Beyond the horizon

New treatment strategies for multiple myeloma

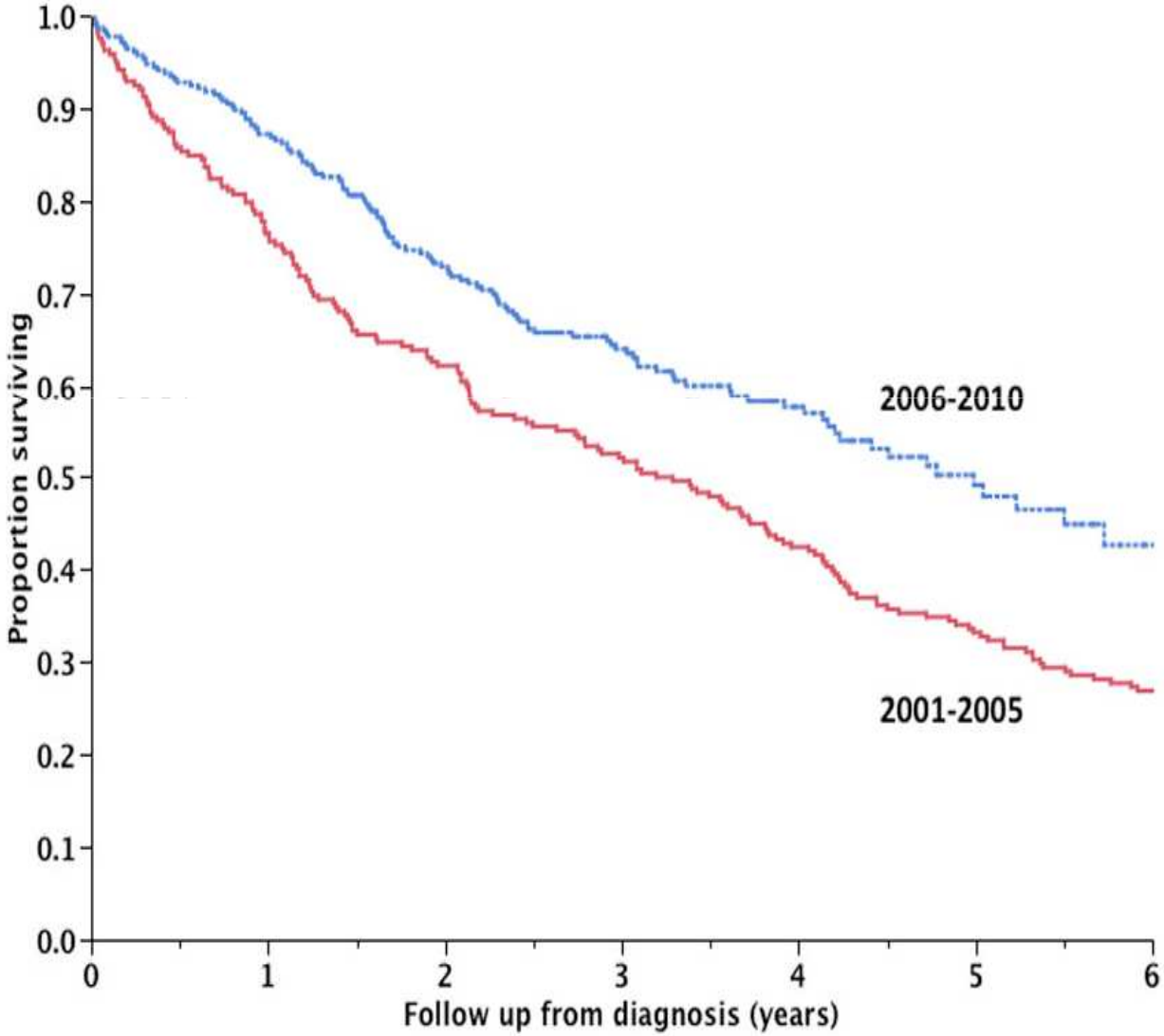
Dominik Dytfeld

March the 14th 2019

Disclosures for Dominik Dytfeld

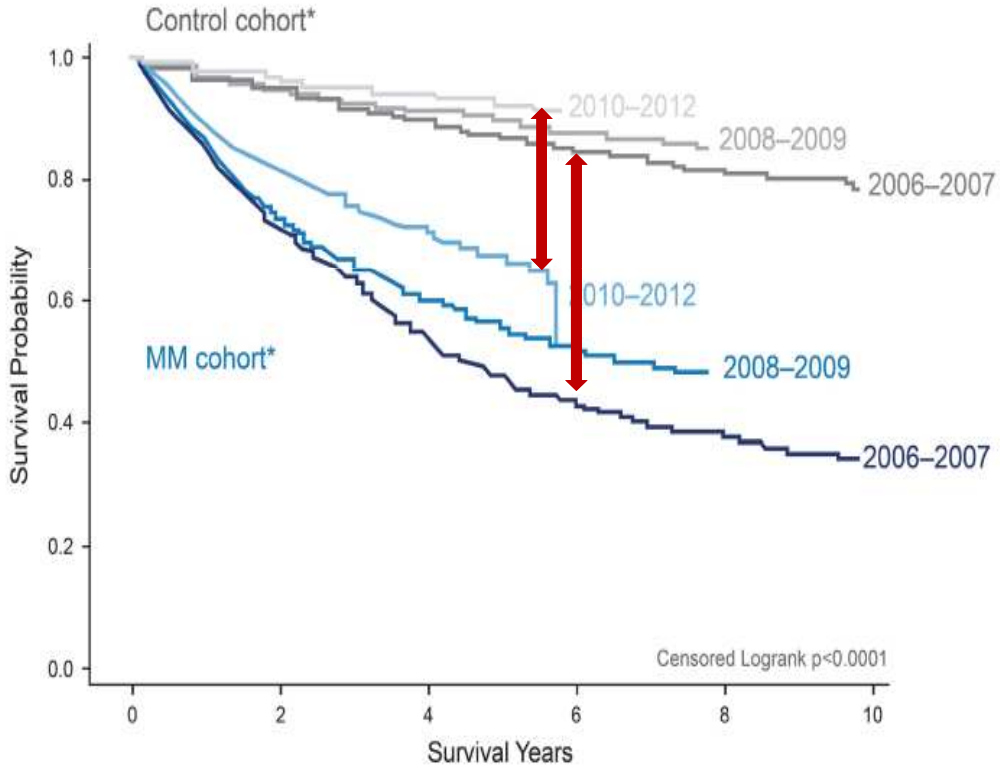
Research Support	Janssen, Celgene, Amgen
Employee	N/A
Consultant	N/A
Major Stockholder	N/A
Speakers' Bureau/ Scientific Advisory Board	Janssen, Amgen, Novartis, Celgene, Takeda, Abbvie

Improved outcome after introduction of bortezomib and lenalidomide



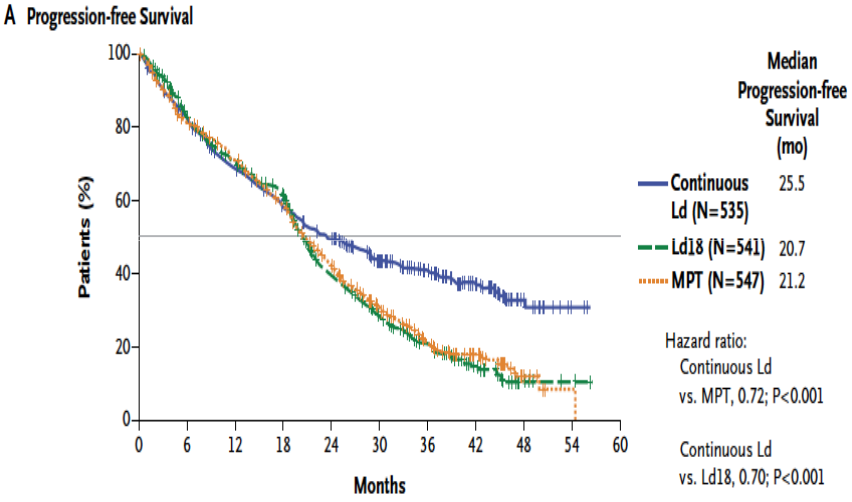
Kumar, 2014

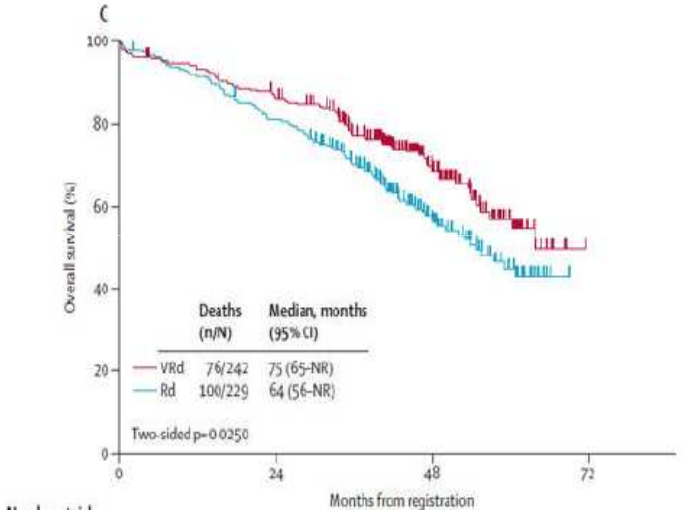
….. but still the there is a **gap**…



Fonseca, 2017

Further improvement can be achieved by bringing the most **effective** treatment **upfront….**



