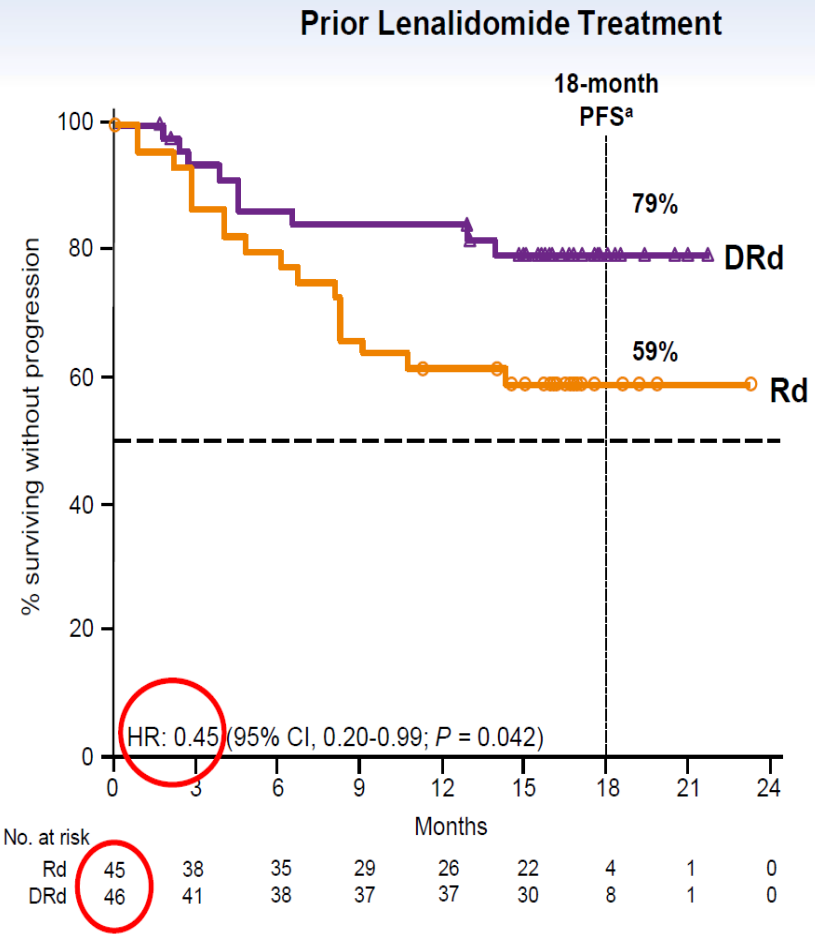
Dimopoulos er al. N Engl J Med 2016;375:1319-31



- Median (range) follow-up: 17.3 (0-24.5) months

PFS: Prior Lenalidomide Treatment





Treatment effect is consistent regardless of prior lenalidomide exposure

Philippe Moreau. abstract 1151 ASH 2016

Rationale for Earlier Use of MoAbs in Myeloma

- Less toxic than traditional cytotoxic agents
- Good partners for lenalidomide (key for MGUS/SMM)
- Immune system less impaired (key for ADCC)
- Improved overall response rate, VGPR+ rate, and PFS
- Increased likelihood of reaching MRD(-) status
- MRD(-) patients may enjoy long PFS even with limited maintenance therapy

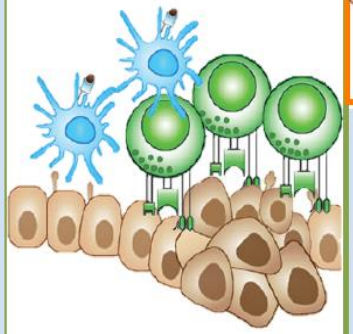
MRD, minimal residual disease; PFS, progression free survival; SMM, smoldering mutliple myeloma; VGPR, very good partial response

Immune response
(anti-tumor effectors)

Immune escape
(pro-tumor immune suppressive cells)

- Antigen strenght
- HLA-expression
- CXCR9, 10 chemokines

Prevalent T cells

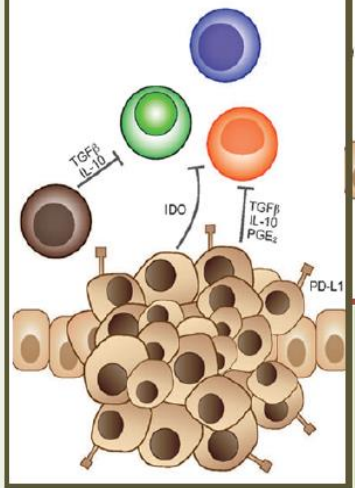


Prevalent NK cells

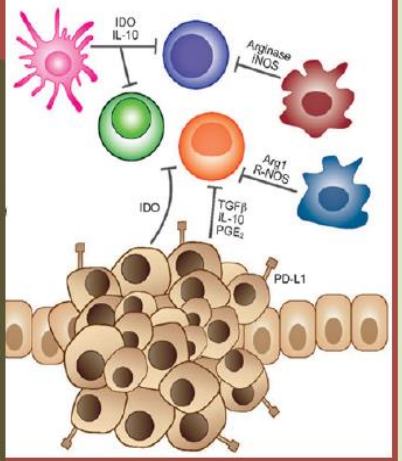
- HLA loss
- IL-12, IL-15
- CCL3, CCL4

- T cell response
- High TCR affinity
- Acute inflammatory factors

Prevalent Treg cells



Prevalent myeloid cells



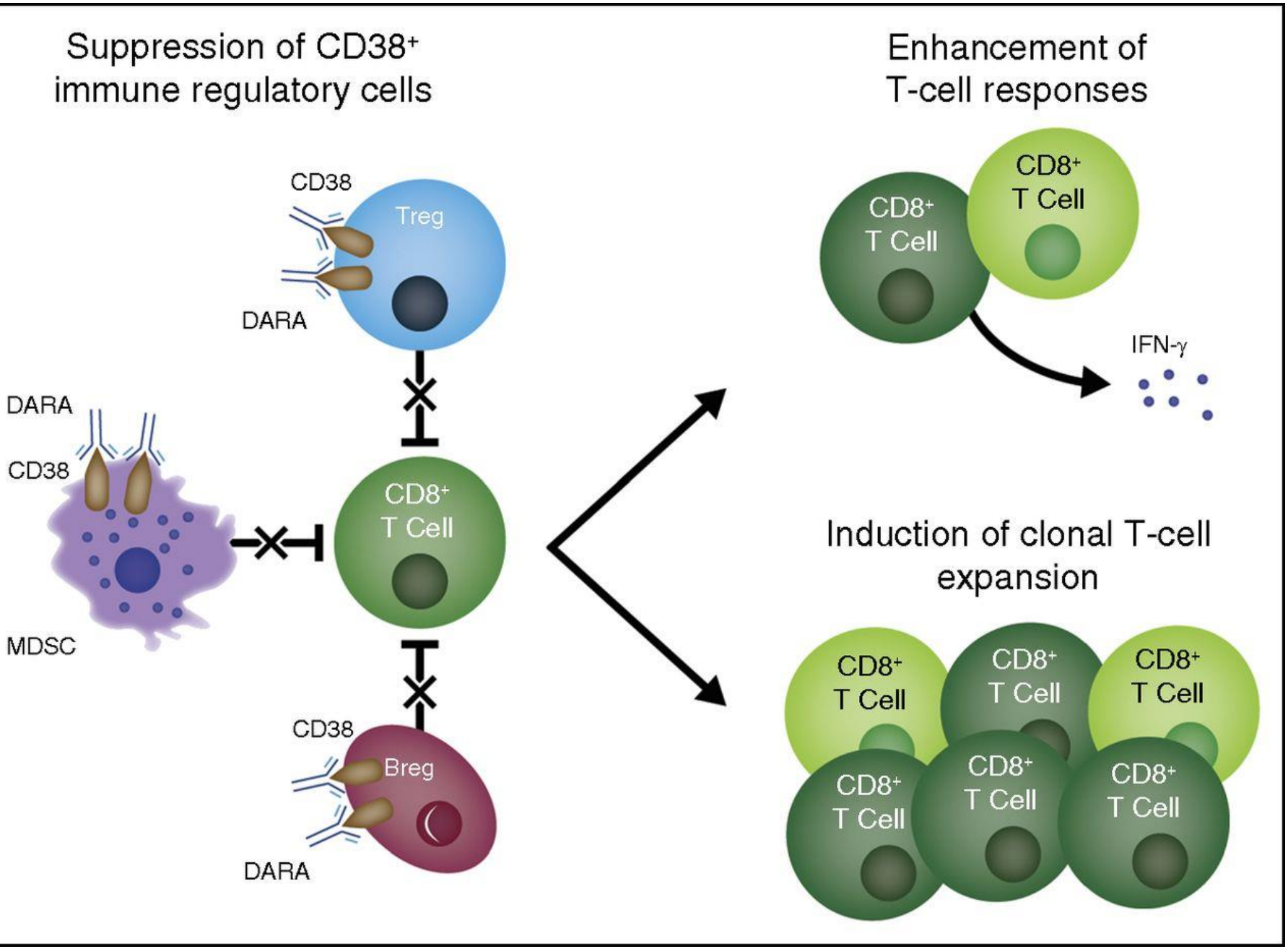
- Wound-healing factors
- G-CSF, GM-CSF, M-CSF

Germinal centre → Bone marrow → Peripheral blood

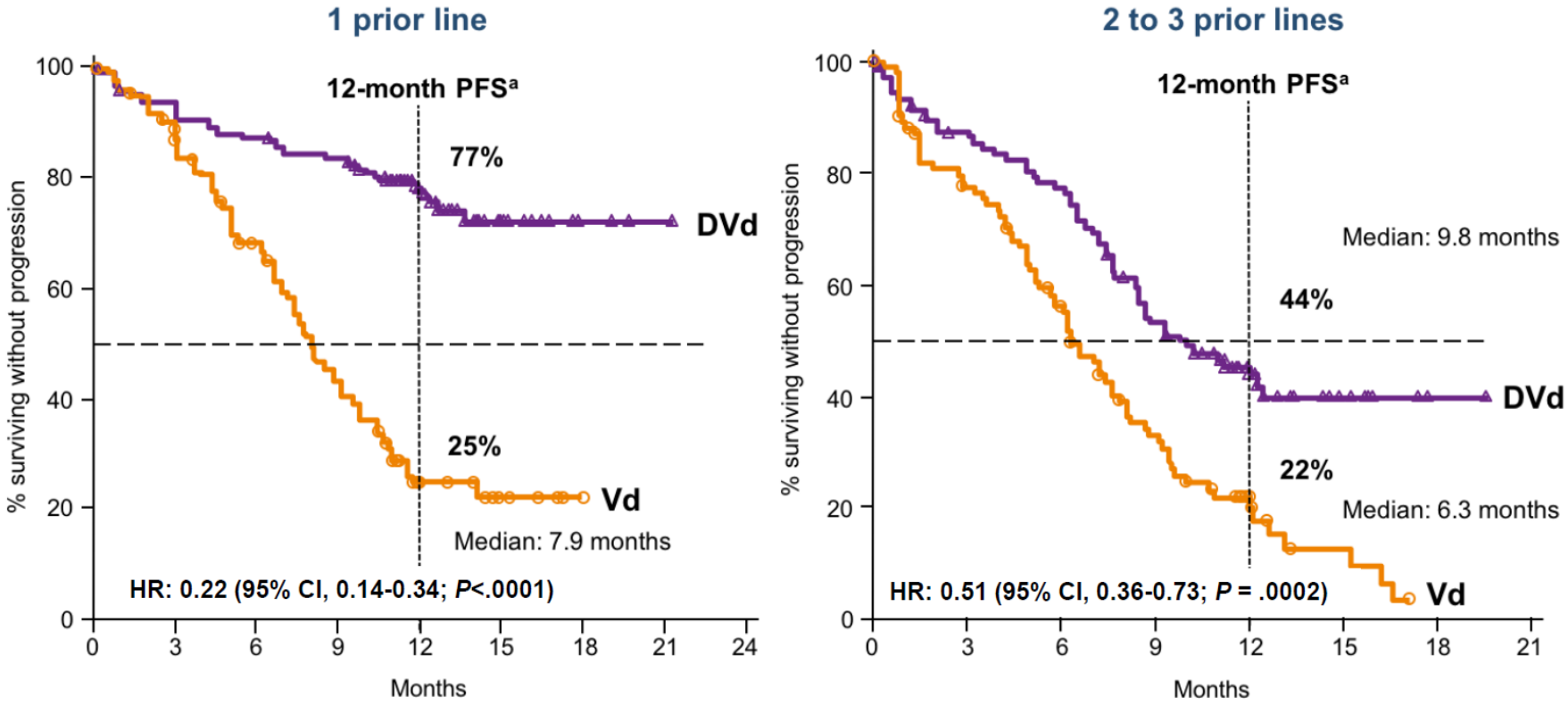
Post-germinal centre B-cells → MGUS → SMOLDERING MYELOMA → MYELOMA → PLASMA CELL LEUKEMIA

Immune microenvironment perturbation

Immune microenvironment perturbation


Suppression of CD38+ immune regulatory cells
CD38
Treg
DARA
DARA
CD38
MDSC
CD8+ T Cell
CD38
Breg
DARA
Enhancement of T-cell responses
CD8+ T Cell
CD8+ T Cell
IFN-γ
Induction of clonal T-cell expansion
CD8+ T Cell
CD8+ T Cell
CD8+ T Cell
CD8+ T Cell
CD8+ T Cell
CD8+ T Cell