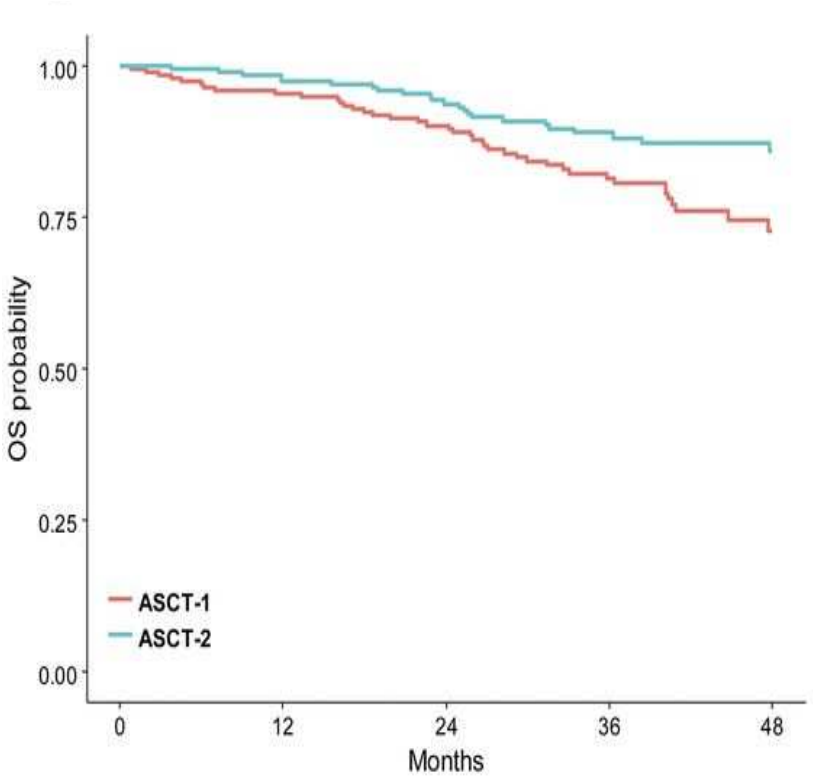


RD vs MPT vs MP frontline

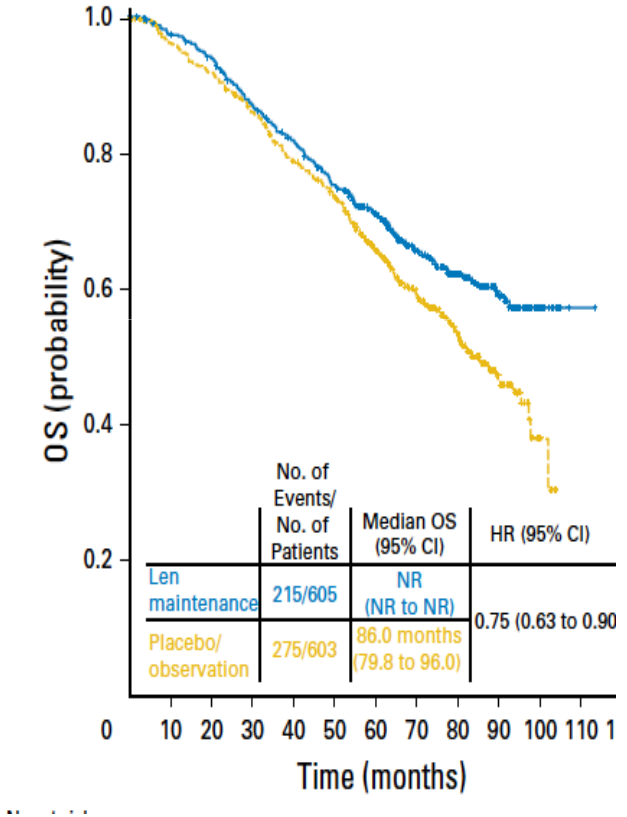
RVD vs RD frontline

Benboubker, 2014
Durie, 2017

… and by **intensifing** it and keep it **continuously**



Double vs single transplant

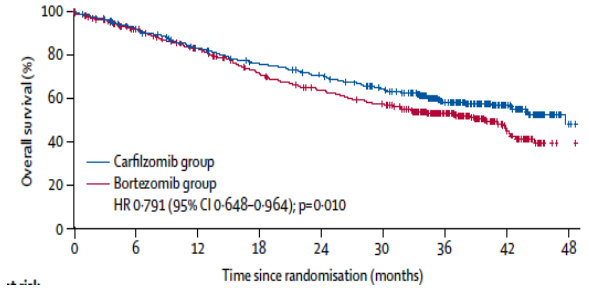


R maintenance

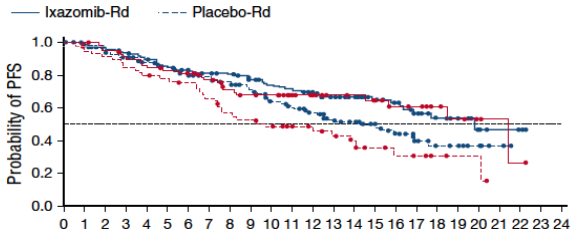
MacCarthy, 2017
Cavo, 2017

…and by introduction of **new generations** of existing drugs

Carfilzomib 2nd generation PI **prolongs survival**

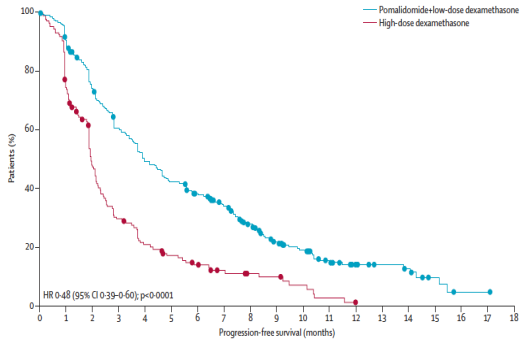


Ixasomib first oral PI **breaks high risk**



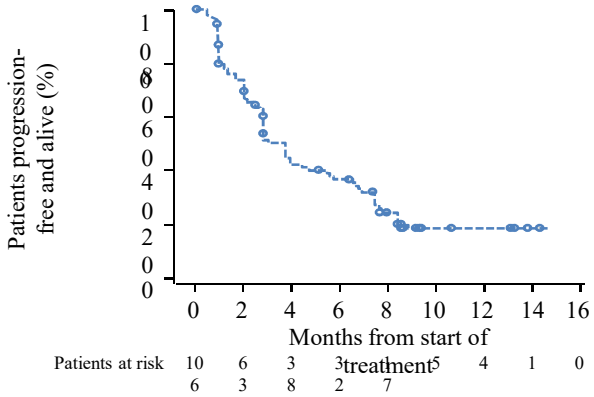
Pomalidomid 3rd generation IMID works in **advanced disease**

Dimopoulos, 2014 and 2017
San Miquel, 2013

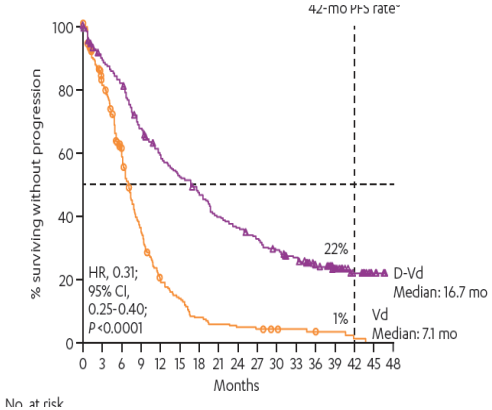


…and monoclonal antibodies expected for soooo long

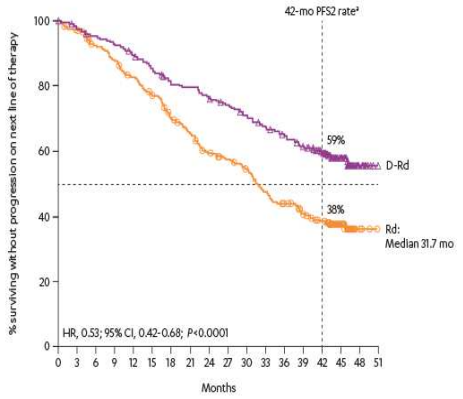
Daratumumab works in **monotherapy** and in **combination** with lenalidomide and bortezomib



Dara mono

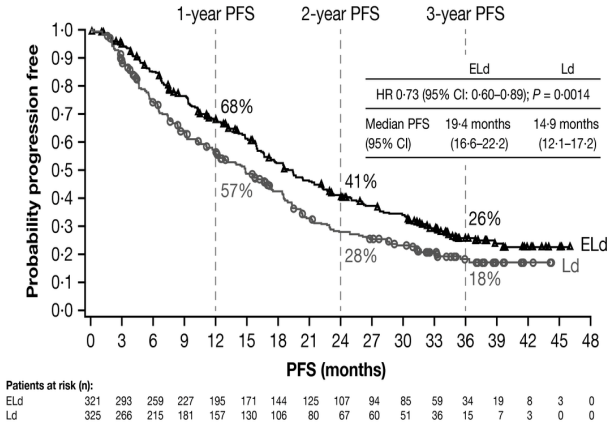


Dara VD vs VD



Dara RD vs VD

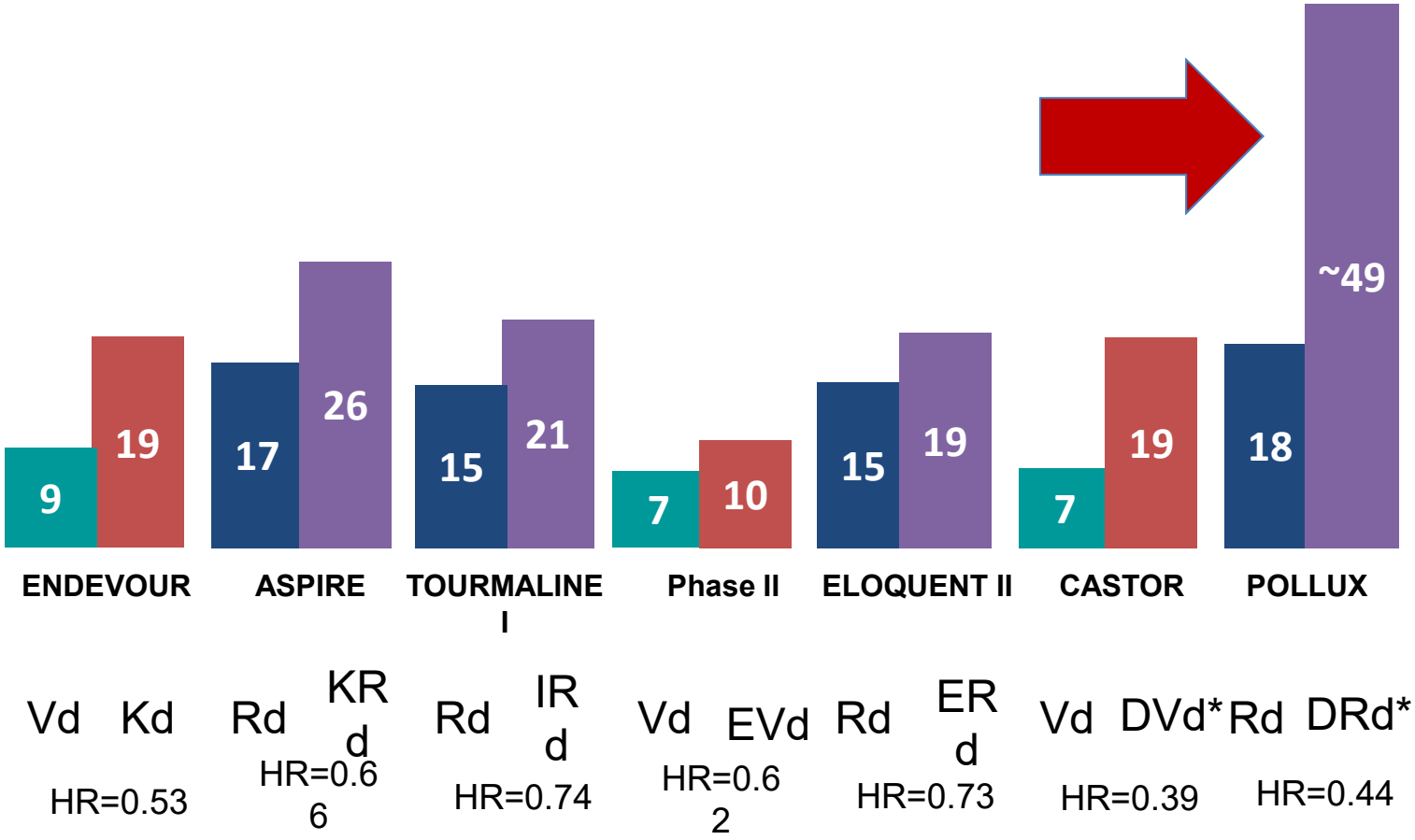
Elotuzumab is active **in combination only…**



Elo RD vs VD

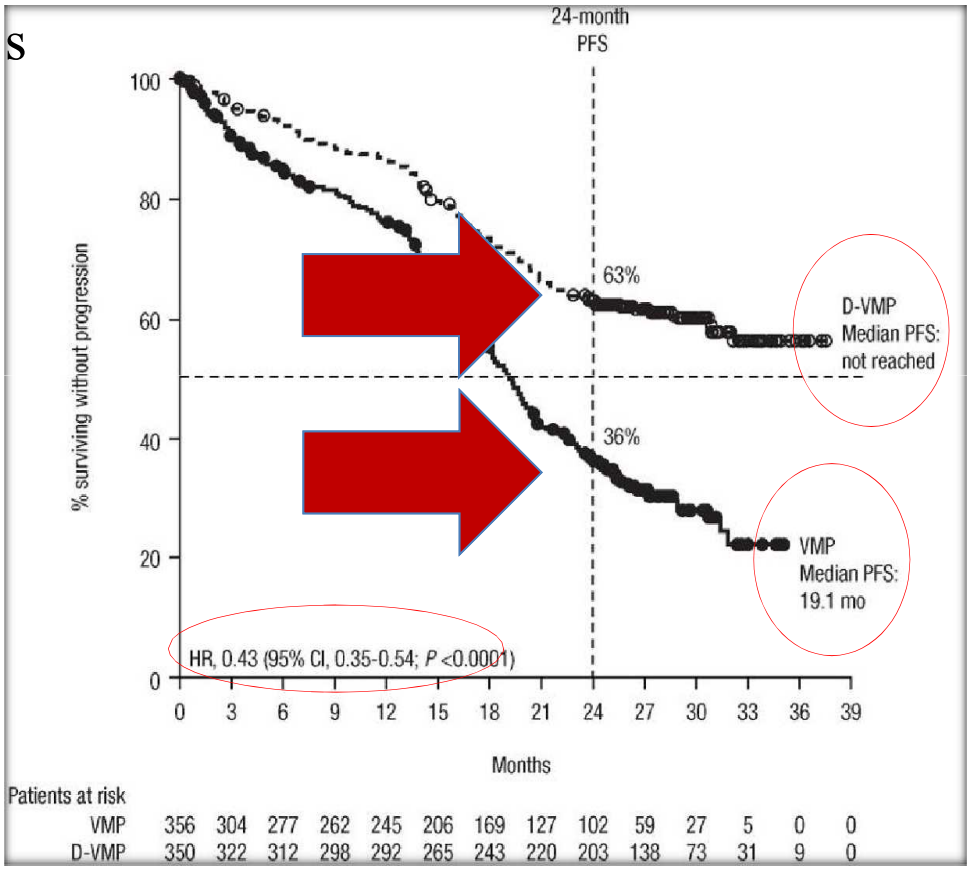
Lonial, 2016
Bahlis, 2018
Mateos, 2018
Dimopoulos, 2017

The best results in refractory myeloma are seen in **daratumumab**-based chemotherapies….

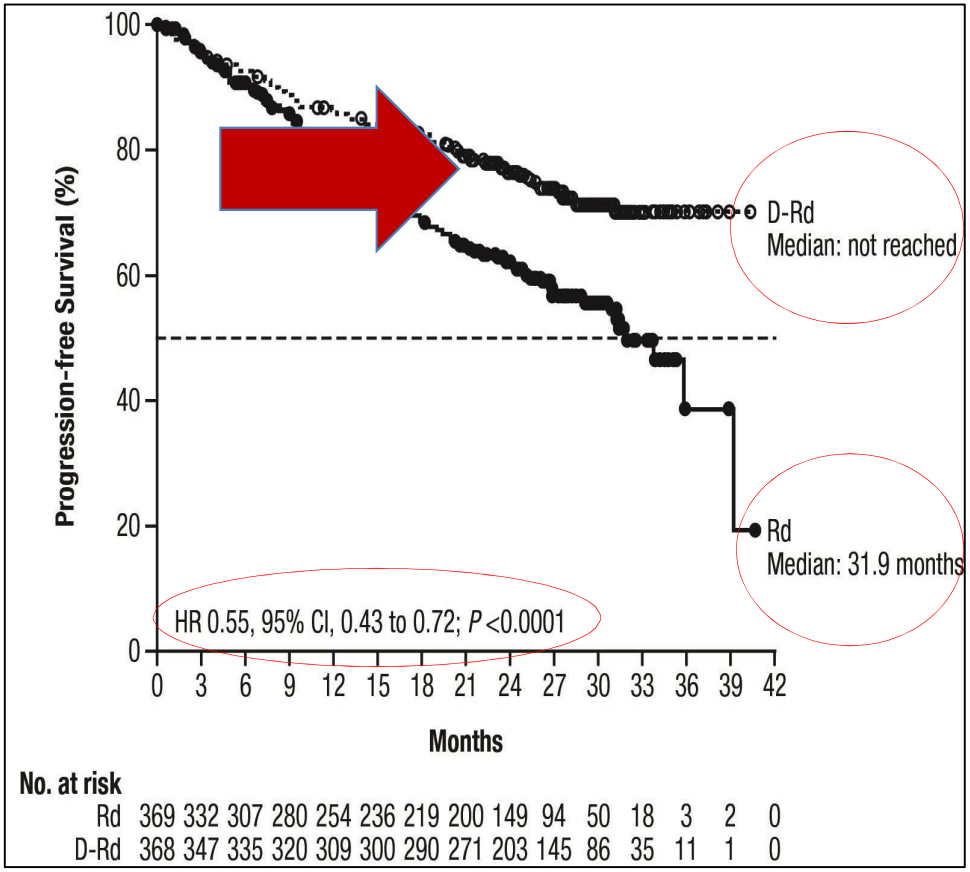


*Results extrapolated from published data to estimate median PFS

What holds even more in frontline setting



Dara VMP vs VMP



Dara RD vs RD

Dimopoulos, 2018
Facon 2018

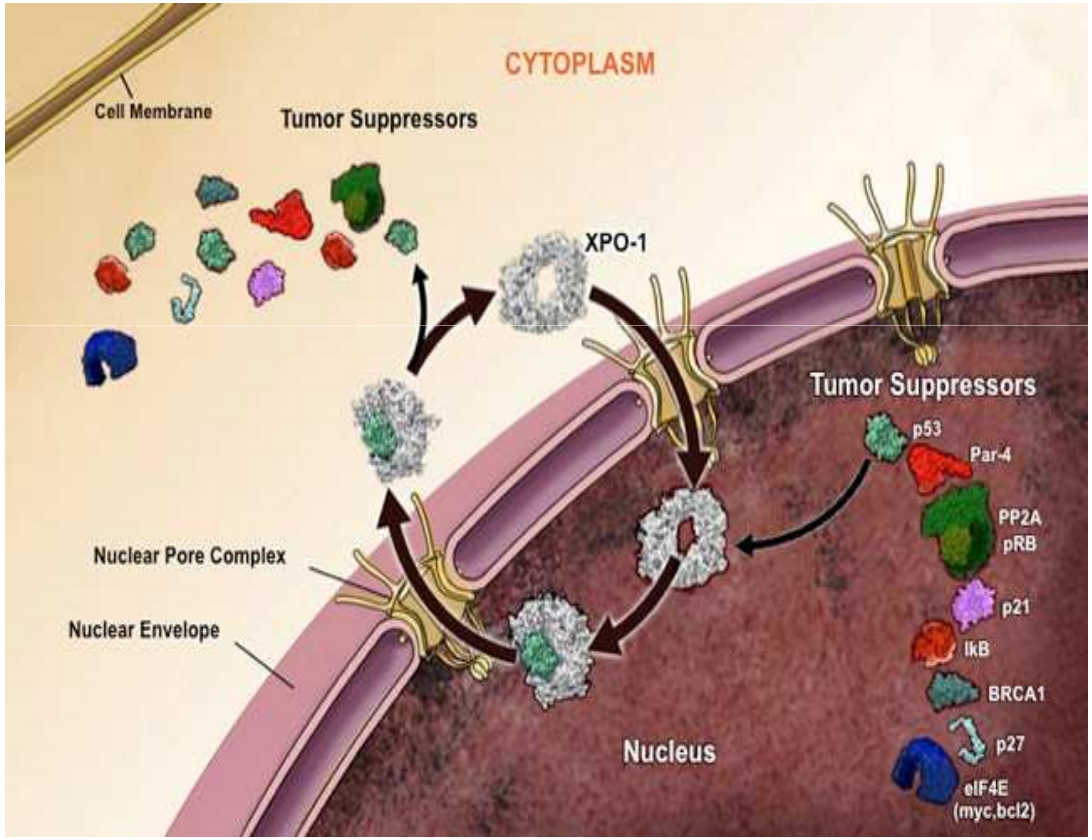
but the game will be lost sooner or later

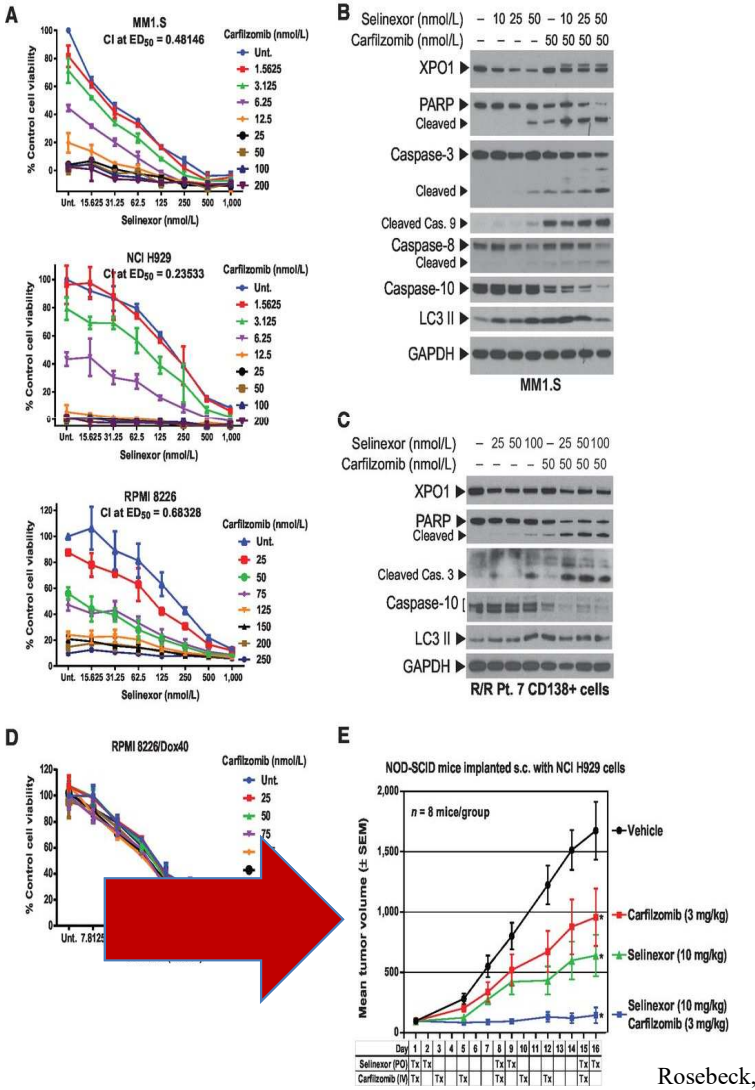
Newer molecules might be a solution

Selinexor

Melflufen

Selinexor
first-in-class oral XPO-1 inhibitor





Rosebeck, 2015

ABSTRACT 598

Results of the Pivotal STORM Study (Part 2) in Penta-Refractory Multiple Myeloma (MM): Deep and Durable Responses With Oral Selinexor Plus Low Dose Dexamethasone in Patients with **Penta Exposed and Triple Class-Refractory MM**