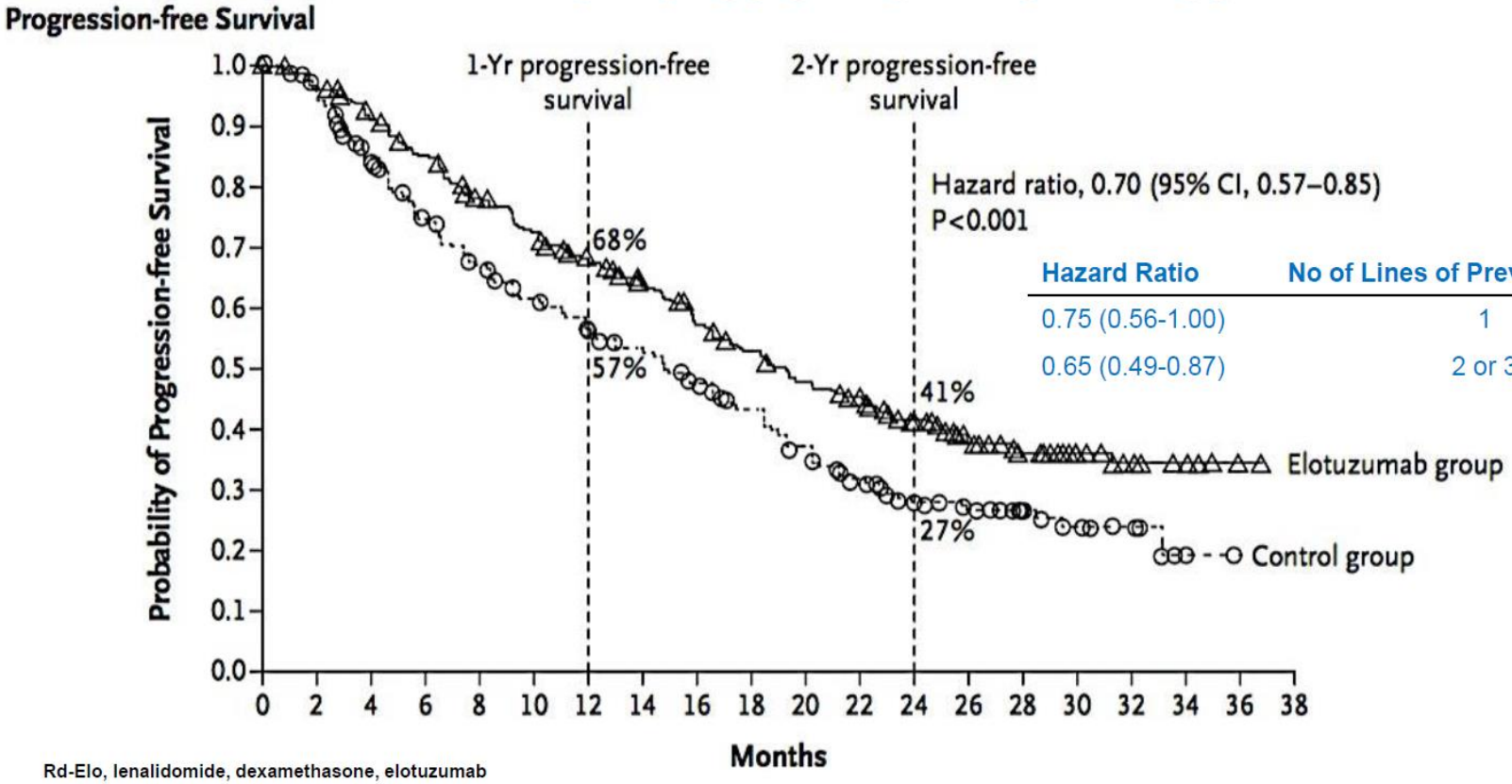
More Pronounced Benefit From Dara Early (CASTOR)



CI, confidence interval; Dara, daratumumab; DVd, daratumumab, bortezomib, dexamethasone; HR, hazard ratio; Vd, bortezomib, dexamethasone

Mateos MV, et al. *Blood.* 2016;128: Abstract 1150.

PFS of Elotuzumab/Rd (ELOQUENT-2) 1 Line Versus 2-3 Prior Lines

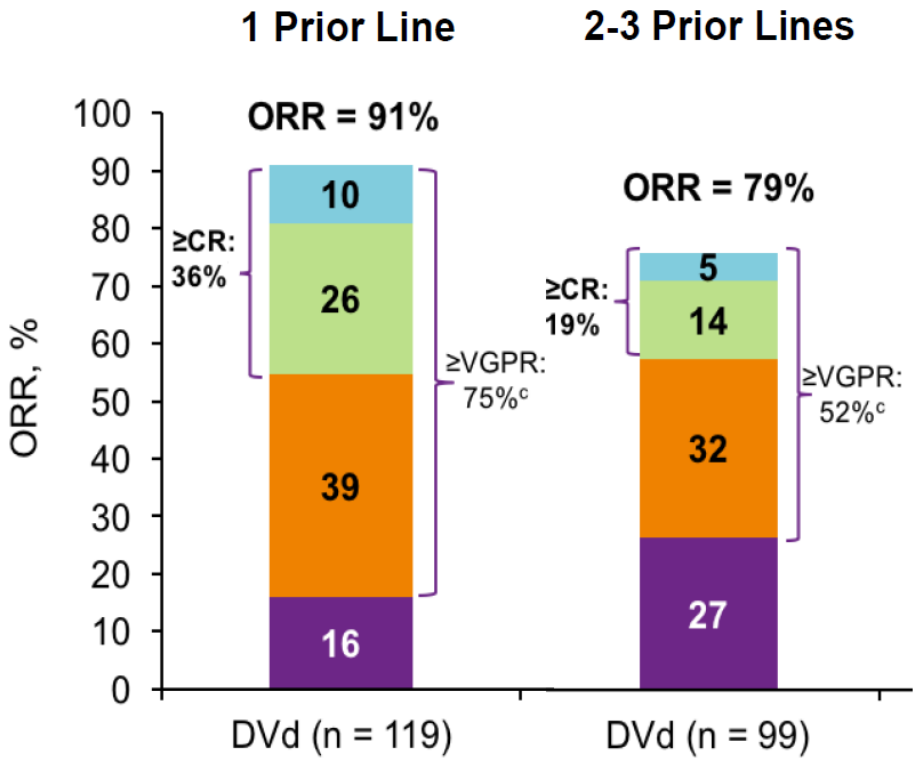


Hazard Ratio	No of Lines of Previous Therapy
0.75 (0.56-1.00)	1
0.65 (0.49-0.87)	2 or 3

Rd-Elo, lenalidomide, dexamethasone, elotuzumab

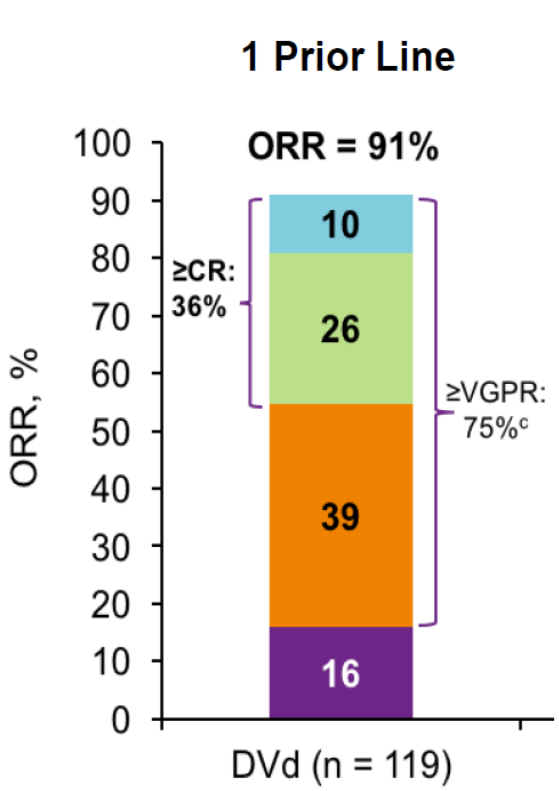
Lonial S, et al. *N Engl J Med.* 2015;373(7):621-631.

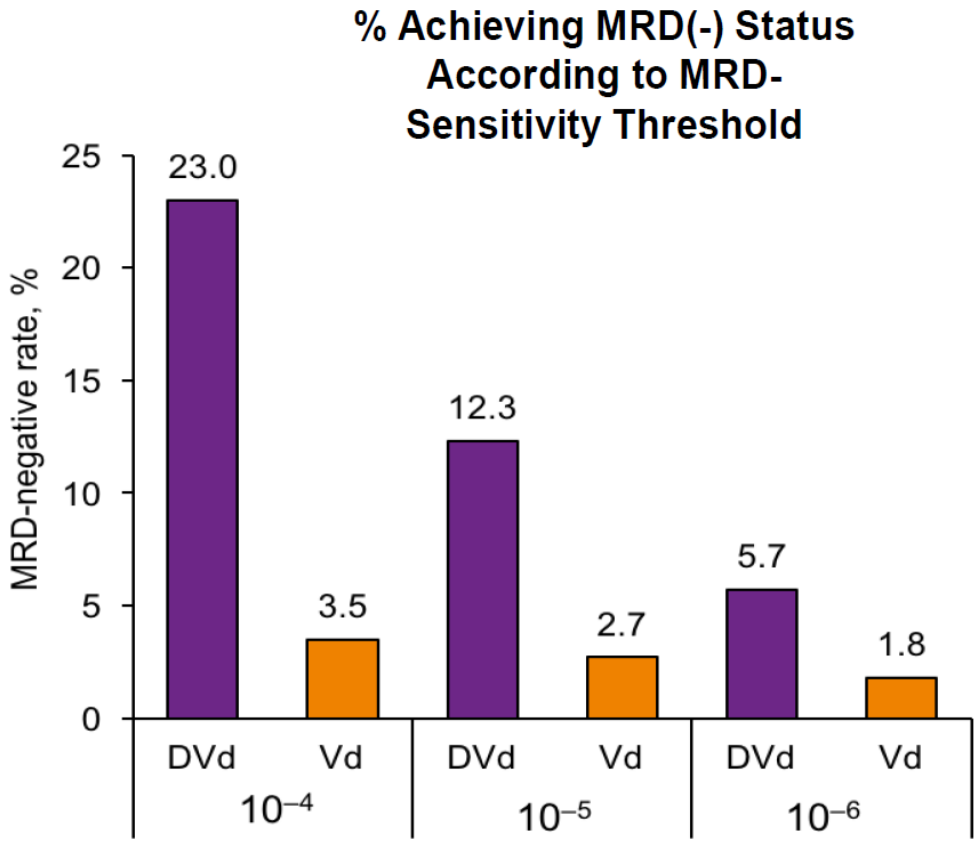
Greater *Depth* of Response After 1 Prior Rx



Mateos MV, et al. *Blood.* 2016;128: Abstract 1150.

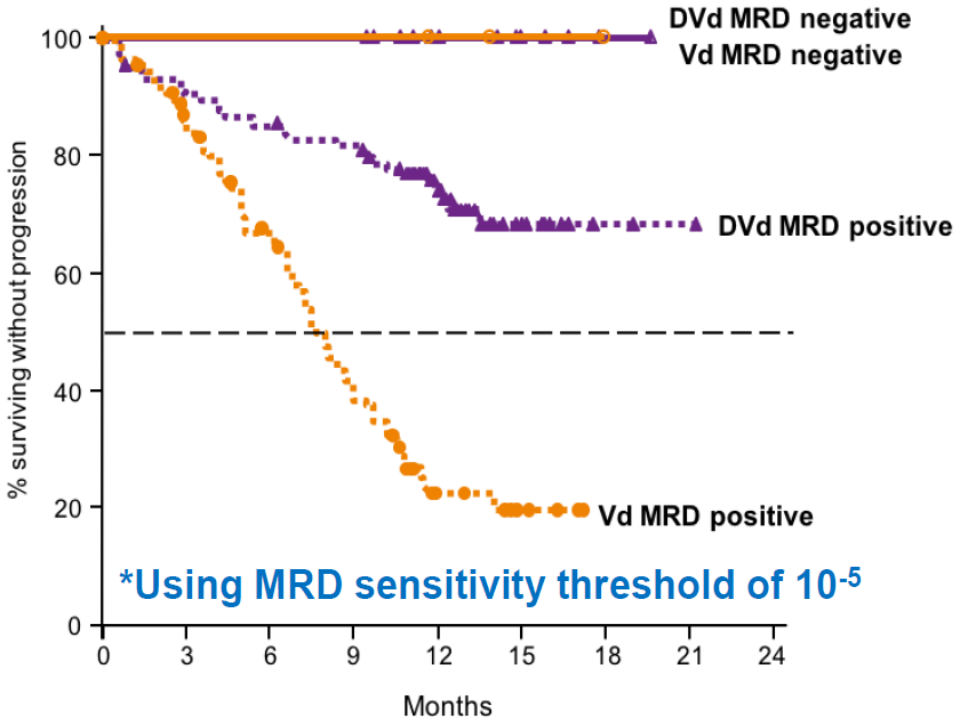
Greater *Depth* of Response After 1 Prior Rx





Mateos MV, et al. *Blood.* 2016;128: Abstract 1150.

MRD(-)* Status Improved PFS in CASTOR



Mateos MV, et al. *Blood.* 2016;128: Abstract 1150. Avet-Loiseau H, et al. *Blood.* 2015;126: Abstract 191. Attal M, et al *Blood.* 2015;126: Abstract 391.