Ajai Chari, Dan T. Vogl, Meletios A. Dimopoulos, Ajay K. Nooka, Carol Ann Huff, Philippe Moreau, Craig E. Cole,
Joshua Richter, David Dingli, Ravi Vij, Sascha A. Tuchman, Marc S. Raab, Katja Weisel, Michel Delforge, David Kaminetzky, Robert Frank Cornell, A. Keith Stewart, James Hoffman, Kelly N. Godby, Terri L. Parker, Moshe Levy, Martin Schreder, Nathalie Meuleman, Laurent Frenzel, Mohamad Mohty, Choquet Sylvain, Andrew J. Yee,
Maria Gavriatopoulou, Luciano J. Costa, Jatin J. Shah, Carla Picklesimer, Jean-Richard Saint-Martin, Lingling Li, Michael G. Kauffman, Sharon Shacham, Paul Richardson, Sundar Jagannath

Oral presentation at the 60th Annual Meeting of the American Society of Hematology December 1–4, 2018

Monday, December 3, 2018 at 07:45 hours

Sd IN PENTA-REFRACTORY MM PATIENTS STUDY DESIGN, PATIENT CHARACTERISTICS, AND RESULTS

Phase 2 STORM (Part 2)
Penta-refractory MM (N = 122)

- Previously treated with BORT, CFZ, LEN, POM, DARA, an alkylator, and glucocorticoids
- Refractory to ≥ 1 PI, ≥ 1 IMiD, DARA, glucocorticoid, and last therapy

Sd
SEL: 80 mg twice weekly
DEX: 20 mg twice weekly
28-day cycle

- **Primary endpoint:** ORR
- **Secondary endpoints:** response duration, CBR, OS, PFS, safety

Patient Characteristics	N = 122
Median age (range), years	65 (40–86)
Median time from diagnosis (range), years	6.6 (1.1–23.4)
High risk cytogenetics, n (%)	65 (53)
Median prior treatment regimens (range), n	7 (3–18)
CFZ, POM, DARA refractory, n (%)	117 (96)
Prior DARA-based therapy n (%)	86 (70)
Prior stem cell transplant, n (%)	102 (84)
Prior CAR T therapy, n (%)	2 (2)

Efficacy Outcomes	N = 122
ORR, %	26.2
Stringent CR	1.6
VGPR	4.9
PR	19.7
[illegible]R), %	39.3
≥ SD, %	78.7
Median response duration, months	4.4
Median OS, months	8.6
Median PFS, months	3.7

- 2 patients who progressed on CAR T therapy achieved PR

Most common (> 10%) grade 3 and 4 treatment-[illegible]s, respectively, included: [illegible]thrombocytopenia (22.8% and 30.9%), anaemia (28.5% and 0.8%), neutropenia (15.4% and 3.3%), fatigue (18.7% and 0%), hyponatraemia (16.3% and 0%), and leucopenia (13.0% and 0%)

- AEs were typically reversible and manageable with dose modification and supportive care

AUTHORS' CONCLUSIONS:

- SEL is the first oral agent with activity in very heavily pretreated, penta-exposed, triple class-refractory MM patients

AE, adverse event; BORT, bortezomib; CAR T, chimeric antigen receptor T-cell; CBR, clinical benefit rate; CFZ, carfilzomib; CR, complete response; DARA, daratumumab; DEX, dexamethasone; IMiD, immunomodulatory drug; LEN, lenalidomide; MR, minimal response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; POM, pomalidomide; PR, partial response,
Sd, selinexor + low-dose dexamethasone; SEL, selinexor; SD, stable disease.

Chari et al. ASH 2018: Abstract 598. Oral presentation.

ABSTRACT 600

OP-106 HORIZON – Melflufen Therapy for RRMM Patients Refractory to Daratumumab and/or Pomalidomide: Updated Results and

Paul Richardson, Enrique Ocio, Albert Oriol, Alessandra Larocca, Paula Rodriguez Otero, Jan Moreb, Joan Bladé, Hani Hassoun, Michele Cavo, Adrián Alegre, Amitabha Mazumder, Christopher Maisel, Agne Paner, Nashat Gabrail, Jeffrey A. Zonder, Dharminder Chauhan, Johan Harmenberg, Sara Thuresson, Hanan Zubair, Maria-Victoria Mateos

Oral presentation at the 60th Annual Meeting of the American Society of Hematology

December 1–4, 2018

Monday, December 3, 2018 at 08:15 hours

MELF IN RRMM PATIENTS REFRACTORY TO DARA AND/OR POM STUDY DESIGN AND UPDATED RESULTS

- Ongoing, single-arm, open-label, multicentre, phase 2 trial to evaluate MELF in pts who have progressed on IMiD and PI and are refractory to POM and/or DARA
- **Primary endpoint:** ORR (N = 83) (at data cutoff October 22 2018, 82 patients were response evaluable)
- **Secondary endpoints:** OS, PFS, duration of response, CBR, TTR, TTP, safety, and tolerability

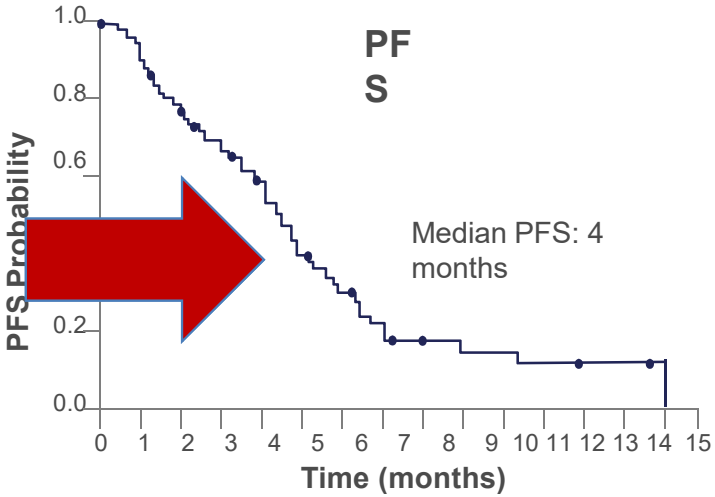
OP-106 HORIZON
- Refractory to POM and/or DARA
- Measurable disease (≥ 1 of the following):

→ **MELF + DEX (N = 83[a])**
MELF: 40 mg i.v. on day 1
DEX: 20[b] / 40 mg on days 1, 8, 15, 22
28-day cycles until PD, withdrawal of consent, or unacceptable toxicity

Response, n (%)	N = 83
ORR	27 (33)
sCR	1 (1)
CR	0
VGPR	9 (11)
PR	17 (21)
MR	5 (6)
SD	37 (45)
PD	12 (15)

Most Common (> Grade 3 or n (%)	N = 83
Any treatment-related grade 3 or 4 AE in ≥ 2 patients	62 (75)
Neutropenia	51 (61)
Thrombocytopenia	49 (59)
Anaemia	21 (25)

- Incidence of non-haematological AEs was low (7.2% infection)
- No treatment-related deaths occurred



AUTHORS' CONCLUSIONS
- MELF shows promising activity in patients with multi-resistant RRMM
- Response was observed irrespective of refractory status
- Treatment was generally well tolerated with a manageable

[a] Enrolment target is N = 150, including QoL data for 50 patients. [b] In patients ≥ 75 years. AE, adverse event; ANC, absolute neutrophil count; CBR, clinical benefit rate; CR, complete response; DARA, daratumumab; DEX, dexamethasone; FLC, free light chain; IMiD, immunomodulatory drug; i.v., intravenous; MELF, melflufen; MR, minimal response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; POM, pomalidomide; PR, partial response; QoL, quality of life; RRMM, relapsed / refractory multiple myeloma; sCR, stringent complete response; SD, stable disease; SFLC, serum free light chain; TTP time to progression; TTR, time to response; VGPR, very good partial response.

Richardson et al. ASH 2018: Abstract 600. Oral presentation

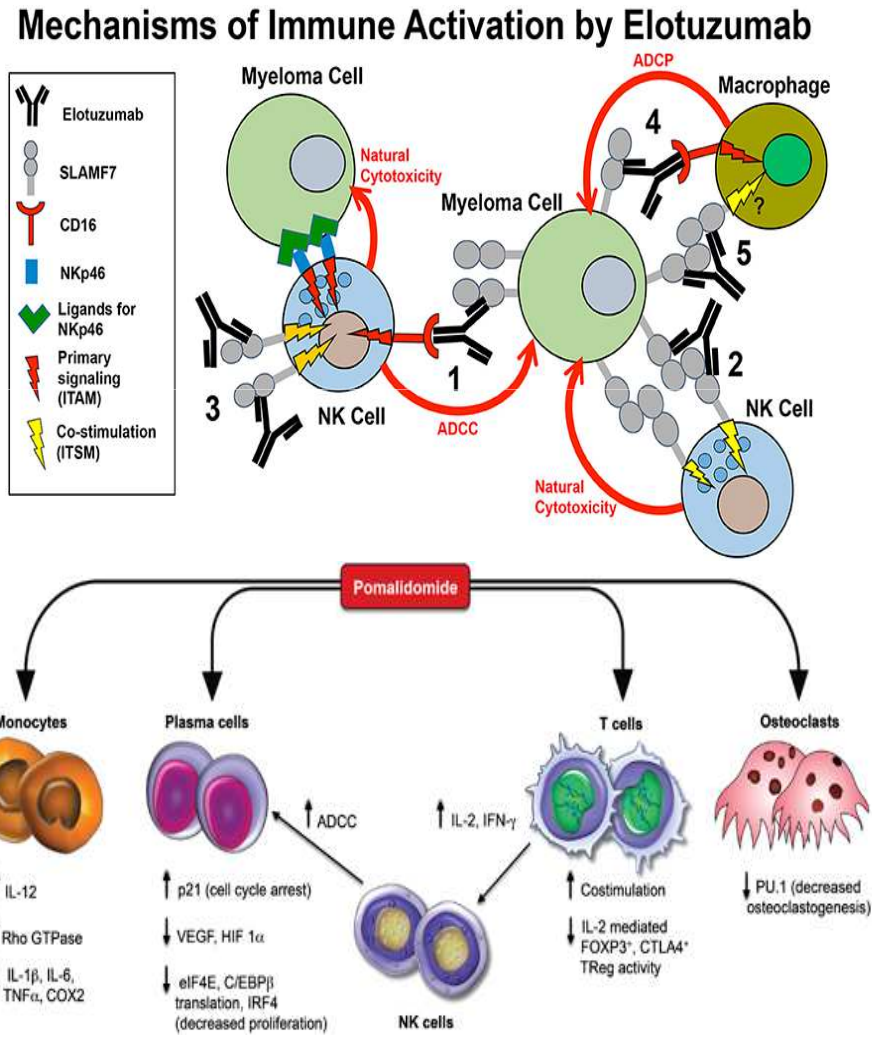
…or totally different approach
involving **immunology** of the patient?