Selected Elo & Dara Trials for MGUS/SMM and NDMM

- **SMM/MGUS:**
  - ERd in high-risk SMM (NCT02279394)
  - Three schedules of Dara for SMM (NCT02316106)
- **Newly-Diagnosed MM:**
  - RD+/-Elo in NDMM (ELOQUENT-1) (NCT01335399)
  - RD+/-Dara in NDMM (NCT02252172)
  - RVd+/-Dara in NDMM (NCT02874742)
  - S1211: RVd+/-Elo in NDMM with high-risk-cyto/FISH (NCT01668719)
  - CyBorD+Dara (NCT02951819)
  - KRD-Elo Ph 2 (NCT02969837)
  - ERd induction, consolidation, maintenance w/ ASCT (NCT02843074)
  - [VRD/ASCT/VRD]+/-Elo, then Rd+/-Elo maint (NCT02495922)

ASCT, autologous stem cell transplant; FISH, fluorescence in situ hybridization; NDMM, newly diagnosed multiple myeloma

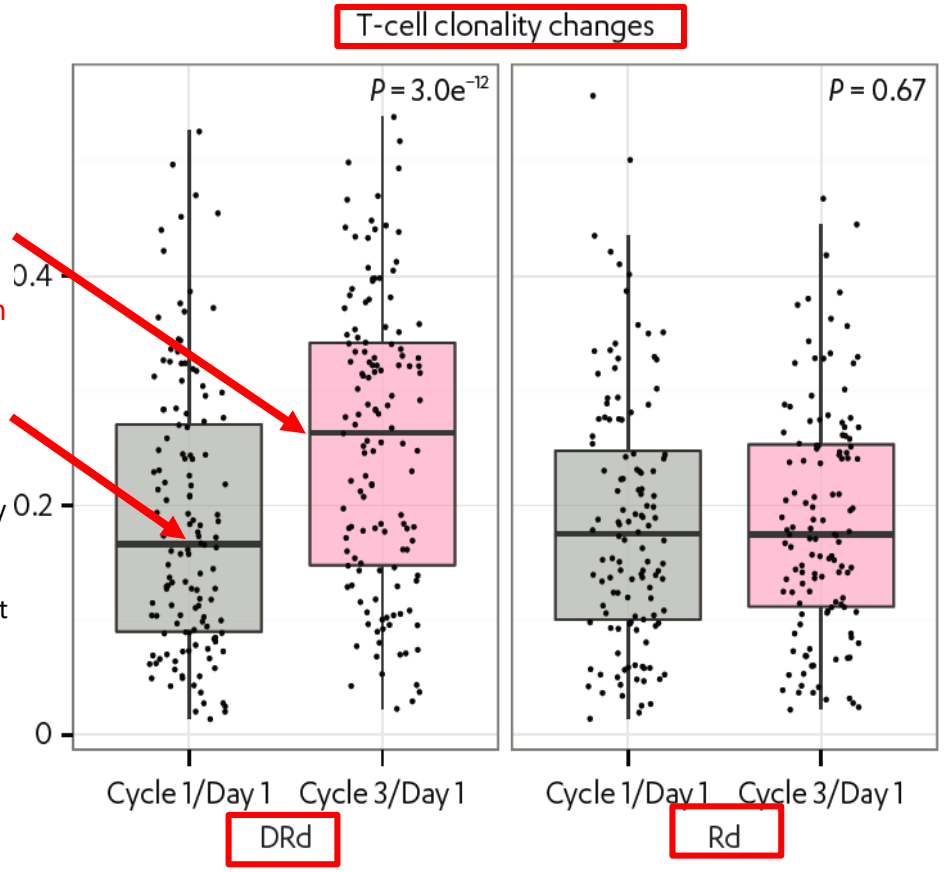
Rationale for DARA + POM-D

- In a randomized, phase 3 study, pomalidomide plus low-dose dexamethasone (POM-D) in patients relapsed from or refractory to previous treatment with bortezomib or lenalidomide resulted in the following[1]:
  - Overall response rate (ORR) = 31%
  - Median progression-free survival (PFS) = 4.0 months
  - Median overall survival (OS) = 12.7 months
- Pomalidomide increases CD38 expression in a time- and dose-dependent fashion in multiple myeloma (MM) cells[2]
- Increases in T-cell clonality were observed with DARA plus lenalidomide and dexamethasone (Rd) but not with Rd alone in POLLUX[3]

1. San Miguel J, et al. *Lancet Oncol*. 2013;14(11):1055-1066.
2. Boxhammer R, et al. Presented at: 51st American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-June 2, 2015; Chicago, IL. Abstract 8588.
3. Chiu, C. et al. Presented at: 58th American Society of Hematology (ASH) Annual Meeting & Exposition; December 3-6, 2016; San Diego, CA. Abstract 4531

T-cell Clonality Increased With DARA Treatment Over Time

- Between Cycle 1/Day 1 and Cycle 3/Day 1, a significant increase in T-cell clonality was observed in the DRd arm ($P = 3.0e^{-12}$),
- but not in the Rd arm ($P = 0.67$)
  - In the DRd arm, the median TCR clonality score at baseline was 0.166, which increased to 0.263 at Cycle 3/Day 1

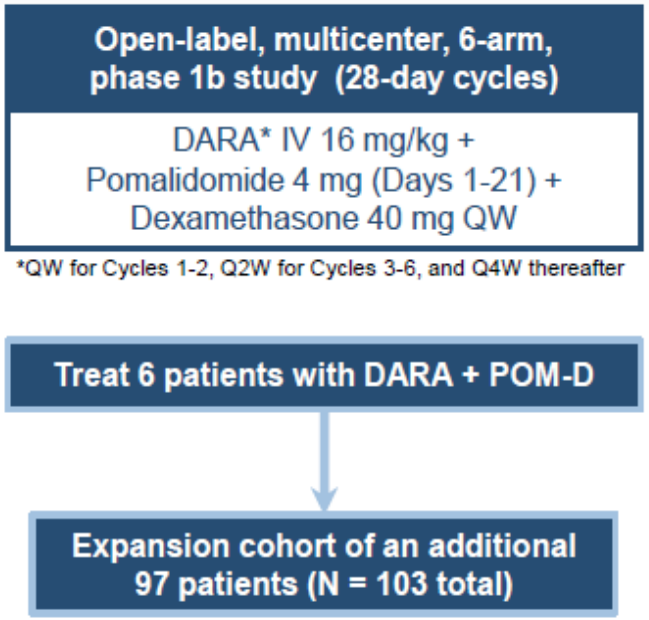


Christopher Chiu et al. Abstract 4531 ASH 2016

MMY1001: DARA + POM-D Cohort

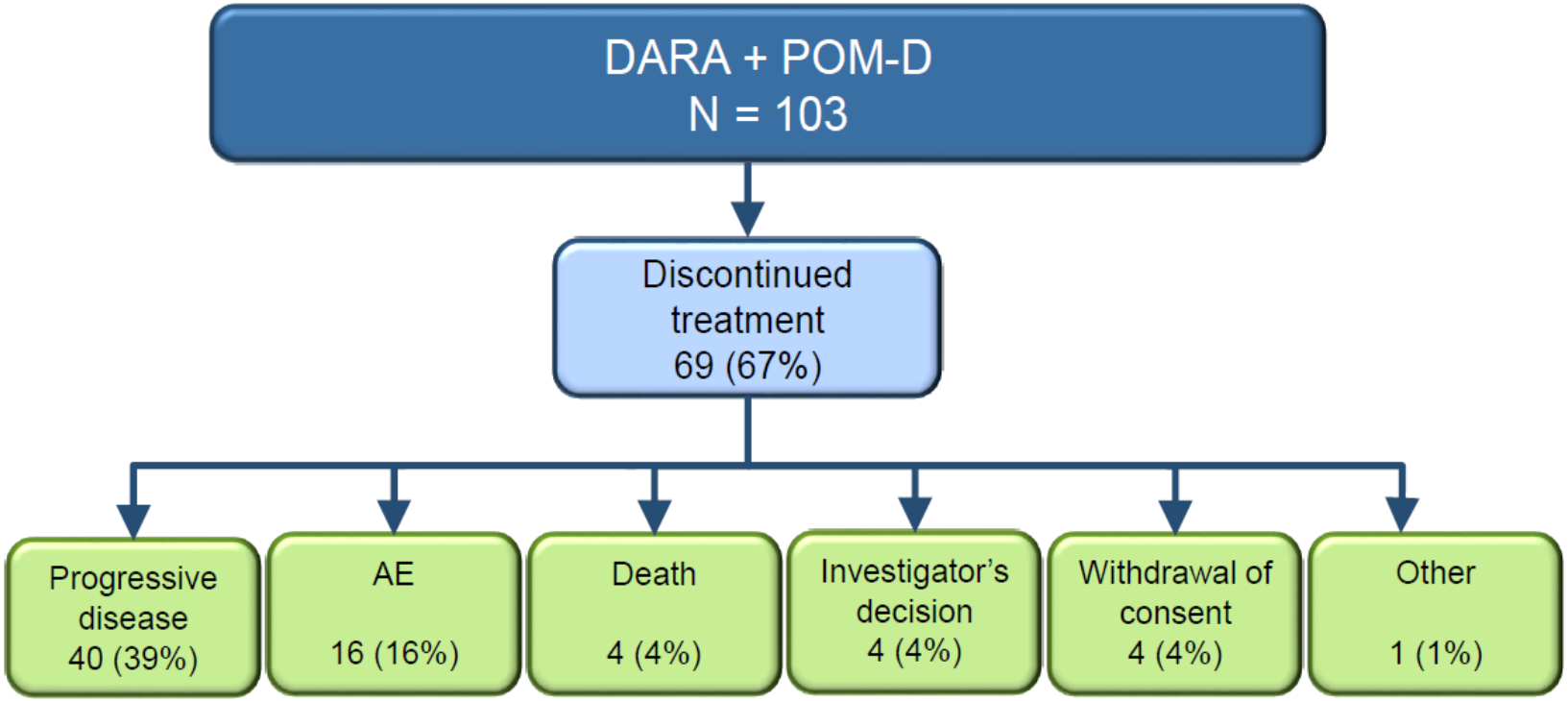
Eligibility criteria

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



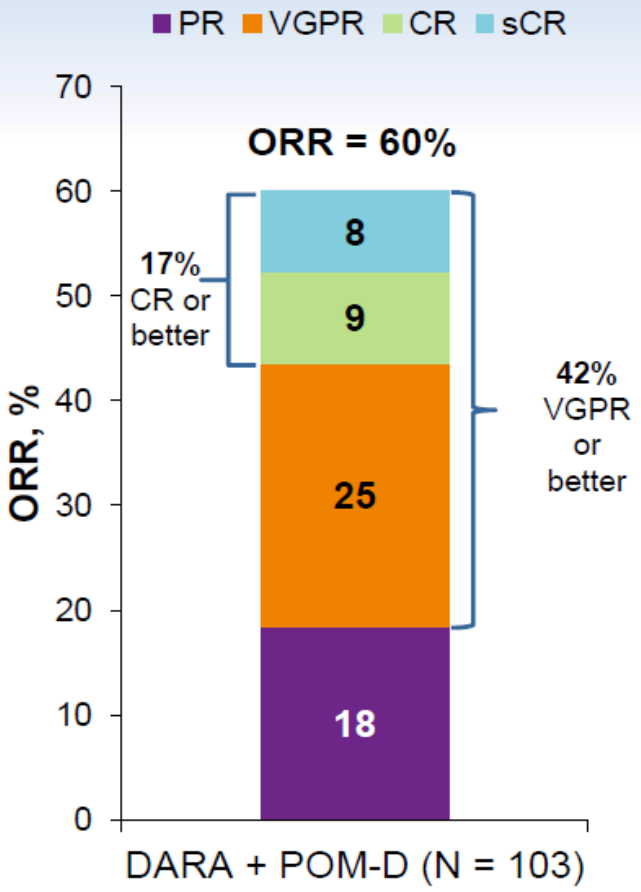
Patient Disposition: DARA + POM-D*

- Median follow-up: 13.1 months (range: 0.2-25.8)
- Median duration of treatment: 6.7 months (range: 0.03-20.0+)



ORR[a]: DARA + POM-D

	DARA + POM-D (N = 103)	
	n (%)	95% CI
ORR (sCR+CR+VGPR+PR)	**62 (60)**	**50.1-69.7**
Best response		
sCR	8 (8)	3.4-14.7
CR	9 (9)	4.1-15.9
VGPR	26 (25)	17.2-34.8
PR	19 (18)	11.5-27.3
MR	2 (2)	0.2-6.8
SD	26 (25)	17.2-34.8
PD	3 (3)	0.6-8.3
NE	10 (10)	4.8-17.1
VGPR or better (sCR+CR+VGPR)	43 (42)	32.1-51.9
CR or better (sCR+CR)	17 (17)	9.9-25.1

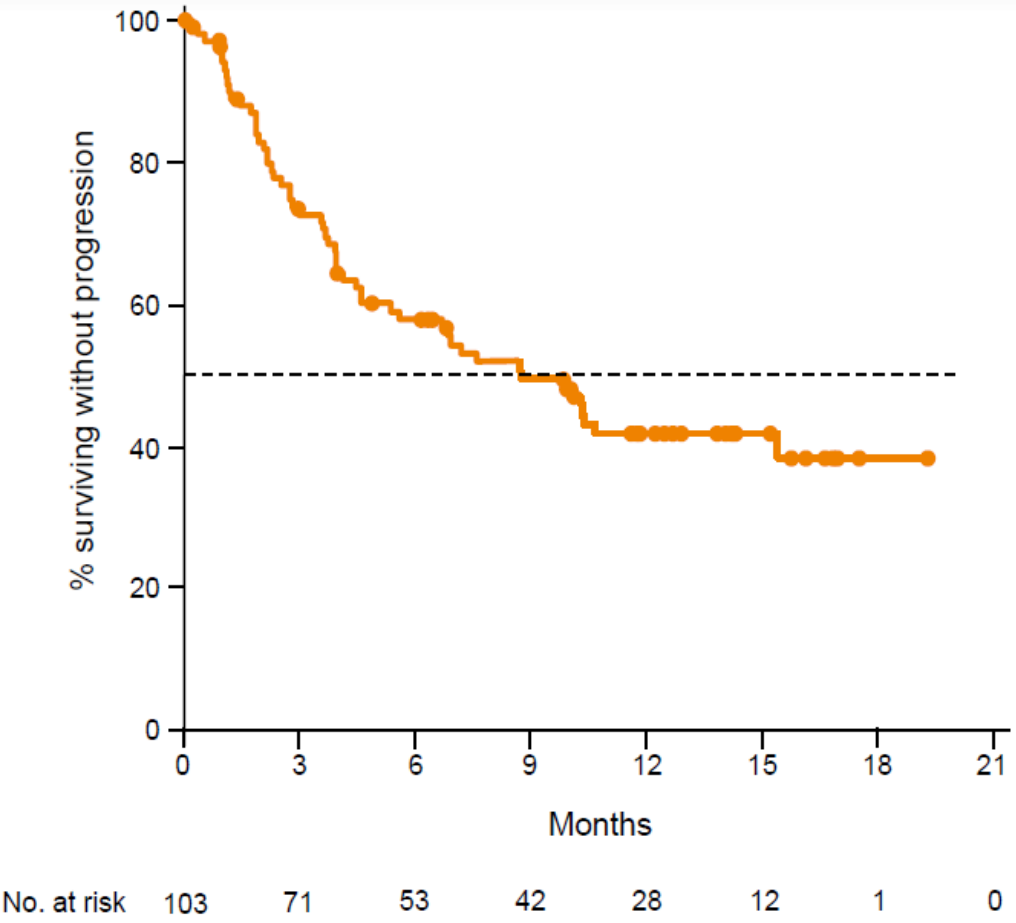


- Among patients with CR or better, the minimal residual disease negative rate at:
  - 10^{-4} threshold = 6/17 (35%)
  - 10^{-5} threshold = 5/17 (29%)
  - 10^{-6} threshold = 1/17 (6%)

Deep responses were observed with DARA + POM-D

ring board assessment. Daratumumab IFE reflex assay was used to mitigate DARA-mediated interference with assessment of CR

PFS: DARA + POM-D

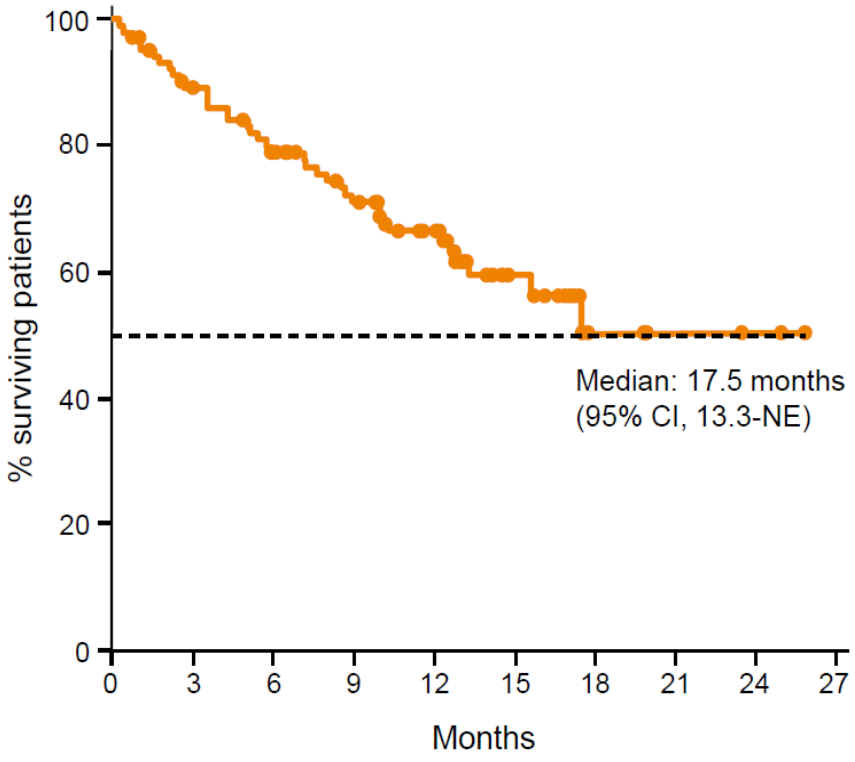


- Median PFS: 8.8 months (95% CI, 4.6-15.4)
- 6-month PFS rate: 57.8% (95% CI, 47.3-66.9)
- 12-month PFS rate: 41.9% (95% CI, 31.5-51.9)

~40% of patients maintain PFS after 1 year

OS: DARA + POM-D

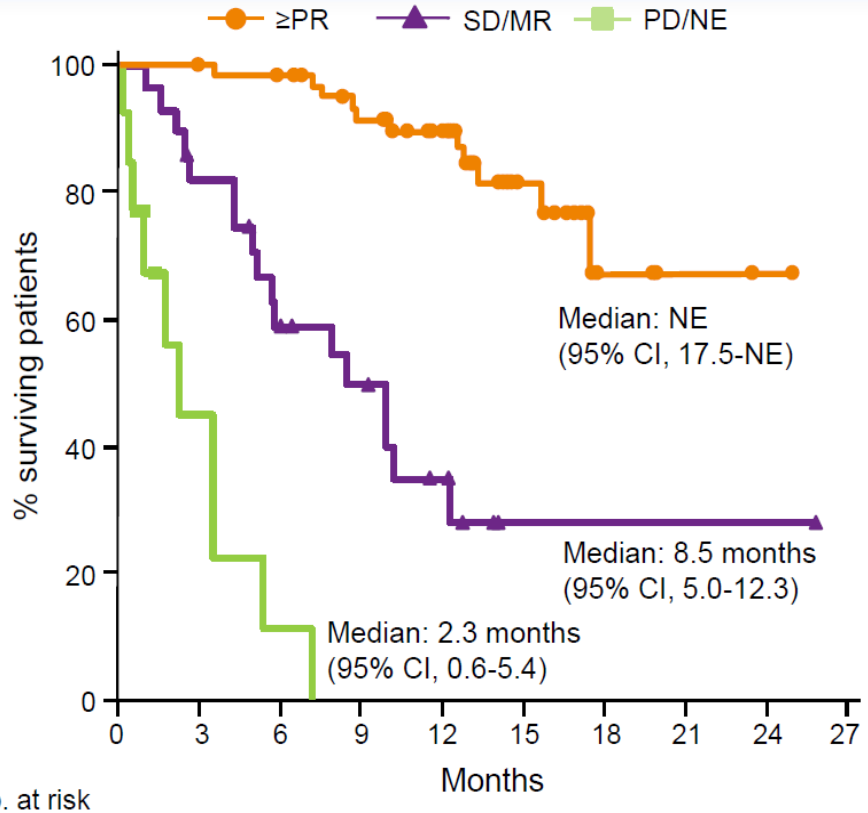
OS



No. at risk	103	88	75	63	49	18	5	3	2	0

- 12-month OS rate: 66.2% (95% CI, 55.6-74.8)

OS by Response Category



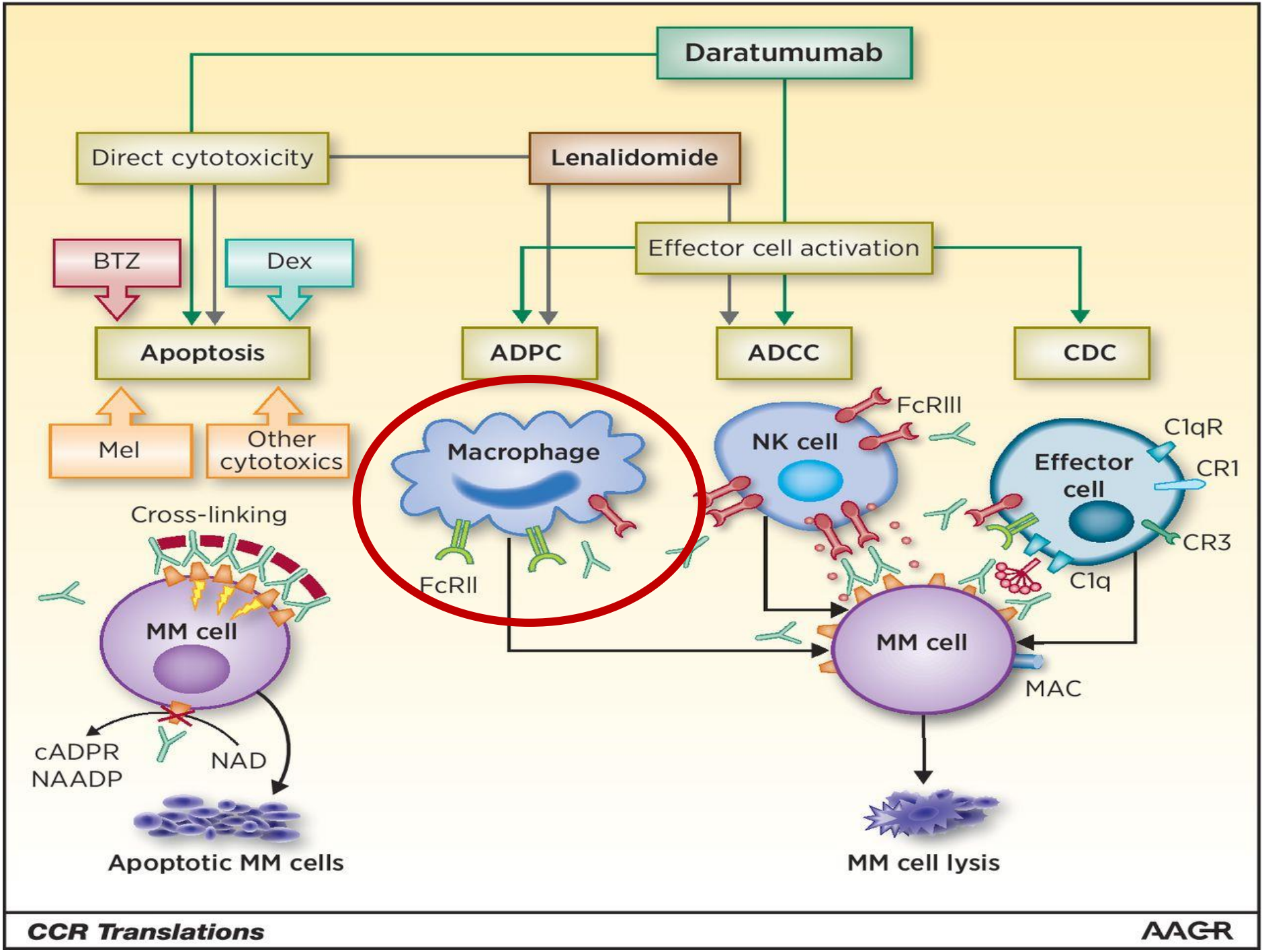
No. at risk										
≥PR	62	62	59	52	43	17	4	2	1	0
SD/MR	28	22	15	11	6	1	1	1	1	0
PD/NE	13	4	1	0	0	0	0	0	0	0

Patients with SD/MR derive survival benefit with DARA + POM-D

Conclusions: DARA + POM-D

- DARA can be safely combined with POM-D
  - High neutropenia rates in a population with 44% baseline neutropenia
  - Febrile neutropenia rates were consistent with POM-D alone
- DARA (16 mg/kg) + POM-D induced deep responses, including MRD negativity, in a heavily pretreated patient population
  - Median of 4 prior lines of therapy
  - 71% of patients were double refractory to a PI and an IMiD
  - High response rate is maintained in double-refractory and high-risk patients
- 40% of patients remain progression-free after 1 year
- The addition of DARA to POM-D is associated with encouraging OS

A phase 3 study is being planned

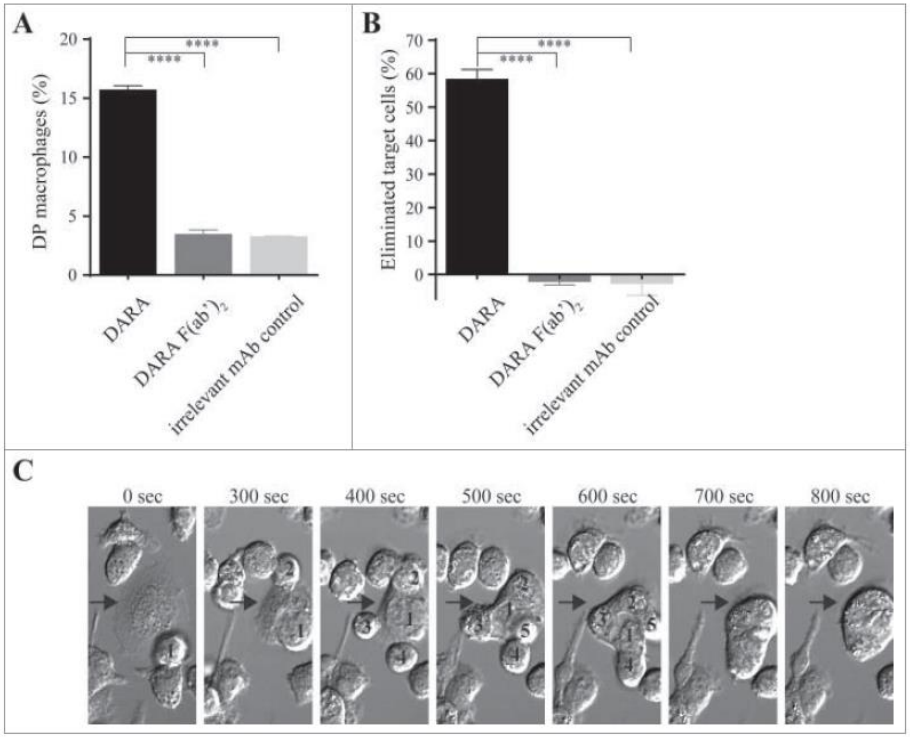

Daratumumab
Direct cytotoxicity
Lenalidomide
BTZ
Dex
Effector cell activation
Apoptosis
ADPC
ADCC
CDC
Mel
Other cytotoxics
Macrophage
FcRIII
NK cell
C1qR
CR1
Effector cell
CR3
C1q
Cross-linking
FcRII
MM cell
MM cell
MAC
cADPR
NAADP
NAD
Apoptotic MM cells
MM cell lysis