ELOTUZUMAB
POMALIDOMI
DD

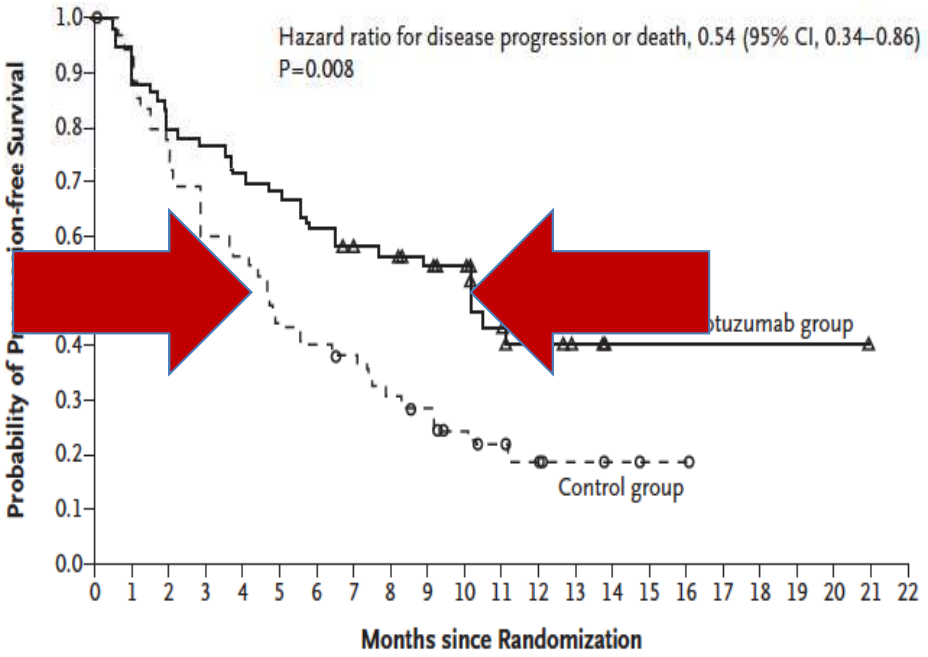
BiTE

CAR-T

Stimulation of NKs by (forgotten?) elotuzumab and pomalidomide



ELO POM DEX vs POM DEX



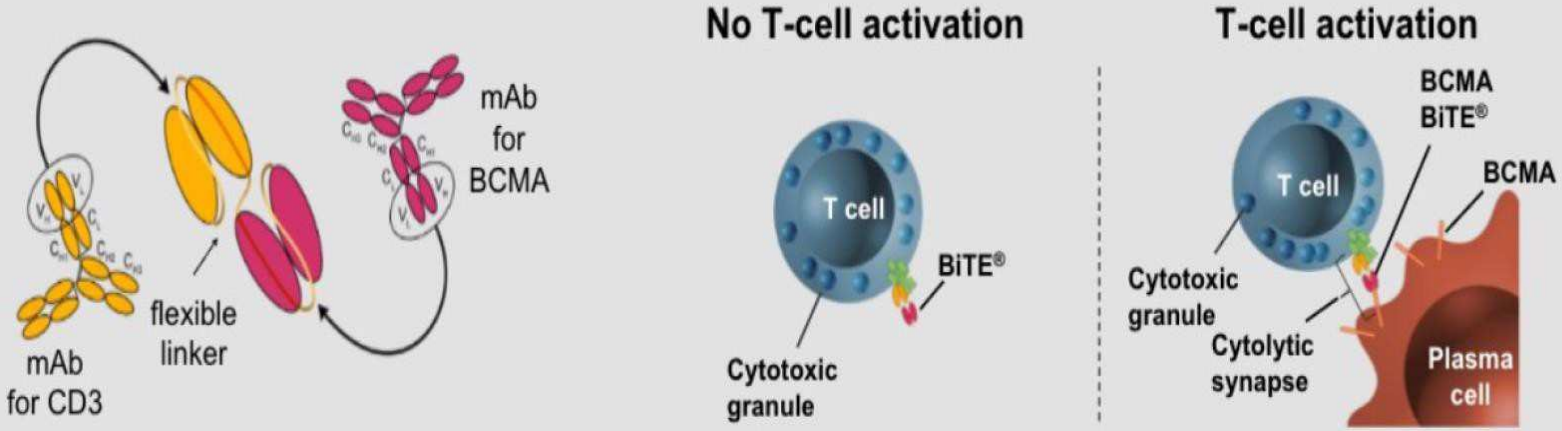
Dimopoulos, 2018

AMG 420, an Anti-BCMA BiTE®, Induces MRD-Negative CRs in Relapsed/Refractory MM Patients: Results of a Dose Escalation FIH Phase 1 Study

Max S Topp,[1] Johannes Duell,[1] Gerhard Zugmaier, [2] Michel Attal,[3] Philippe Moreau,[4] Christian Langer,[5] Jan Krönke,[6] Thierry Facon,[7] Hermann Einsele,[1*] Gerd Munzert[8*]

[1]Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany, [2]Amgen Research (Munich), Munich, Germany, [3]University of Toulouse, Toulouse, France, [4]Hematology Department Chair, University Hospital Center of Nantes, Nantes, France, [5]Kempten Clinic, Kempten, Germany, [6]Ulm University, Ulm, Germany, [7]Regional University Hospital of Lille, Lille, France, [8]Boehringer Ingelheim, Ingelheim am Rhein, Germany
*Contributed equally

Background



- B-Cell Maturation Antigen (BCMA), or TNFRSF17, is expressed on multiple myeloma (MM) cells, plasma cells, and mature B cells.[1-4]
- AMG 420* binds BCMA on tumor cells and plasma cells and CD3 on T cells, resulting in T-cell mediated lysis of BCMA+ cells[5] at least in part through a Fas-mediated mechanism.[6]

* Formerly BI 836909. 1. Madry C, et al. *Int Immunol.* 1998;10:1693-1702. 2. Coquery CM, Erickson LD. *Crit Rev Immunol.* 2012;32:287-305. 3. Laabi Y, et al. *Nucleic Acids Res.* 1994;22:1147-54. 4. Gras MP, et al. *Int Immunol.* 1995;7:1093-1106. 5. Topp MS et al. *J Clin Oncol.* 2016;34:8067 (Abs). 6. Ross SL, et al. *PLoS One.* 2017;12:e0183390.

Topp et al; ASH2018, Abs#1010, oral presentation

CRS AEs and Serious AEs (SAEs)

		N=42	# Gr 1	# Gr 2	# Gr 3	# Gr 4	# Gr 5
CRS	All treatment-related	16 (38%)	13	2	1	-	-
SAEs in ≥2 patients	Infections	12 (29%)	-	3	7	-	2*
	Peripheral polyneuropathy	2 (5%)	-	-	2	-	-
Treatment-related SAEs	Peripheral polyneuropathy	2 (5%)	-	-	2	-	-
	Edema	1 (2%)	-	-	1	-	-

*One patient died of aspergillus / flu and one of liver failure secondary to adenovirus infection.

- Of those with serious AEs (n=20, 48%), 17 patients were hospitalized and 4 had prolonged hospitalization (one patient had both on separate occasions).
- No grade 3 or 4 central nervous system toxicities were observed.
- Regarding any neurologic AEs, except for 1 case of worsening asthenia and 2 of peripheral polyneuropathy, all AEs were grade 1 and 2 and were generally nonspecific (eg, headache, fatigue).

Topp et al; ASH2018, Abs#1010, oral presentation

Conclusions

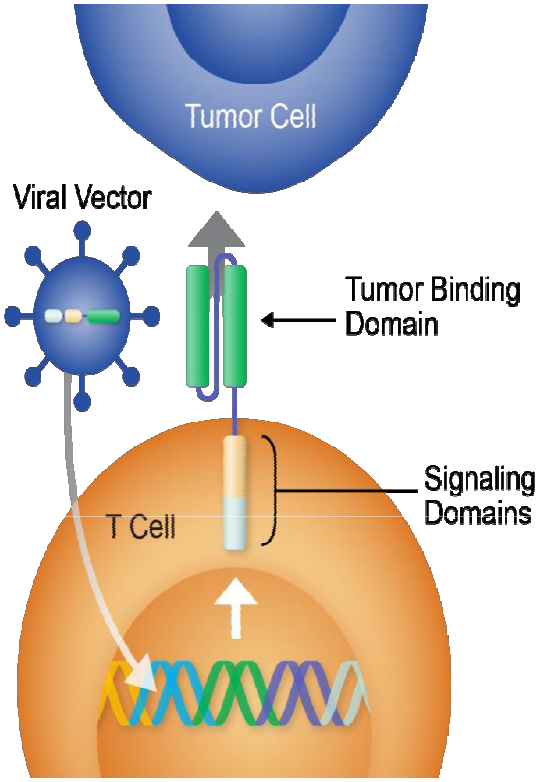
In this FIH dose escalation study, AMG 420, a short half-life BiTE® targeting BCMA, demonstrated clinical activity in patients with heavily pretreated multiple myeloma:

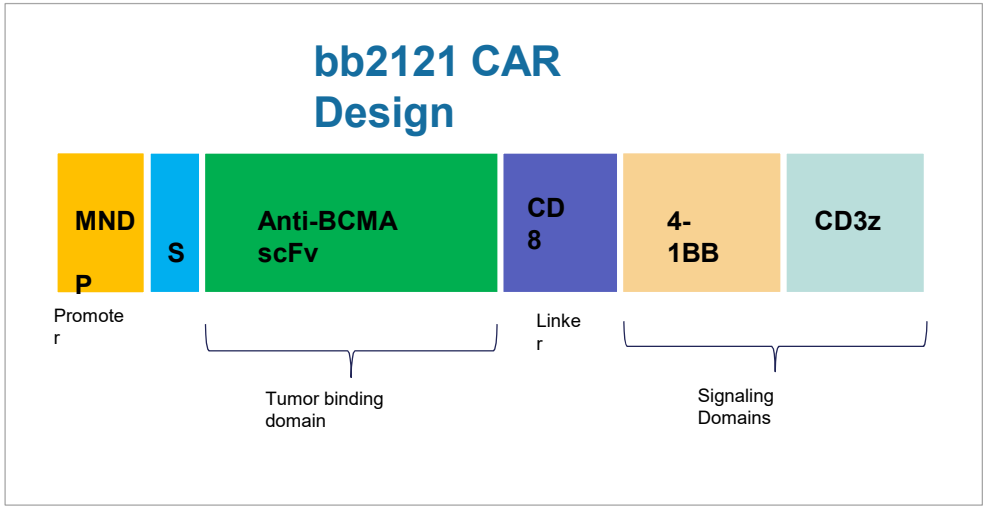
- No major toxicities prior to DLTs at 800 µg/d of CRS and polyneuropathy; a patient in the subsequent 400 µg/d dose expansion also had a DLT of polyneuropathy, which resolved.
- Careful evaluation of infections should be conducted in future clinical trials to enable development of optimal management guidelines.
- Of doses tested in this study, 400 µg/d was the MTD; other doses may be [illegible]
- There was encouraging evidence of activity, with 13 responders overall
  - 7/10 (70%) of patients dosed with 400 µg/d had responses, 4 of which were MRD-negative sCRs
  - 3 patients at lower doses attained CRs, one of which was also an MRD-negative sCR
- These data warrant further clinical investigation of AMG 420; a phase 1b trial will be starting in Q1 2019.