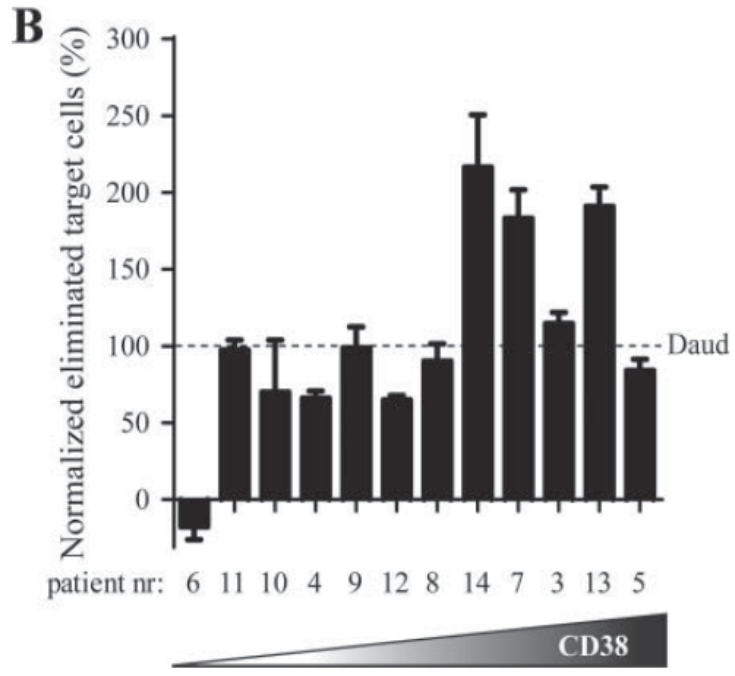
REPORT

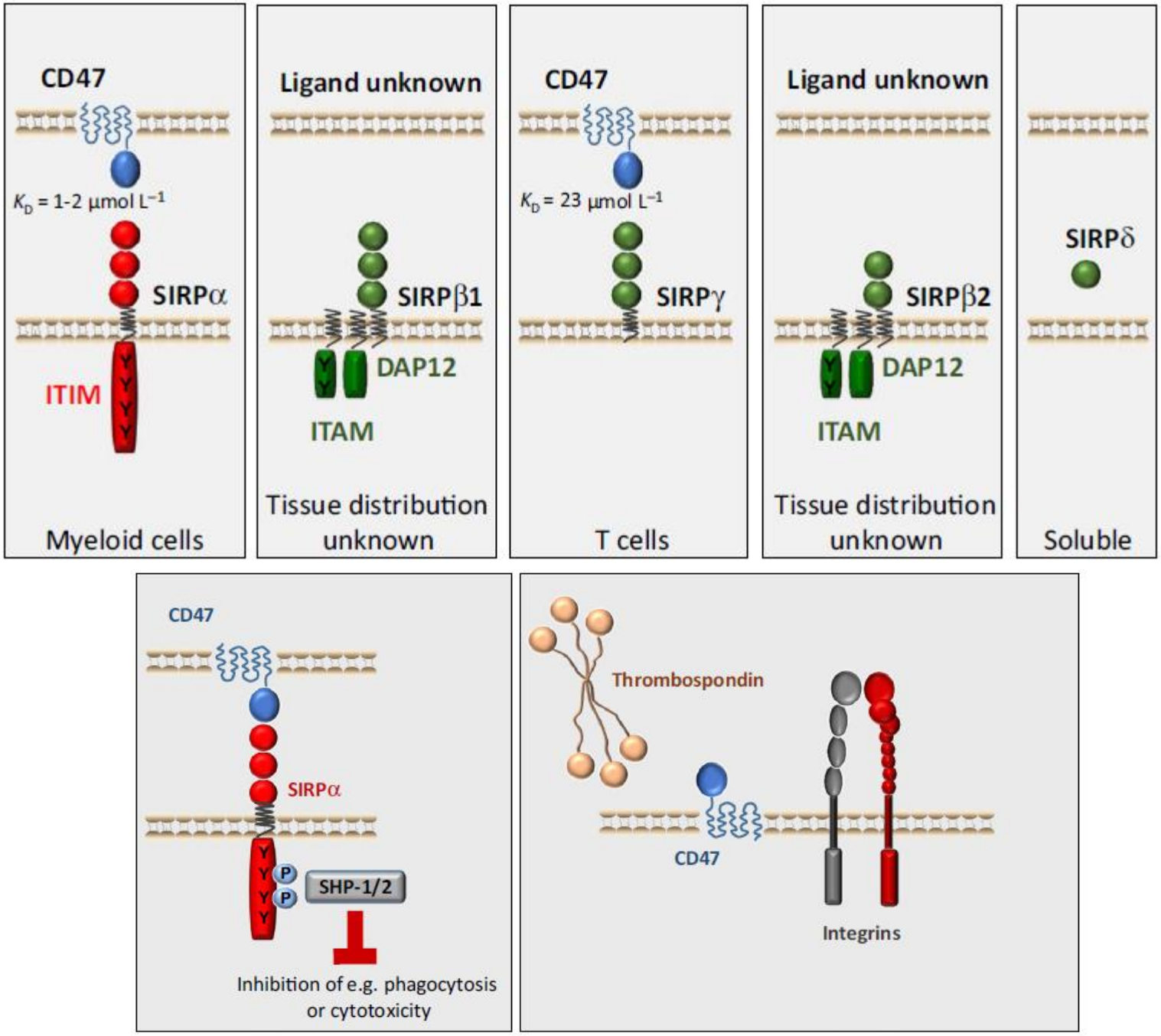
mAbs 7:2, 311–320; March/April 2015; Published with license by Taylor & Francis Group, LLC

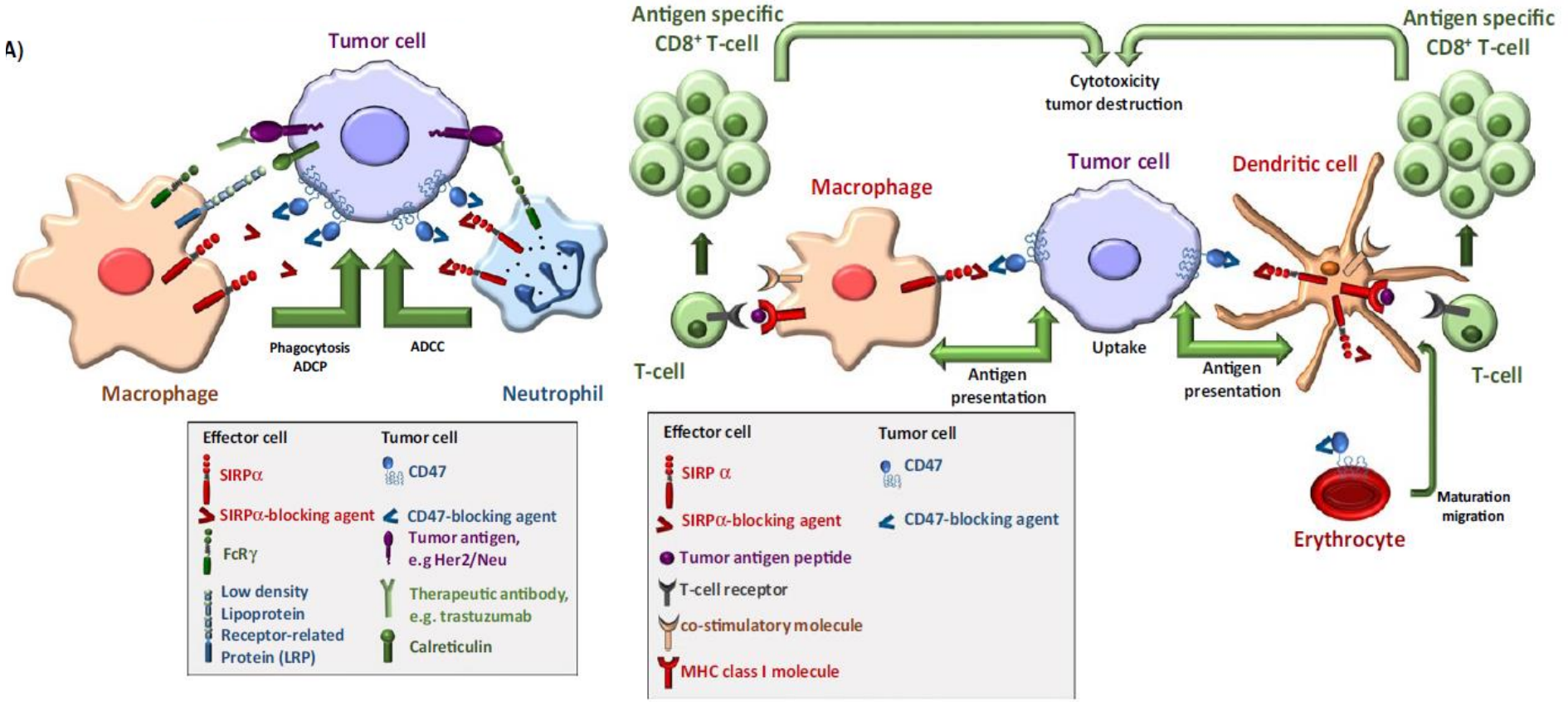
Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma

Marije B Overdijk[1], Sandra Verploegen[1], Marijn Bögels[2,3], Marjolein van Egmond[2,3], Jeroen J Lammerts van Bueren[1], Tuna Mutis[4], Richard WJ Groen[5], Esther Breij[1], Anton CM Martens[5,6], Wim K Bleeker[1], and Paul WHI Parren[1,7,8,*]






CD47
K_D = 1-2 µmol L^{-1}
SIRPα
ITIM
Myeloid cells
Ligand unknown
SIRPβ1
DAP12
ITAM
Tissue distribution unknown
CD47
K_D = 23 µmol L^{-1}
SIRPγ
T cells
Ligand unknown
SIRPβ2
DAP12
ITAM
Tissue distribution unknown
SIRPδ
Soluble
CD47
SIRPα
P
P
SHP-1/2
Inhibition of e.g. phagocytosis or cytotoxicity
Thrombospondin
CD47
Integrins


A)
Tumor cell
Phagocytosis
ADCP
ADCC
Macrophage
Neutrophil
Effector cell
SIRPα
SIRPα-blocking agent
FcRγ
Low density Lipoprotein Receptor-related Protein (LRP)
Tumor cell
CD47
CD47-blocking agent
Tumor antigen, e.g Her2/Neu
Therapeutic antibody, e.g. trastuzumab
Calreticulin
Antigen specific CD8+ T-cell
Cytotoxicity tumor destruction
Antigen specific CD8+ T-cell
Macrophage
Tumor cell
Dendritic cell
T-cell
Antigen presentation
Uptake
Antigen presentation
T-cell
Maturation migration
Erythrocyte
Effector cell
SIRP α
SIRPα-blocking agent
Tumor antigen peptide
T-cell receptor
co-stimulatory molecule
MHC class I molecule
Tumor cell
CD47
CD47-blocking agent

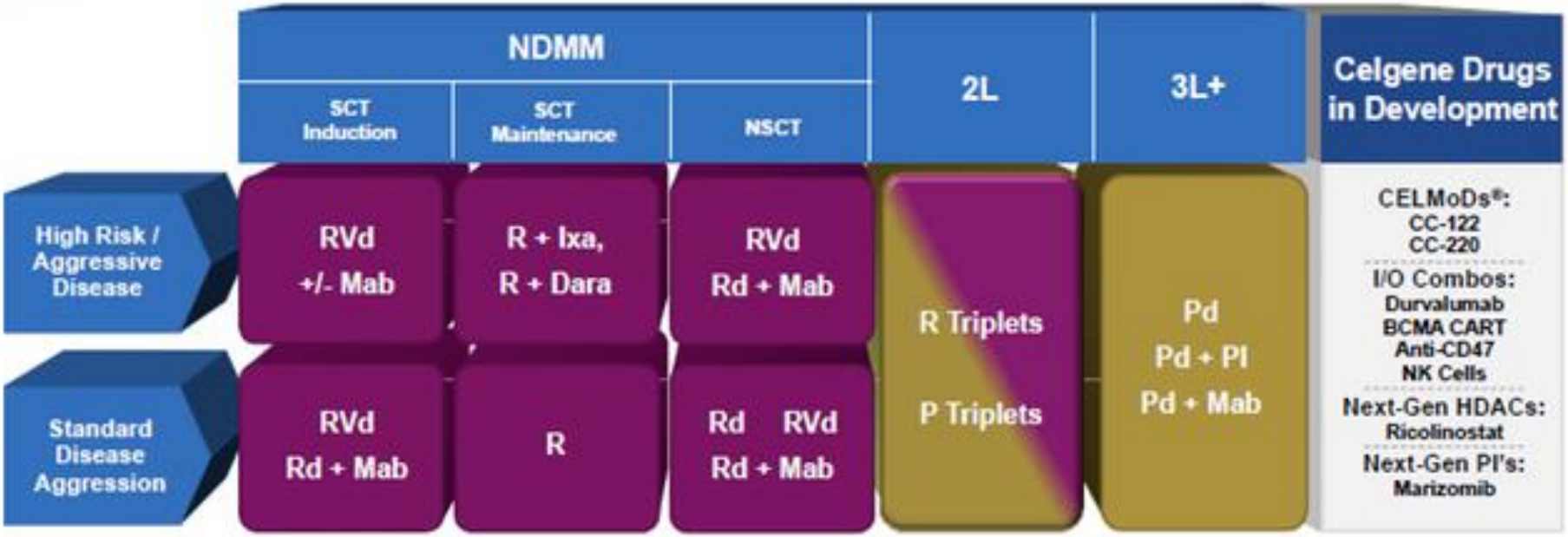
CD47-Targeting Drug Development

Agent (Industry developer)	Description	Tumor Types in Clinical Trials (all phase I) (Clinicaltrials.gov identifier)
Hu5F9-G4 (Forty Seven)	Humanized anti-CD47 monoclonal antibody	• Advanced solid tumors (NCT02216409) • CAMELLIA—Relapsed/refractory AML (NCT02678338)
CC-90002 (Celgene)	Humanized anti-CD47 monoclonal antibody	• Advanced solid and hematologic malignancies (NCT02367196) • AML and high-risk MDS (NCT02641002)
TTI-621 (Trillium Therapeutics)	Recombinant fusion protein incorporating the N-terminal CD47 binding domain of human SIRPα and the Fc domain of human IgG1	• Relapsed/refractory hematologic malignancies (NCT02663518) • Intratumoral injections in patients with relapsed/refractory solid tumors and mycosis fungoides (NCT02890368)

AML indicates acute myeloid leukemia; MDS, myleodysplastic syndrome; SIRPα, signal regulatory protein alpha.