31% ORR (n=42)

Topp et al; ASH2018, Abs#1010, oral presentation

bb2121: AN OPTIMAL BCMA CAR T CELL DESIGN



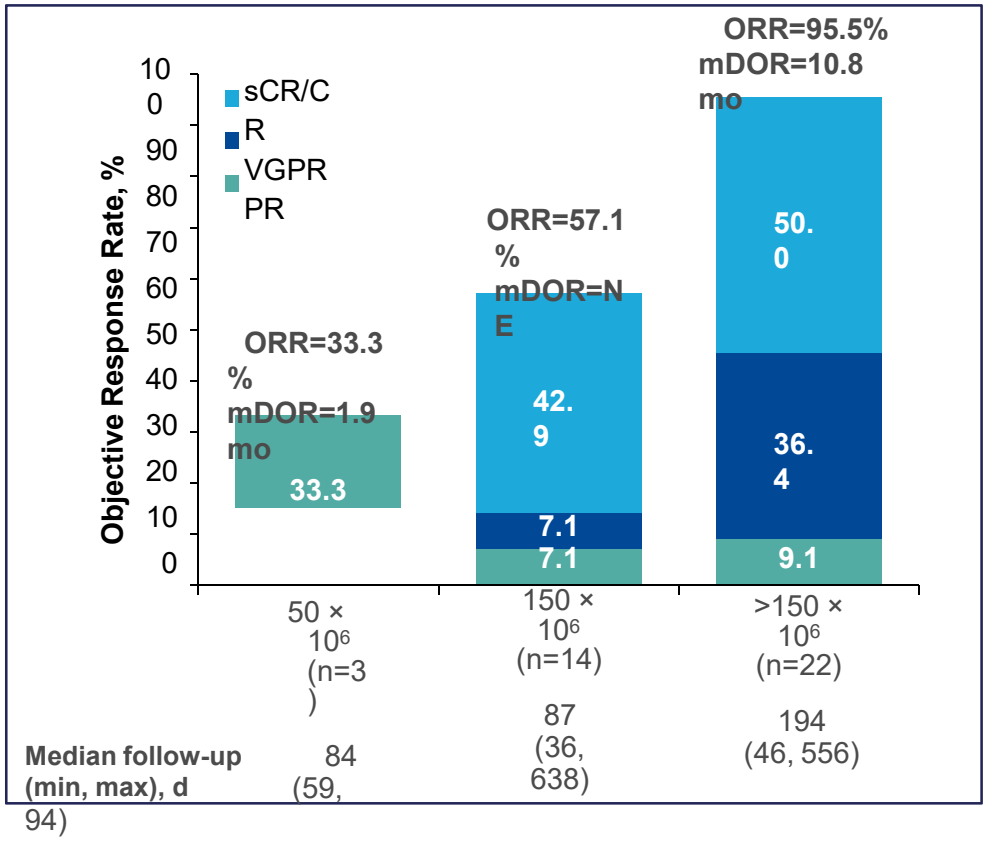


- Autologous T cells transduced with a lentiviral vector encoding a CAR specific for human BCMA
- State of the art lentiviral vector system
- Optimal 4-1BB costimulatory signaling domain: associated with less acute toxicity and more durable CAR T cell persistence than CD28 costimulatory domain[1]

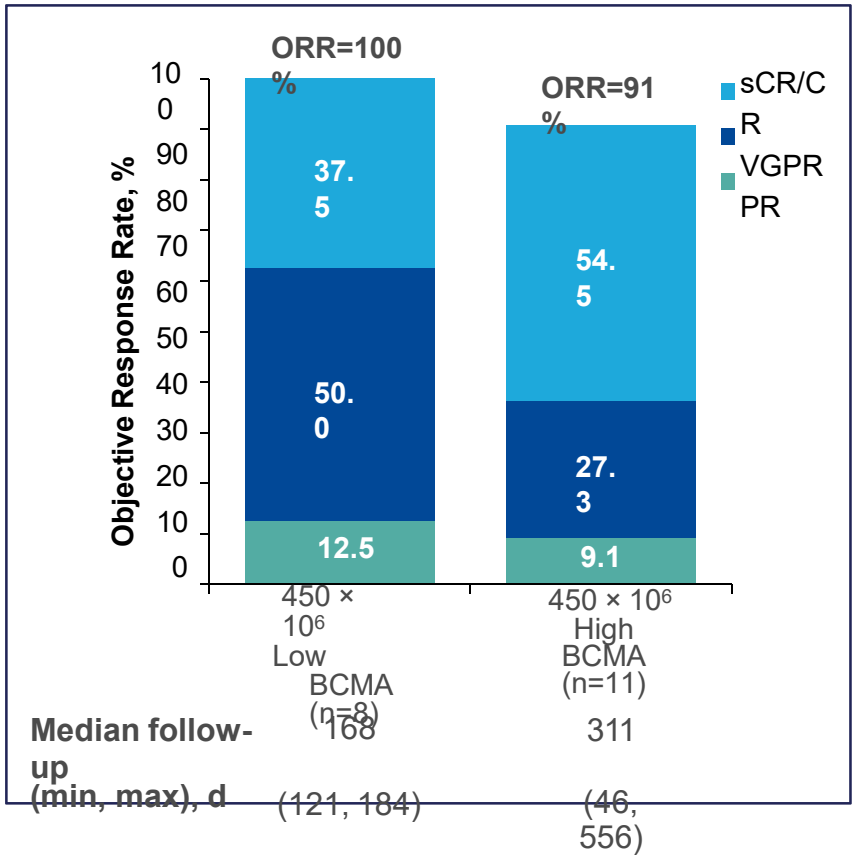
Raje N *et al*, Abstract 8007; Presented at ASCO 2018, Chicago, Illinois;
1. Ali SI, *et al. Blood*. 2016;**128**:1688–700.

TUMOR RESPONSE: DOSE-RELATED; INDEPENDENT OF TUMOR BCMA EXPRESSION

Tumor Response By Dose[a]



Tumor Response By BCMA Expression[a]



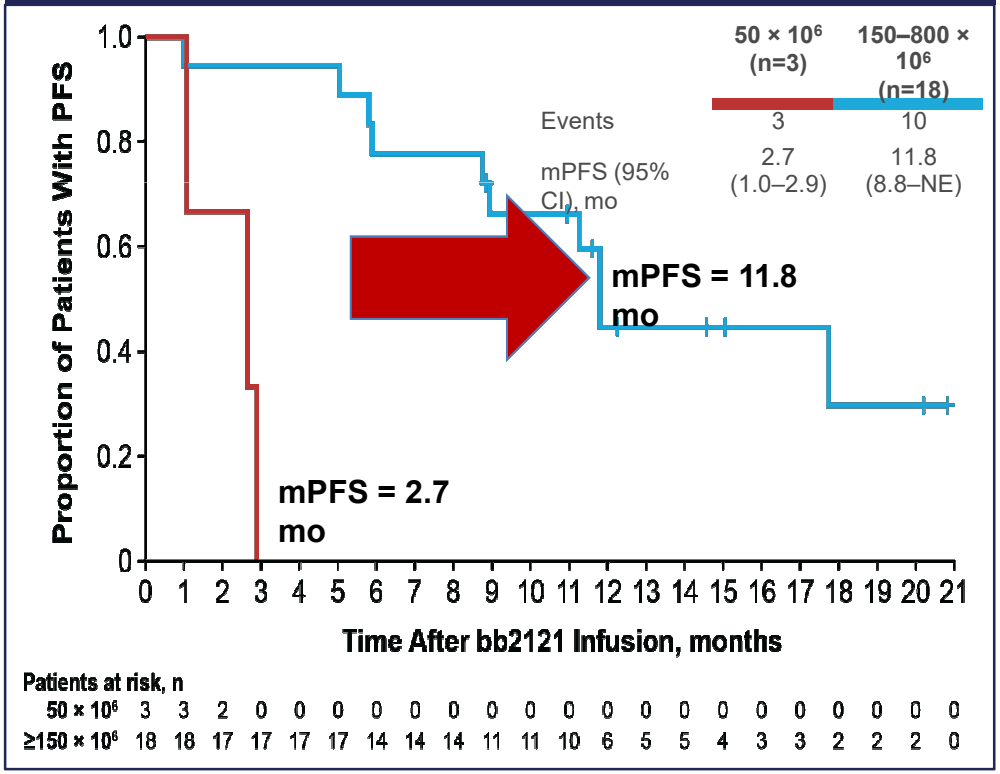
Data cutoff: March 29, 2018. CR, complete response; mDOR, median duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; sCR, stringent CR; VGPR, very good partial response. [a]Patients with ≥2 months of response data or PD/death within <2 months. ORR is defined as attaining sCR, CR, VGPR, or PR, including confirmed and unconfirmed responses. Low BCMA is <50% bone marrow plasma cells expression of BCMA; high BCMA is defined as ≥50%.

Raje N *et al*, Abstract 8007; Presented at ASCO 2018, Chicago, Illinois.

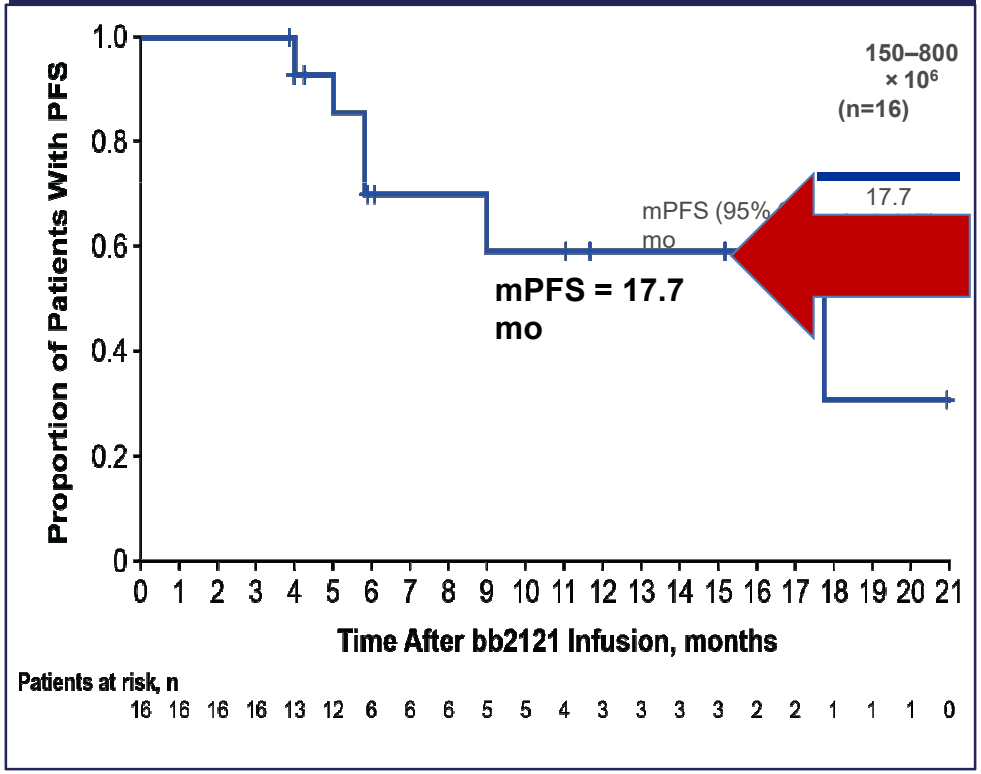
PROGRESSION-FREE SURVIVAL

- mPFS of 11.8 months at active doses (≥150 × 10^6 CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative

PFS at Inactive (50 × 10^6) and Active (150–800 × 10^6) Dose Levels[a]



PFS in MRD-Negative Patients[a]

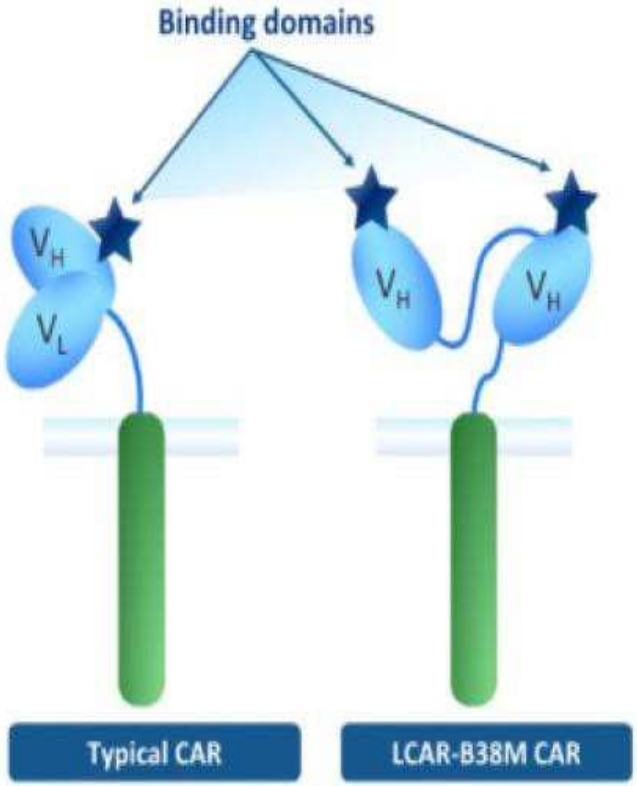


Data cutoff: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable. [a]PFS in dose escalation cohort.

Raje N *et al*, Abstract 8007; Presented at ASCO 2018, Chicago, Illinois.

LEGEND-2 Study

- **LCAR-B38M is a chimeric antigen receptor (CAR) T cell therapy with 2 BCMA targeting domains**
  - Confers high avidity binding and distinguishes LCAR-B38M from other BCMA-targeted CAR T cell therapies
- **LEGEND-2 (N=74): Phase 1 investigator-initiated study in R/R multiple myeloma (MM) conducted at 4 sites in China**
  - Variable preconditioning regimens (Cy-Flu vs. Cy)
  - Variable CAR T infusion methods (split vs. single infusion)
- **LEGEND-2 results previously presented**
  - First 35/57 patients at the Xi'an site at ASCO and EHA 2017
  - First 11/17 patients at the 3 other sites at ASH 2017
- **57 patient experience at Xi'an site as of 25 June 2018 are presented here, with a 12-month (0.7–25.1) follow-up**



BCMA=B-cell maturation antigen; Cy=cyclophosphamide; Flu=fludarabine; R/R=relapsed/refractory; V_H=variable heavy chain; V_L=variable light chain

Zhao et al; ASH2018, Abs#955, oral presentation

Adverse Events

AEs (≥20% in All Patients)	Grade 1	Grade 2	Grade 3	Grade 4	Total (N=57)
Pyrexia	14 (25)	27 (47)	10 (18)	1 (2)	52 (91)
Cytokine release syndrome	27 (47)	20 (35)	4 (7)	0	51 (90)
Thrombocytopenia	8 (14)	7 (12)	3 (5)	10 (18)	28 (49)
Leukopenia	3 (5)	7 (12)	15 (26)	2 (4)	27 (47)
Increased AST	7 (12)	3 (5)	12 (21)	0	22 (39)
Anemia	2 (4)	5 (9)	9 (16)	1 (2)	17 (30)
Hypotension	7 (12)	2 (4)	3 (5)	0	12 (21)
Other AE of interest					
Neurotoxicity[a]	1 (2)	0	0	0	1 (2)

[a]Aphasia, seizure-like activity, and agitation reported in one patient dosed at $1x10^6$ cells/kg

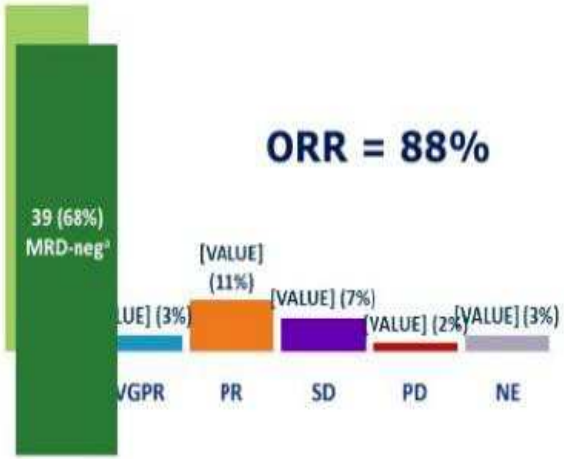
60th ASH Annual Meeting 2018. Zhao W-H, et al. Abstract #955.

CRS=cytokine release syndrome

Zhao et al; ASH2018, Abs#955, oral presentation

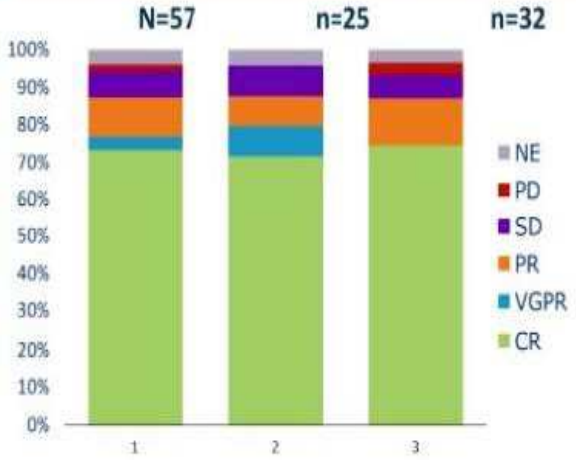
Efficacy

Best Overall Response (N=57)



- mDOR = 16 mo (95% CI, 12–NR)
- mDOR for MRD-neg CR = 22 mo (95% CI, 14–NR)
- Median time to initial response = 1 mo (0.4–3.6)

Best Overall Response by Dose



All Doses	<0.5x10^6 cells/kg	≥0.5x10^6 cells/kg

BCMA <40% (n=26/53)[b] = 92% ORR
BCMA ≥40% (n=27/53)[b] = 82% ORR

[a]8-color flow cytometry with cell count up to 500,000 cells; [b]BCMA expression data available for 53 patients

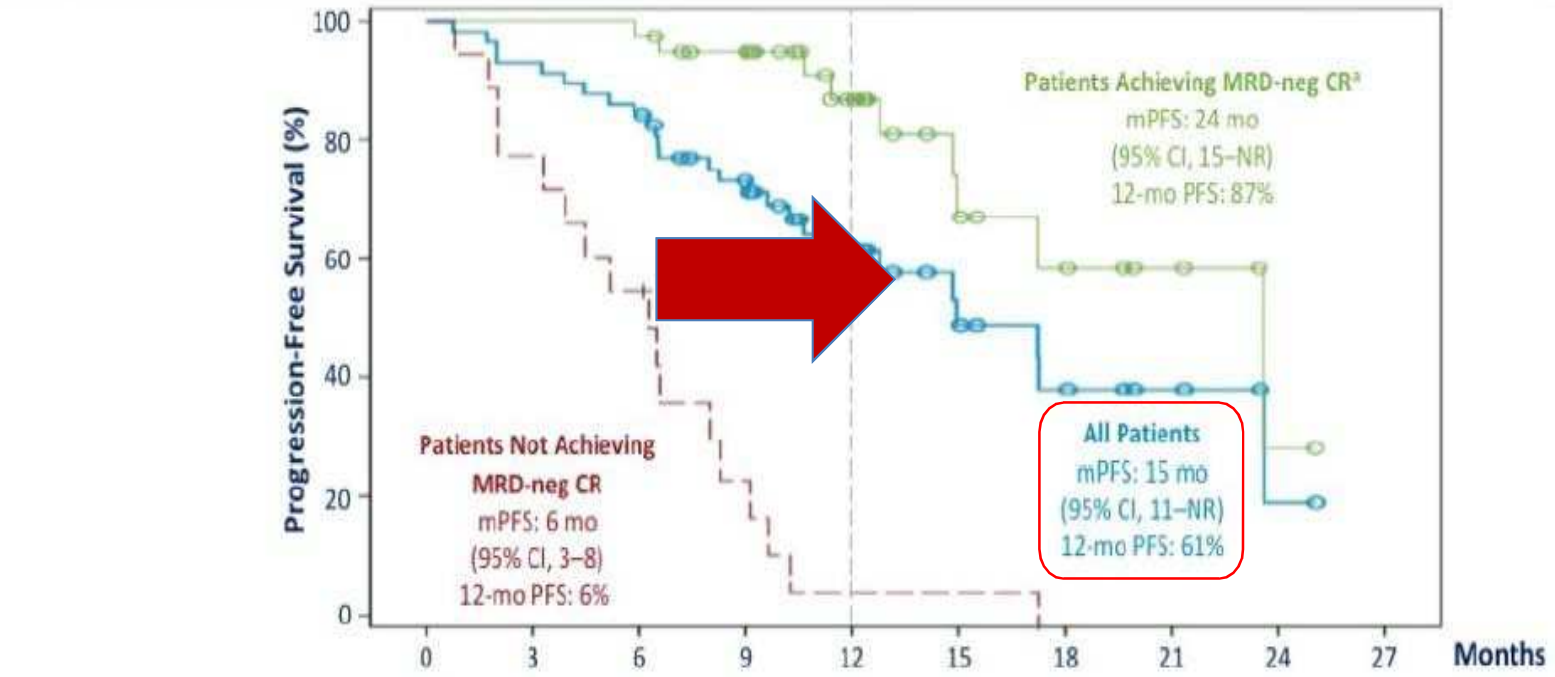
CR=complete response; mDOR=median duration of response; MRD-neg=minimal residual disease-negative; NE=not evaluable; ORR=overall response rate; PD=progressive disease; PR=partial response; SD=stable disease; VGPR=very good partial response

60th ASH Annual Meeting 2018. Zhao W-H, et al. Abstract #955

7

Zhao et al; ASH2018, Abs#955, oral presentation

Progression-Free Survival



Patients at risk:										
All Patients	57	53	48	37	21	11	7	4	1	0
Patients Achieving MRD-neg CR	39	39	38	33	20	10	7	4	1	0
Patients Not Achieving MRD-neg CR	18	14	10	4	1	1	0	0	0	0

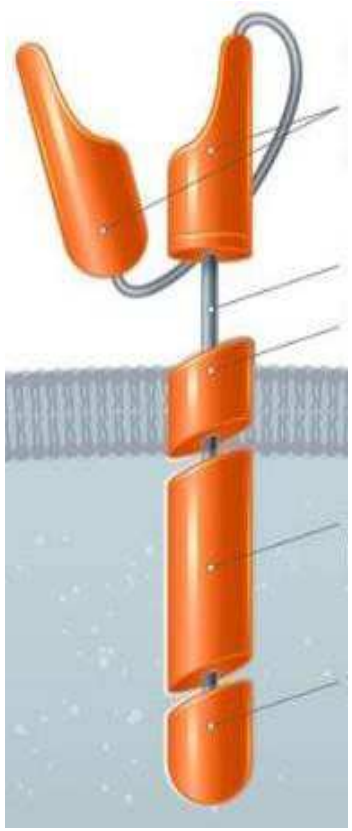
[a]30/39 patients still in remission

60th ASH Annual Meeting 2018, Zhao W-H, et al. Abstract #955.

mPFS=median progression-free survival 8

Zhao et al; ASH2018, Abs#955, oral presentation

JCARH125—DESIGN AND MANUFACTURING FEATURES



- **JCARH125 CAR construct**
  - Fully human binder with low affinity for sBCMA[1]
  - Modified spacer to enhance binding to BCMA on target cells
  - Minimized tonic signaling to reduce antigen-independent exhaustion[2]
  - Active on target cells that express low BCMA density
- **Manufacturing process**