Expanding Leadership in Multiple Myeloma

Building on the IMiD® Backbone Across All Lines of Multiple Myeloma



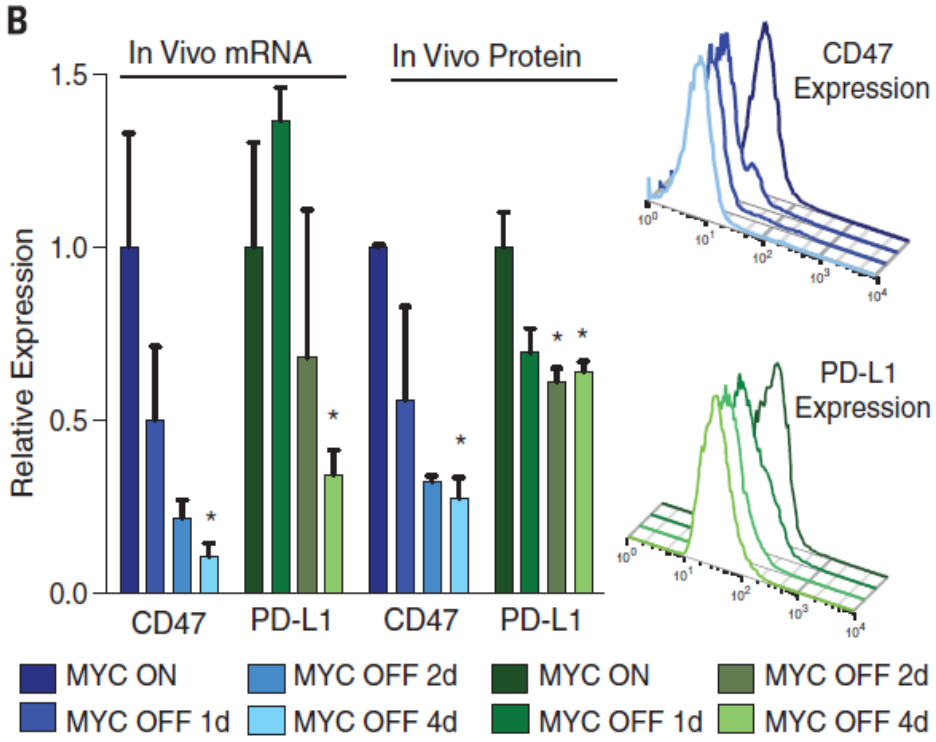
Note: Reflects currently approval and combinations under investigation

Market Realist

Source: Celgene Investor Presentation

MYC regulates the antitumor immune response through CD47 and PD-L1

Stephanie C. Casey,[1] Ling Tong,[1] Yulin Li,[1] Rachel Do,[1] Susanne Walz,[2] Kelly N. Fitzgerald,[1] Arvin M. Gouw,[1] Virginie Baylot,[1] Ines Gütgemann,[1,3] Martin Eilers,[2,4] Dean W. Felsher[1]*



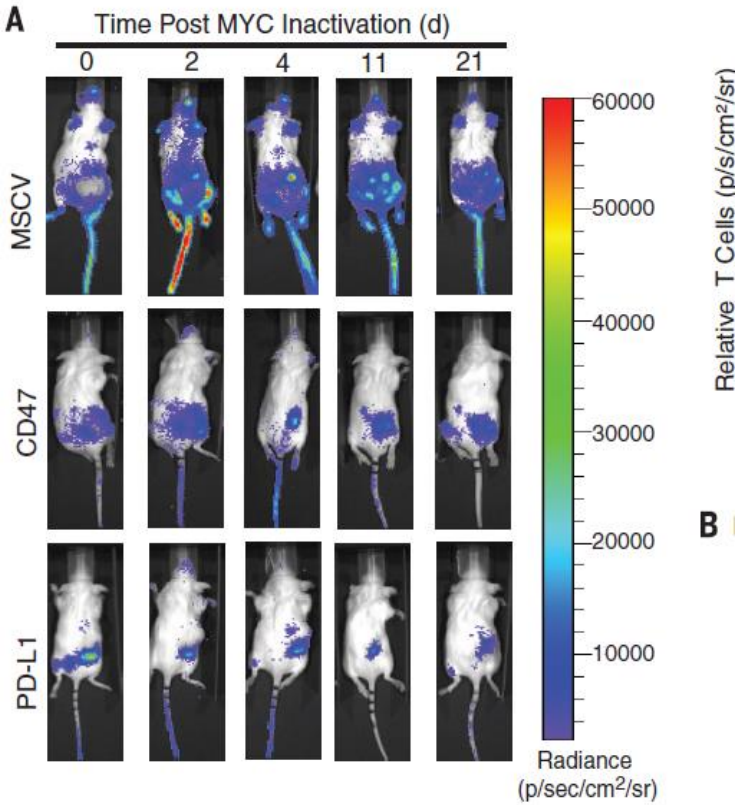
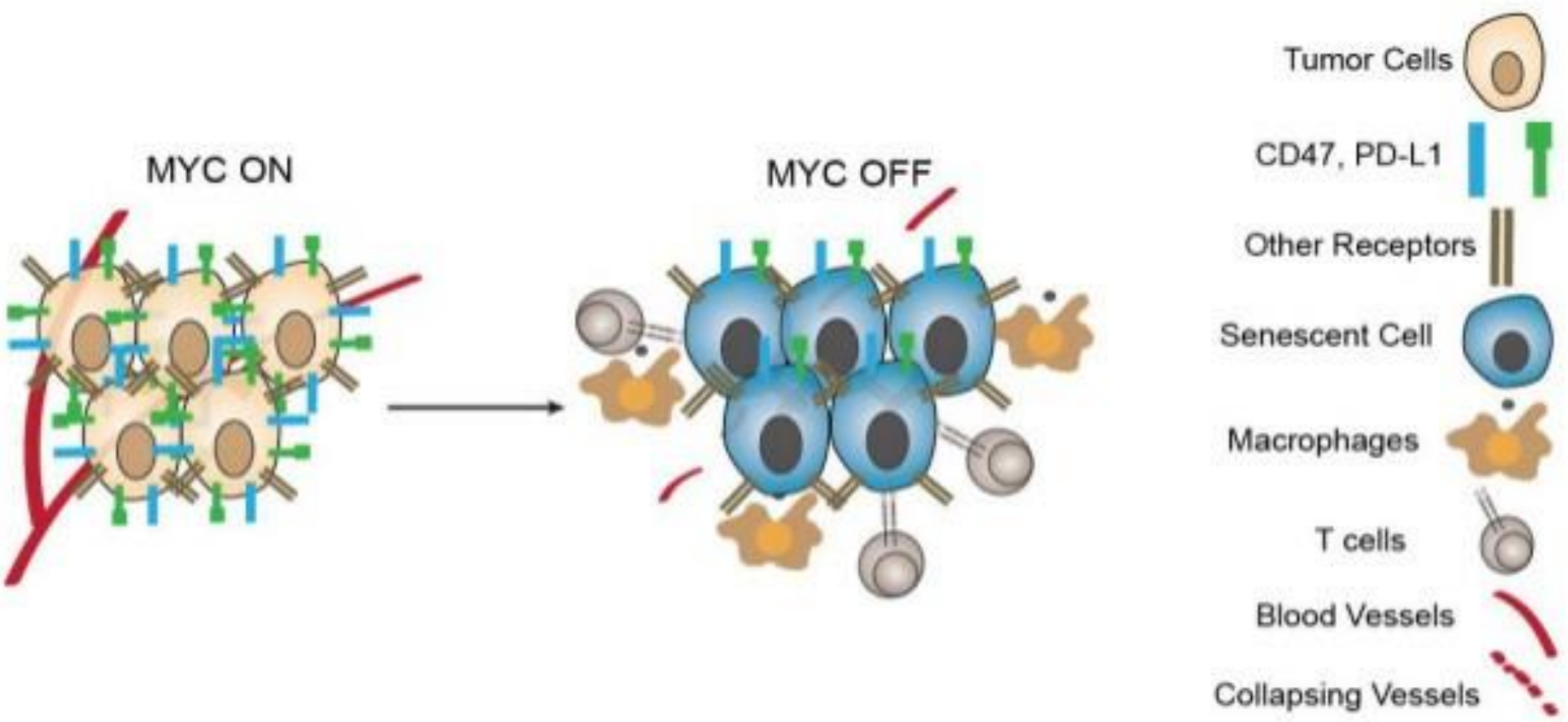


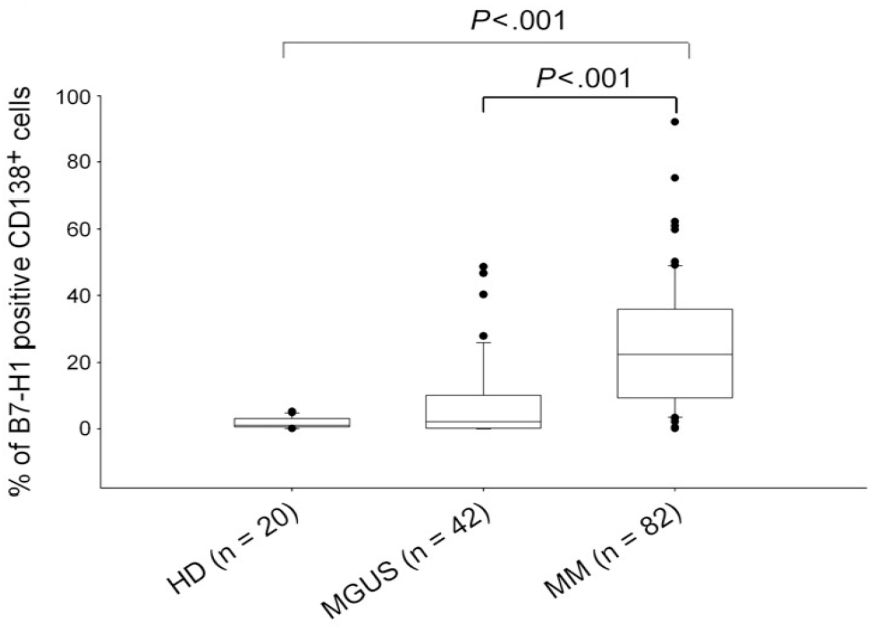
Fig. 3. Constitutive expression of CD47 and PD-L1 in mouse MYC T-ALL 4188 cells prevents recruitment of immune effectors after MYC inactivation. (**A**) Quantification of $CD4^+$ T cells in transplanted control (gray) or constitutive CD47- or PD-L1–expressing (colored) tumors

MYC regulates immune response through CD47 & PD-L1

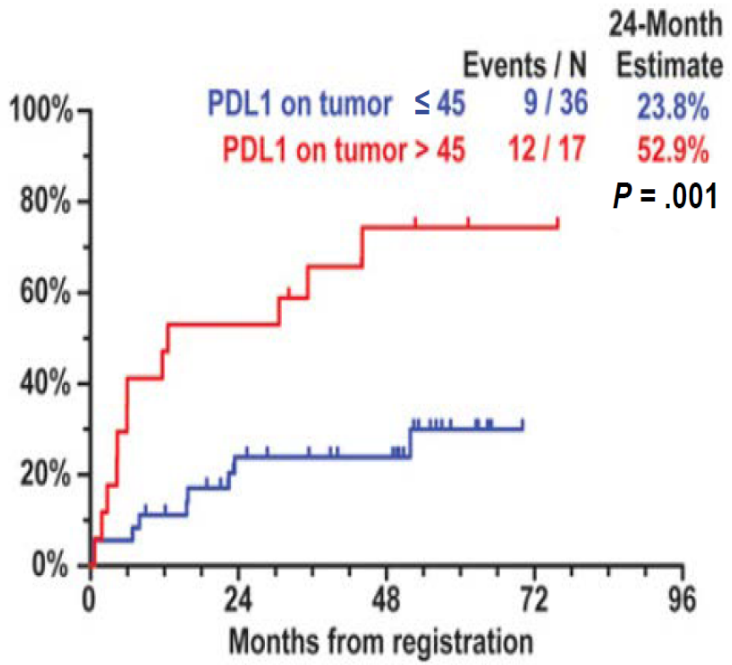


PD-L1 Expression in Myeloma

B7-H1 Expression Measured in CD138-Selected Cells



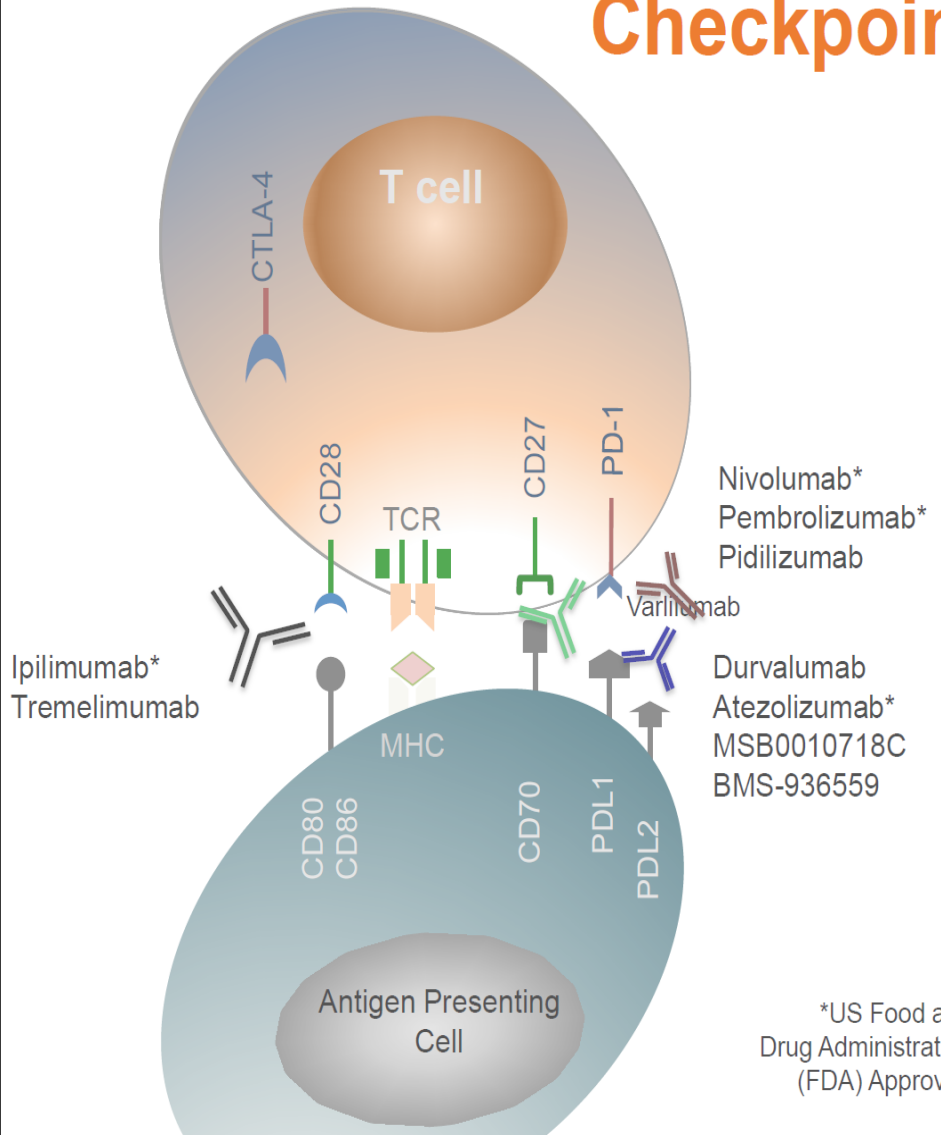
Time to MM Requiring Treatment from S0120 Registration by PD-L1 on Tumor



B7-H1, PD-L1, a B7-related protein that inhibits T-cell responses
HD, healthy donors; MGUS, monoclonal gammopathy of undetermined significance

Liu J, et al. *Blood.* 2007;110(1):296-304. Dhodapkar MV, et al. *Blood.* 2015;126(22):2475-2478.

Checkpoints and Agonists



*US Food and Drug Administration (FDA) Approved

Predictors of Clinical Activity
(based on solid tumor experience)

- Tumor antigen–specific T cells (neoantigens,[1,2] shared antigens[3])
- Antigen presentation[1,5]
- Evidence of immune recognition
  - Adaptive resistance[5,6]
- "Target expression" [4-6]

1.Snyder A, et al. *N Engl J Med.* 2014;371(23):2189-2199. 2. Rizvi NA, et al. *Science.* 2015;348(6230):124-128. 3. Yuan J, et al. *Proc Natl Acad Sci U S A.* 2011;108(40):16723-16728. 4. Tumeh PC, et al. *Nature.* 2014;515(7528):568-571. 5. Herbst RS, et al. *Nature.* 2014;515(7528):563-567. 6. Topalian SL, et al. *N Engl J Med.* 2012;366(26):2443-2454.

Clinical Activity of Nivolumab in Myeloma

- **Some responses in non-Hodgkin lymphoma (NHL)**
- **Limited efficacy in relapsed multiple myeloma**

Tumor	OR, n (%)	CR, n (%)	PR, n (%)	SD, n (%)
B-cell lymphoma (n = 31)	8 (26)	3 (10)	5 (16)	16 (52)
DLCBL (n = 11)	4 (36)	2 (18)	2 (18)	3 (27)
FL (n = 10)	4 (40)	1 (10)	3 (30)	6 (60)
Other B-cell lymphoma (n = 10)	0	0	0	7 (70)
T-cell lymphoma (n = 23)	4 (17)	0	4 (17)	10 (43)
MF (n = 13)	2 (15)	0	2 (15)	9 (69)
PTCL (n = 5)	2 (40)	0	2 (40)	0
Other CTCL (n = 3)	0	0	0	0
Other non-CTCL (n = 2)	0	0	0	1 (50)
Multiple myeloma (n = 27)	1 (4)	1 (4)*	0	17 (63)

CR, complete response; CTCL, cutaneous T-cell lymphoma; DLCBL, diffuse large b-cell lymphoma; FL, follicular lymphoma; MF, mycosis fungoides; OR, overall response; PR, partial response; PTCL, peripheral t-cell lymphoma; SD, stable disease

Lesokhin AM, et al. *J Clin Oncol.* 2016;34(23):2698-2704.

Pembrolizumab in Combination With Lenalidomide and Low-Dose Dexamethasone for Relapsed/Refractory Multiple Myeloma: Final Efficacy and Safety Analysis

KEYNOTE 023

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Mateos M-V, et al. *J Clin Oncol.* 2016;34(suppl): Abstract 8010.

Antitumor Activity—Central Review (IMWG 2006)

Best Overall Response n (%)	Efficacy Population† (n = 40)	Lenalidomide Refractory (n = 29)
ORR	**20 (50)**	**11 (38)**
Stringent CR (sCR)	1 (3)	1 (3)
Very good PR (VGPR)	5 (13)	3 (10)
PR	14 (35)	7 (24)
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)

Mateos M-V, et al. *J Clin Oncol.* 2016;34(suppl): Abstract 8010.

KEYNOTE 185: Study Design

- **An open-label, randomized phase III trial in newly diagnosed multiple myeloma (NDMM)**

Key eligibility criteria

- NDMM
- <65 years of age
- ECOG 0-1

RANDOMIZE

Pembrolizumab 200 mg IV
Day 1 Q3W
Lenalidomide 25 mg PO
Day 1-21
Dexamethasone 40 mg PO
Weekly

Lenalidomide 25 mg PO
Day 1-21
Dexamethasone 40 mg PO
Weekly

Cycles repeat every 28 days

- **Primary endpoint: PFS up to 41 months**
- **Secondary endpoint: OS up to 341 months**

Summary of Responses

Response Category	Evaluable Patients (N = 45)		Double Refractory (N = 32)		High-Risk Cytogenetics (N = 27)	
Overall response, n (%)	29 (65)		22 (68)		15 (56)	
Clinical benefit, n (%)	32 (72)		23 (69)		16 (60)	
Best response, n (%)						
sCR	3 (7)		1 (3)		2 (7)	
CR	1 (2)	29%	1 (3)	24%	1 (4)	15%
VCPR	9 (20)		6 (18)		1 (4)	
PR	16 (36)		14 (44)		11 (41)	
MR	3 (7)		1 (3)		1 (4)	
SD	11 (23)		7 (22)		9 (31)	
PD	2 (5)		2 (4)		2 (7)	

Badros A, et al. *Blood.* 2016;128: Abstract 490.

KEYNOTE 183: Study Design

- **An open-label, randomized phase III trial in relapsed and refractory multiple myeloma (RRMM)**

Key eligibility criteria

- RRMM
- ≥2 lines of prior therapy incl IMiD and PI or in combination
- ECOG 0-1

RANDOMIZE

Pembrolizumab 200 mg IV
Day 1 Q3W
Pomalidomide 4 mg PO
Day 1-21
Dexamethasone 40 mg PO
Day 1, 8, 15, 22

Pomalidomide 4 mg PO
Day 1-21
Dexamethasone 40 mg PO
Day 1, 8, 15, 22

Cycles repeat every 28 days

- **Primary endpoint: PFS up to 33 months**
- **Secondary endpoint: OS up to 33 months**

National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/ NCT02576977. Accessed: February 22, 2017.

Ongoing Clinical Trials Evaluating Checkpoint blockade in Combination with IMiD in Myeloma

Table 2. Selected immune checkpoint blockers under clinical trials.

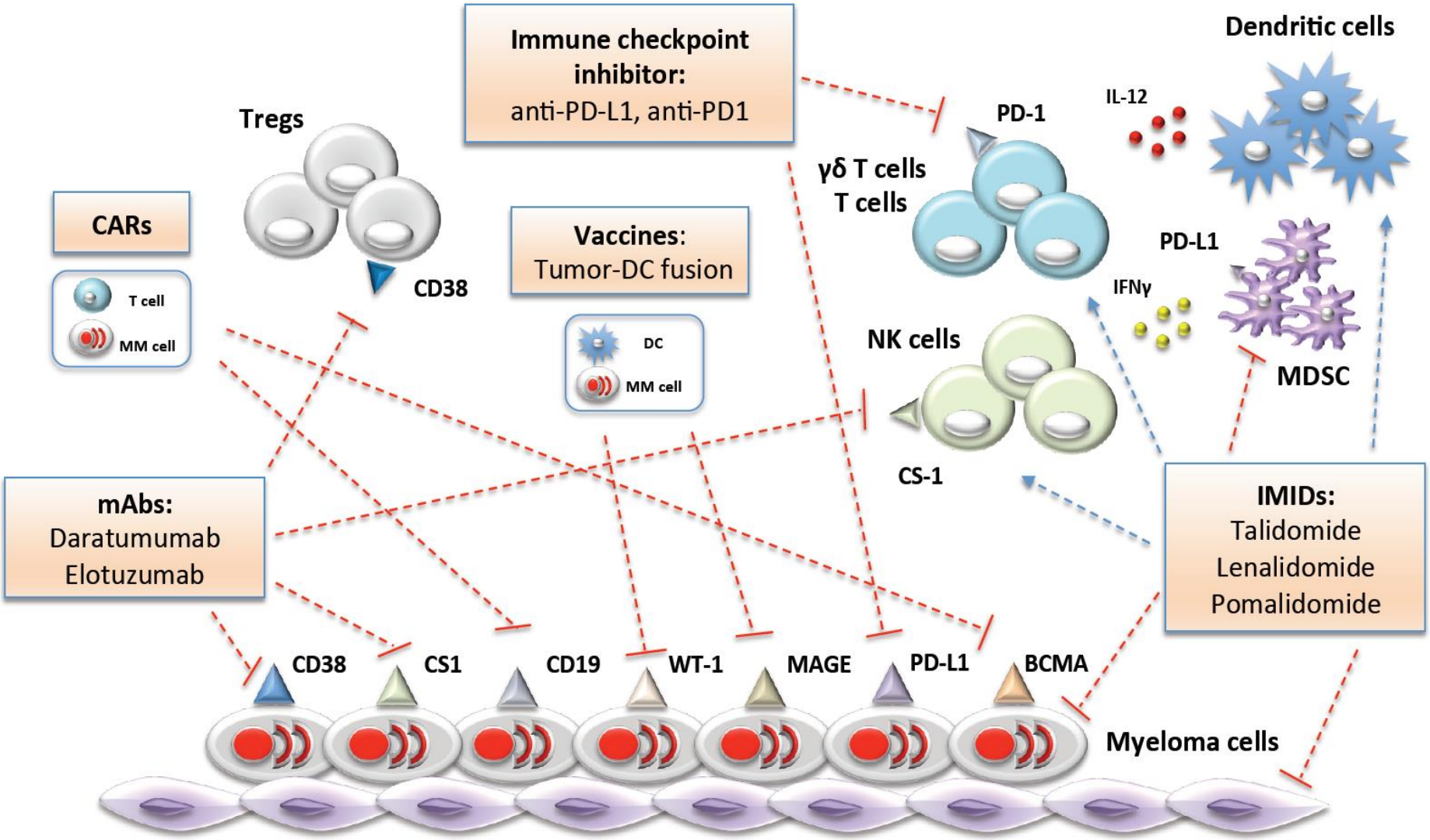
Setting	PD1 Antibody	IMiD	Additional Intervention	Phase	Status	Identifier
NDMM	Pembrolizumab	Lenalidomide	n/a	III	R	NCT02579863
RRMM	Pembrolizumab	Lenalidomide	n/a	I	R	NCT02036502
RRMM	Pembrolizumab	Pomalidomide	n/a	I/II	R	NCT02289222
RRMM	Pembrolizumab	Pomalidomide	n/a	III	R	NCT02576977
RRMM	Pidilizumab	Lenalidomide	n/a	I/II	R	NCT02077959
Post ASCT	Pembrolizumab	Lenalidomide	n/a	II	R	NCT02331368
RRMM	Nivolumab	n/a	Ipilimumab Lirilumab	I	R	NCT01592370
Post ASCT	Pidilizumab	n/a	DC/MM	II	ONR	NCT01067287
Locally advanced/metastatic solid tumors or hematological malignancies	MPDL3280A	n/a	n/a	I	R	NCT01375842
MM	MPDL3280A	Lenalidomide	n/a	Ib	R	NCT02431208

NDMM: Newly diagnosed multiple myeloma; RRMM: Relapsed refractory multiple myeloma; ASCT: Autologous stem cell transplantation; R: Recruiting; U: Unknown; C: Completed; ONR: Ongoing, not recruiting; W: Withdrawn prior to enrollment; n/a : not applicable.

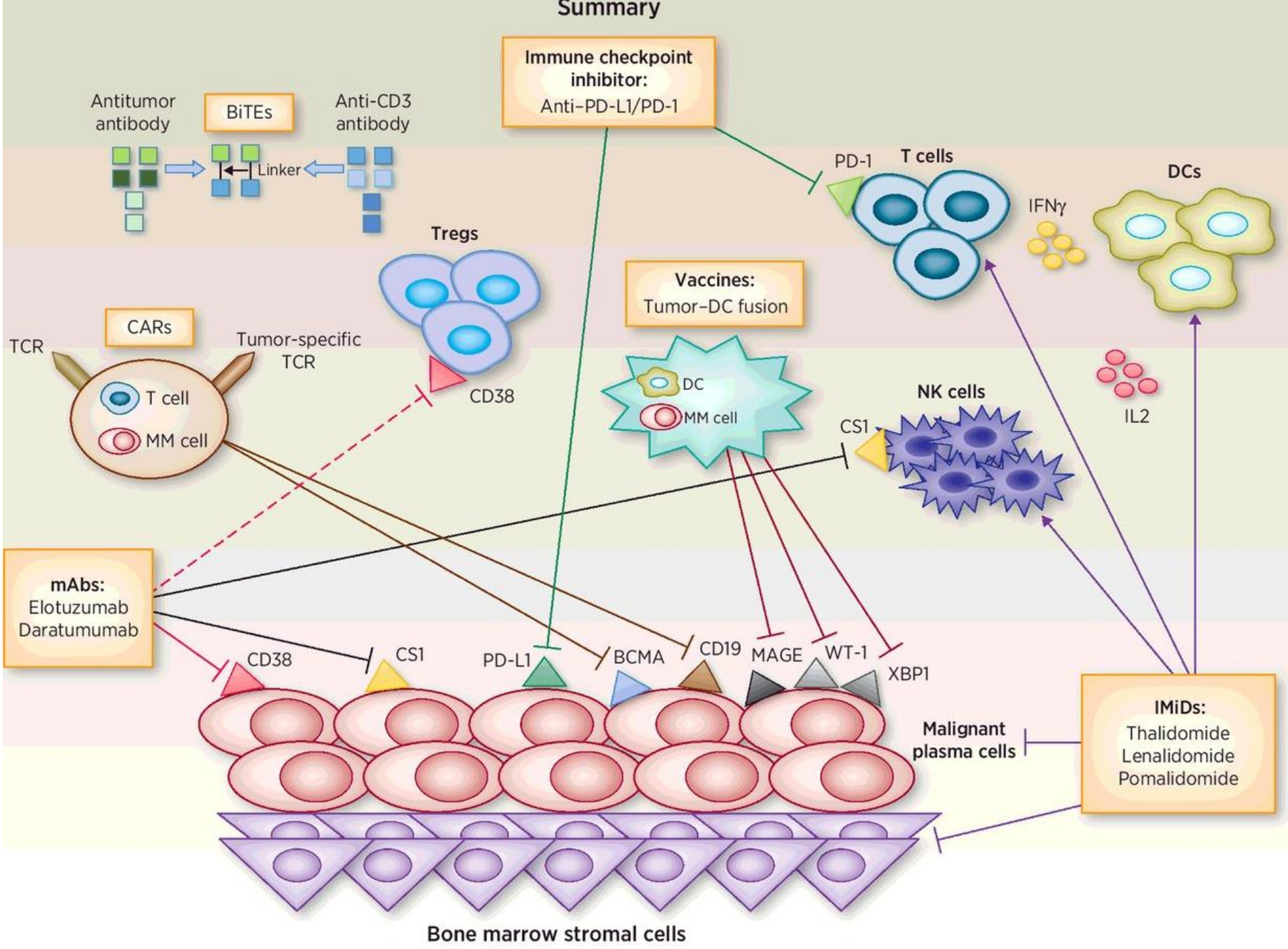
PD-1 Pathway Blockade Combined With Daratumumab +/- IMiDs is an Area of Active Research