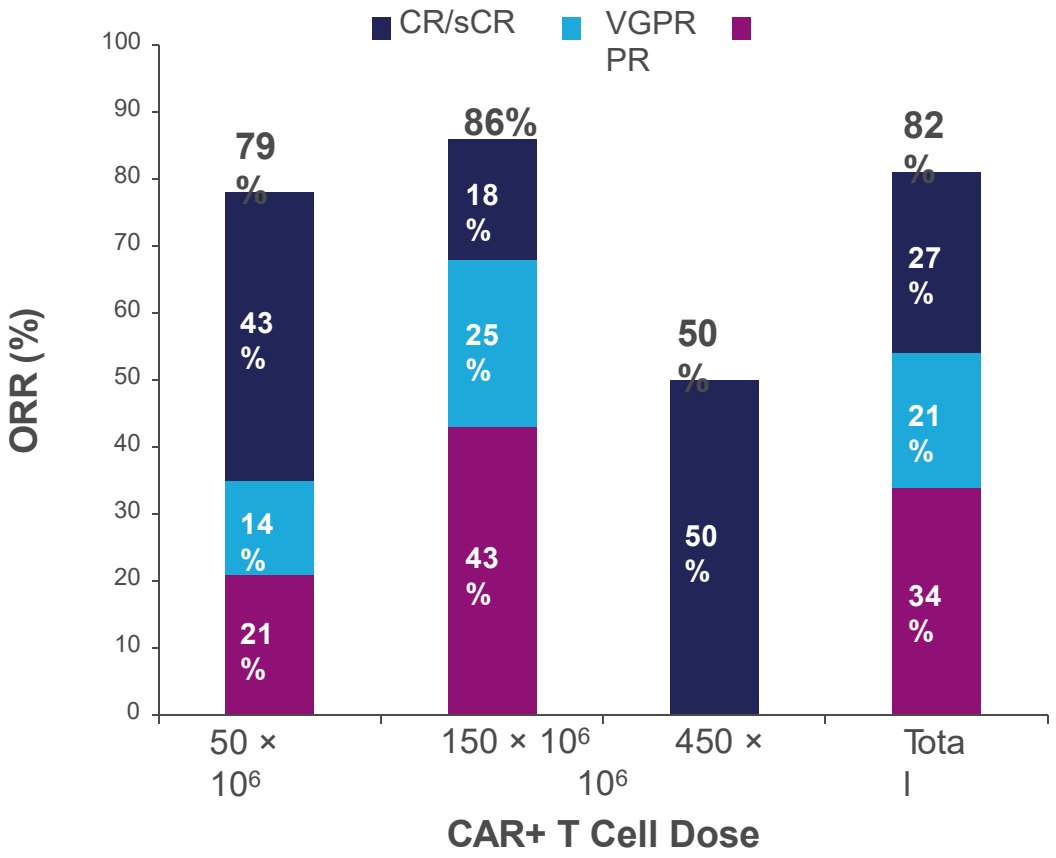
  Optimized to deliver a defined cell product comprised of purified CD4 and CD8 CAR+ T cells enriched for central memory phenotype cells, potentially increasing persistence and durability

To date, JCARH125 has been successfully manufactured for all patients

1. Smith et al. *Mol Ther*. 2018;26:1447-1456. 2. Long et al. *Nat Med*. 2015;21(6):581–590.
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; sBCMA, soluble B-cell

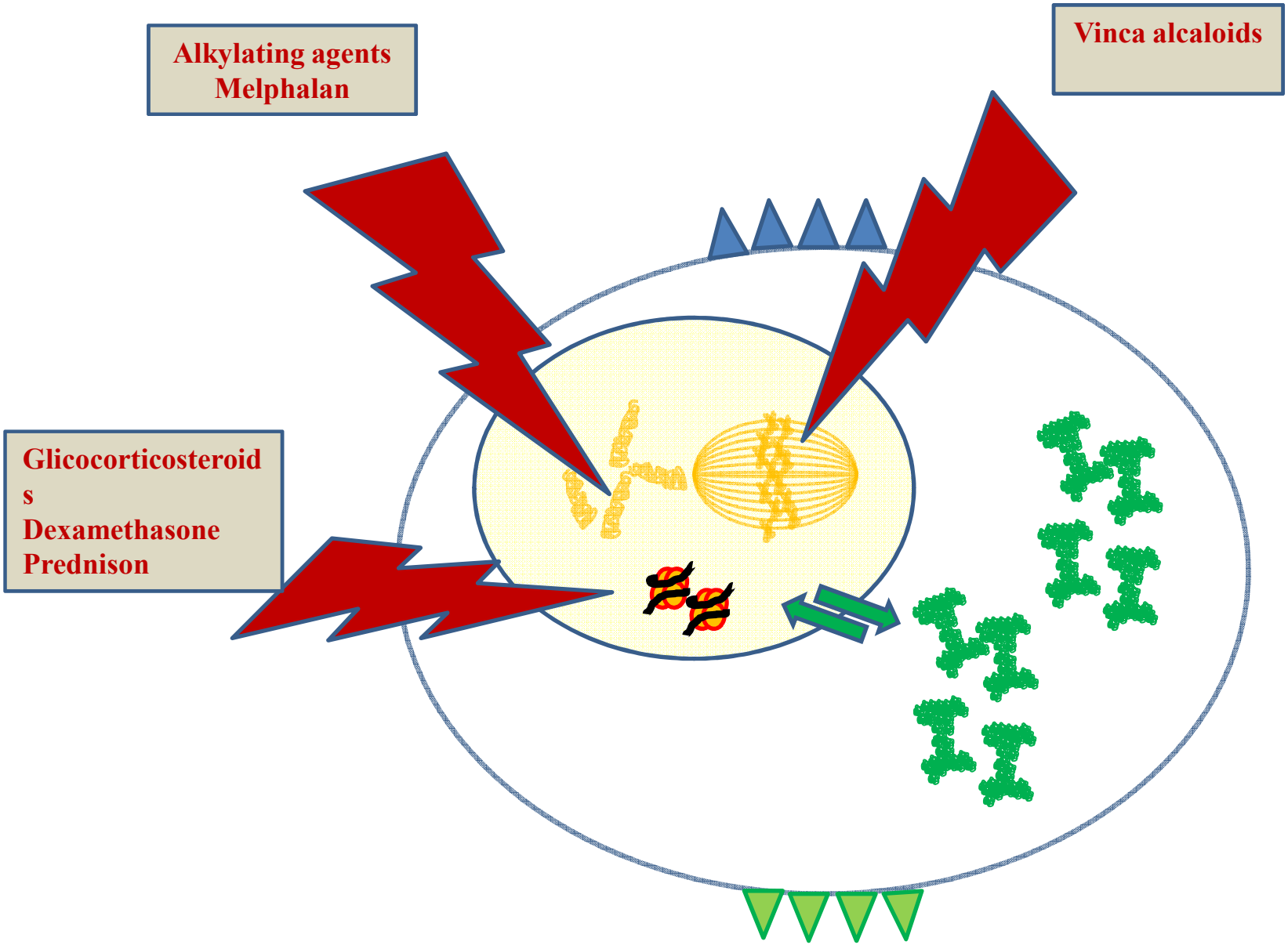
BEST OVERALL RESPONSE

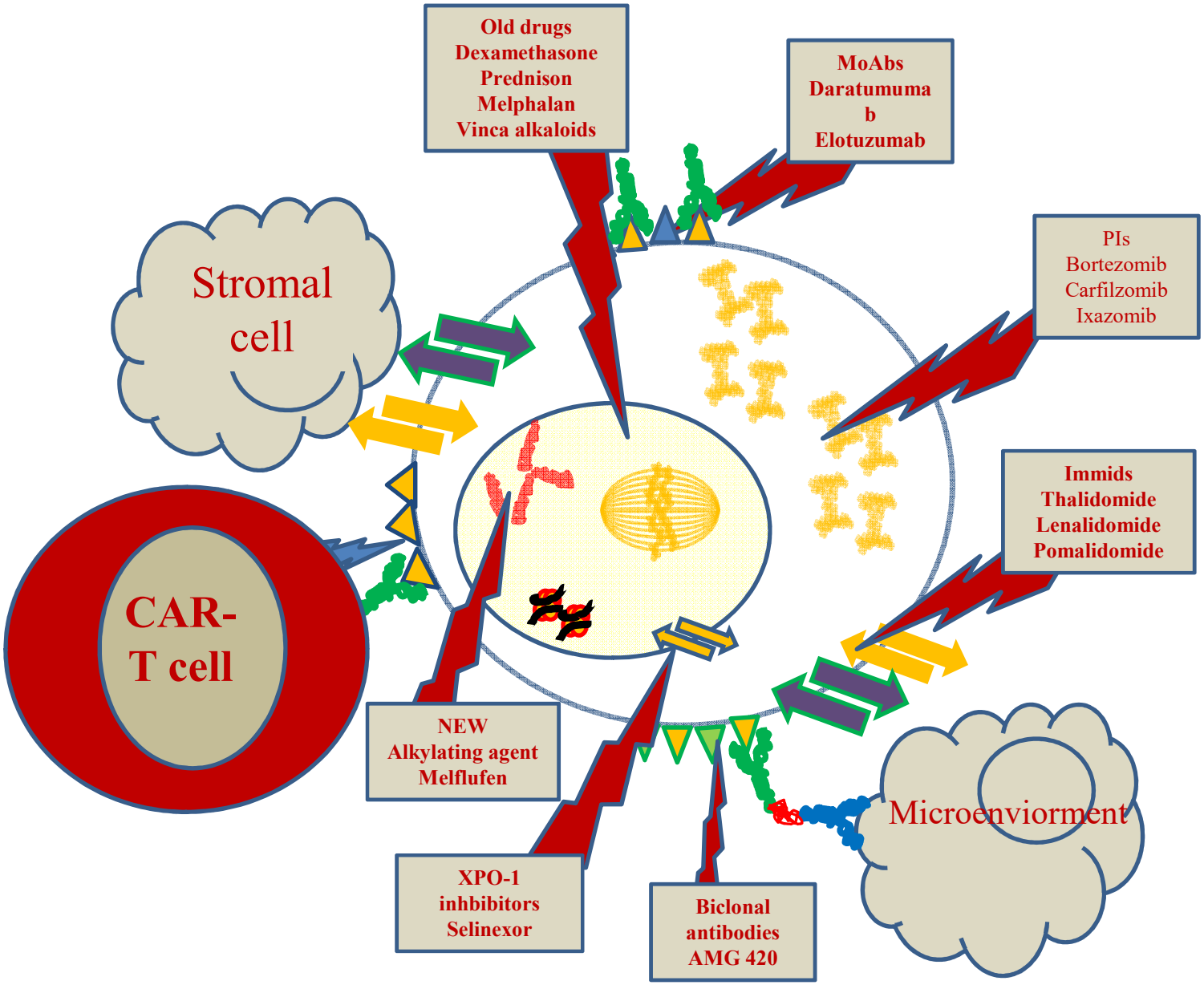
ORR 82%, with 48% ≥VGPR



Patients, n:	**14**	**28**	**2[a]**	**44**
	1	**9**	**7**	**11**
Median follow-up, weeks:	**7**			

[a]One patient was not evaluable for efficacy (no postbaseline response evaluation at Day 29).
CAR, chimeric antigen receptor; CR, complete response; ORR, objective response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.


Alkylating agents
Melphalan
Vinca alcaloids
Glicocorticosteroids
Dexamethasone
Prednison


Old drugs
Dexamethasone
Prednison
Melphalan
Vinca alkaloids
MoAbs
Daratumumab
Elotuzumab
PIs
Bortezomib
Carfilzomib
Ixazomib
Immids
Thalidomide
Lenalidomide
Pomalidomide
Stromal cell
CAR-T cell
NEW
Alkylating agent
Melflufen
XPO-1
inhbibitors
Selinexor
Biclonal
antibodies
AMG 420
Microenviorment

..this is a team game where every player counts

and new players will show up in the pitch soon

Beyond the horizon

New treatment strategies for multiple myeloma

Dominik Dytfeld

Polish Myeloma Consortium

March the 14th 2019