- **NCT02431208 (Genentech-Roche)**
  - A Phase Ib Study of the Safety and Pharmacokinetics of Atezolizumab (Anti-PD-L1 Antibody) Alone or in Combination With an Immunomodulatory Drug and/or Daratumumab in Patients With Multiple Myeloma (Relapsed/Refractory and Post-Autologous Stem Cell Transplantation)
- **NCT02807454 (Medimmune-Celgene)**
  - A Phase 2, Multicenter, Open-label, Study to Determine the Safety and Efficacy for the Combination of Durvalumab (DURVA) and Daratumumab (DARA) (D2) in Subjects With Relapsed and Refractory Multiple Myeloma (RRMM)
- **NCT01592370 (BMS)**
  - Multiple Phase 1 Safety Cohorts of Nivolumab Monotherapy or Nivolumab Combination Regimens Across Relapsed/Refractory Hematologic Malignancies

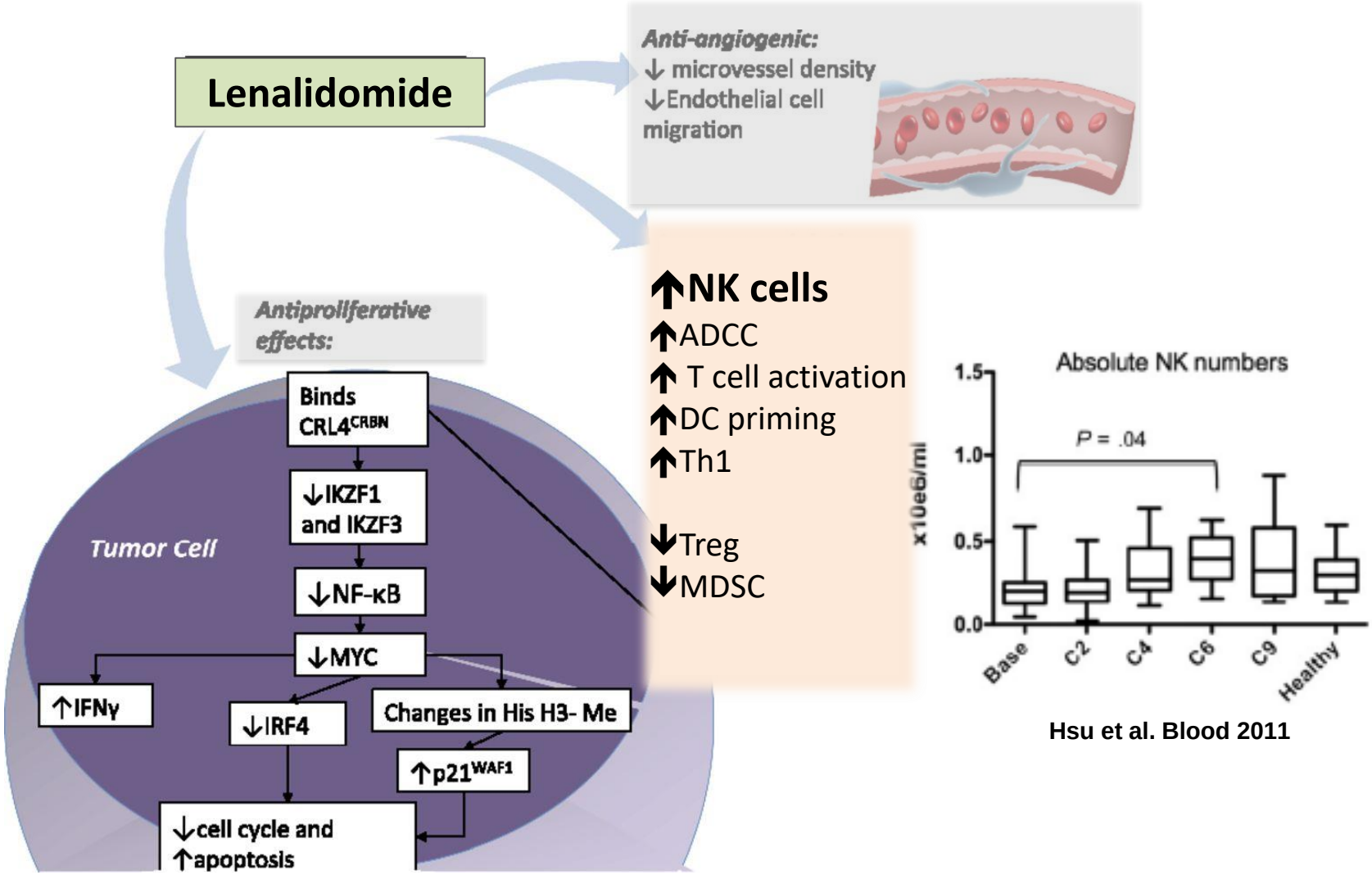
National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT02431208. Accessed: February 22, 2017.
National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT02807454. Accessed: February 22, 2017.
National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT01592370. Accessed: February 22, 2017.



Adapted from Neri P., *Clin Cancer Res 2016* ; 22(24):5959-5965


Summary
Immune checkpoint inhibitor:
Anti–PD-L1/PD-1
Antitumor antibody
BiTEs
Anti-CD3 antibody
Linker
PD-1
T cells
DCs
IFNγ
Tregs
Vaccines:
Tumor–DC fusion
CARs
TCR
Tumor-specific TCR
T cell
MM cell
CD38
DC
MM cell
NK cells
CS1
IL2
mAbs:
Elotuzumab
Daratumumab
CD38
CS1
PD-L1
BCMA
CD19
MAGE
WT-1
XBP1
Malignant plasma cells
IMiDs:
Thalidomide
Lenalidomide
Pomalidomide
Bone marrow stromal cells

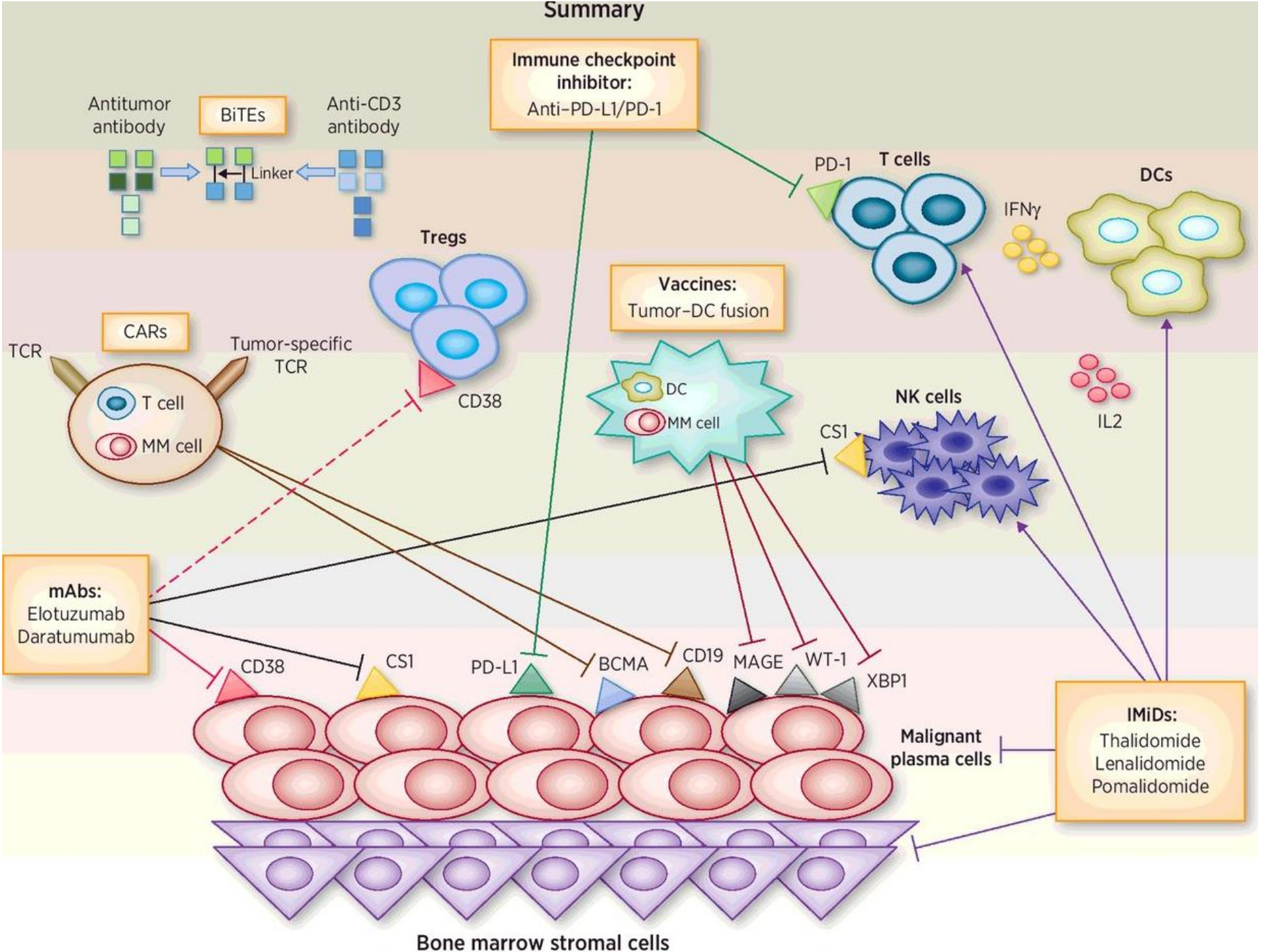
Rationale for combination therapy with immunomodulating mAb and lenalidomide



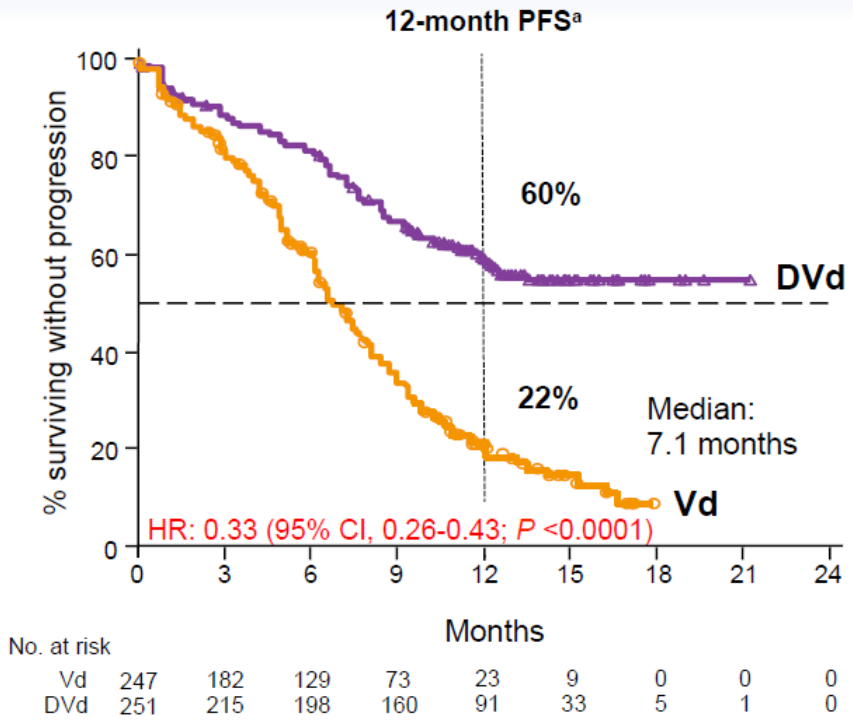
Kritharis et al. Blood 2015

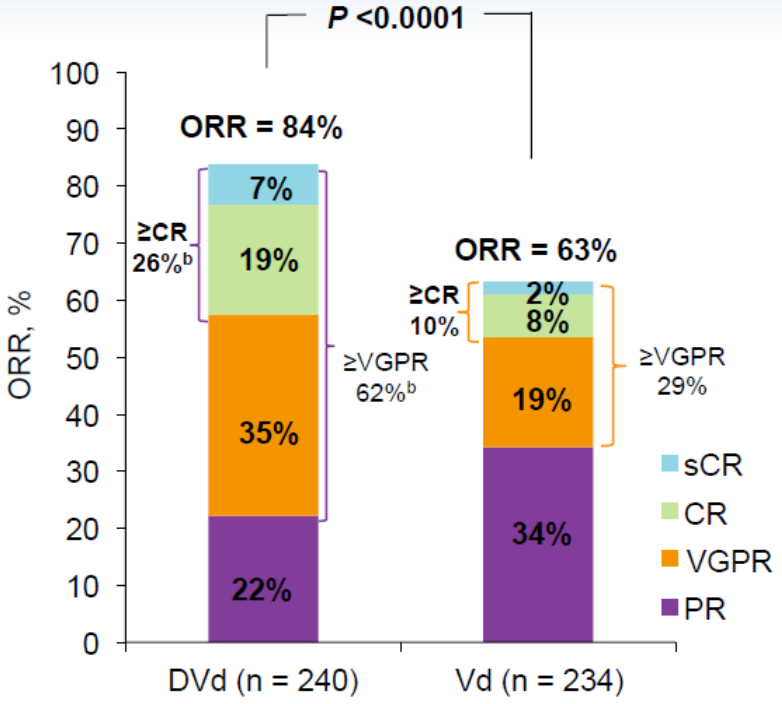
Hsu et al. Blood 2011

blood


Summary
Immune checkpoint inhibitor: Anti–PD-L1/PD-1
Antitumor antibody
BiTEs
Anti-CD3 antibody
Linker
PD-1
T cells
DCs
IFNγ
Tregs
Vaccines: Tumor–DC fusion
CARs
TCR
Tumor-specific TCR
T cell
MM cell
CD38
DC
MM cell
NK cells
CS1
IL2
mAbs: Elotuzumab Daratumumab
CD38
CS1
PD-L1
BCMA
CD19
MAGE
WT-1
XBP1
Malignant plasma cells
IMiDs: Thalidomide Lenalidomide Pomalidomide
Bone marrow stromal cells

Updated Efficacy





- 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.
Kaplan-Meier estimate.
P <0.0001 for DVd versus Vd.