CLINICAL RESULTS WITH IMMUNOTHERAPY STRATEGIES

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Is there a role for immunotherapy strategies in MM?

Maybe YES

The Microenvironment & Immunosurveillance in MM

Impaired induction of allogeneic T-cell responses:

Reduced CD4+ T cell numbers.
Abnormal Th1/Th2 cytokine profile.
Impaired cytotoxic T cell response

Reduced B cell numbers:

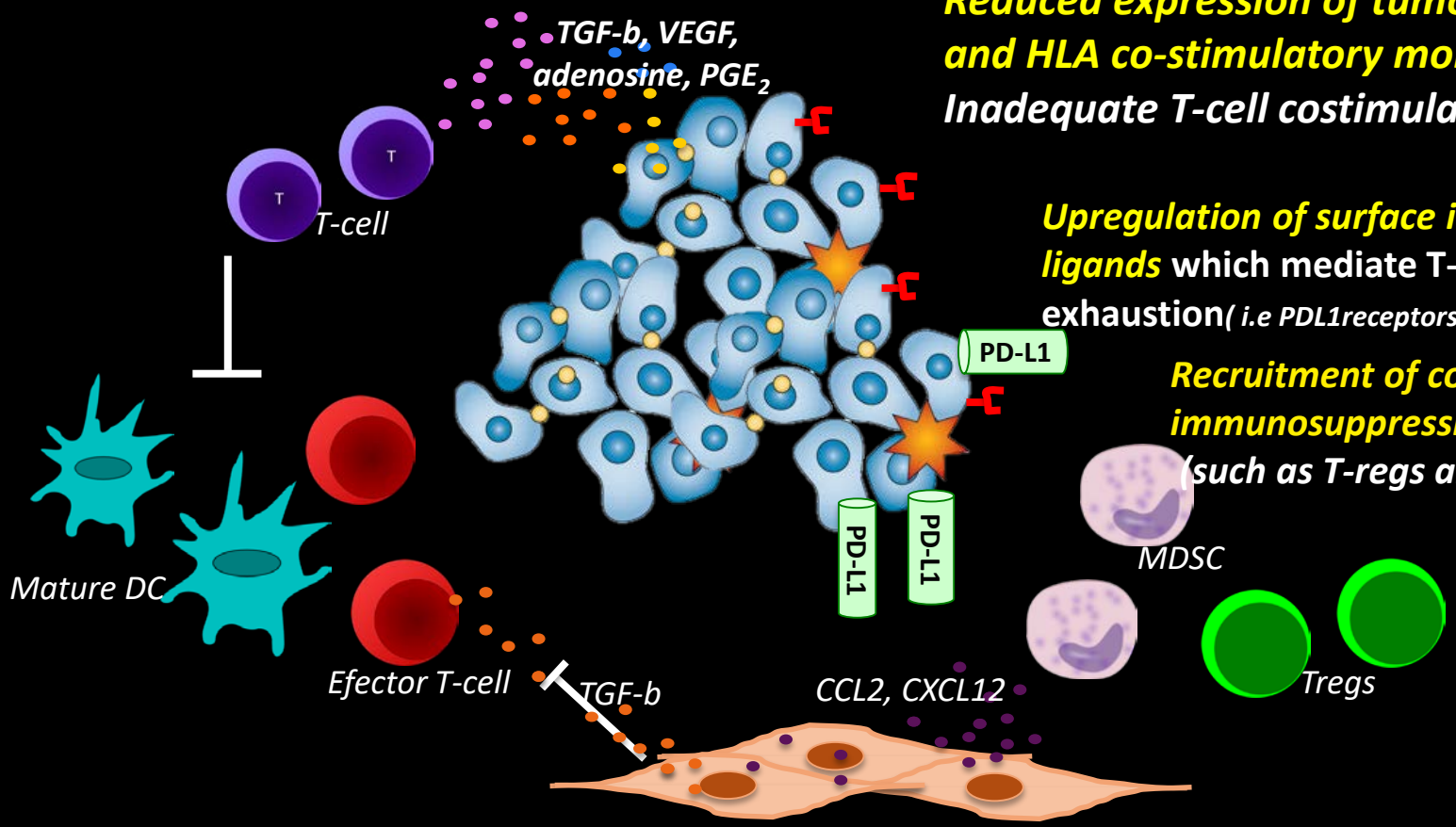
Impaired B cell differentiation and Ab response.

Reduced expression of tumor antigens and HLA co-stimulatory molecules[6]

Inadequate T-cell costimulation

Upregulation of surface inhibitory ligands* which mediate T-cell anergy / exhaustion*(i.e PDL1receptors)

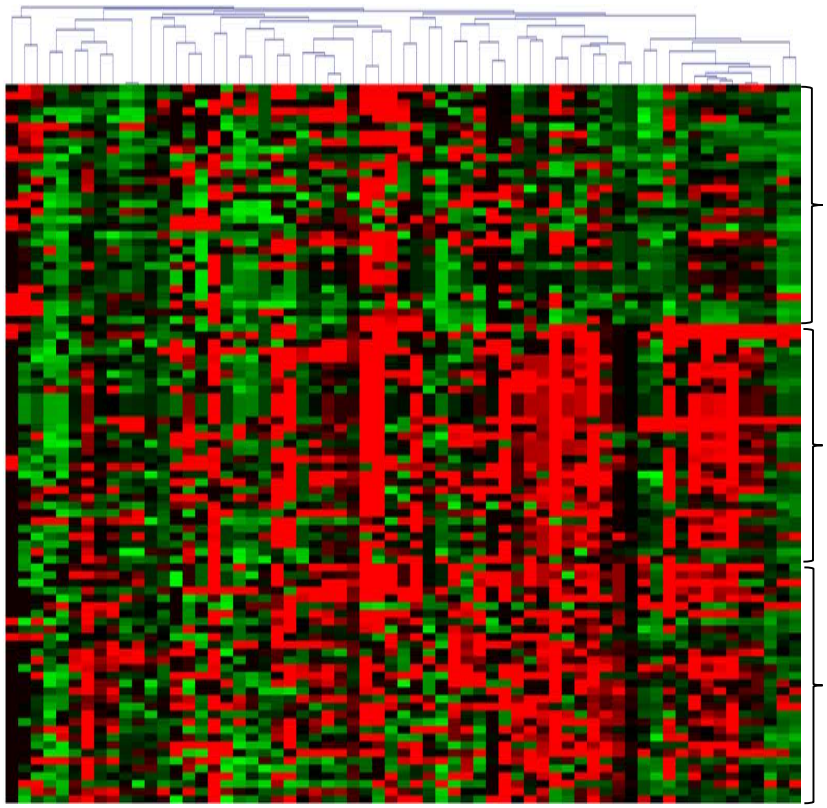
Recruitment of counterregulatory/ immunosuppressive cells (such as T-regs and MDSCs)

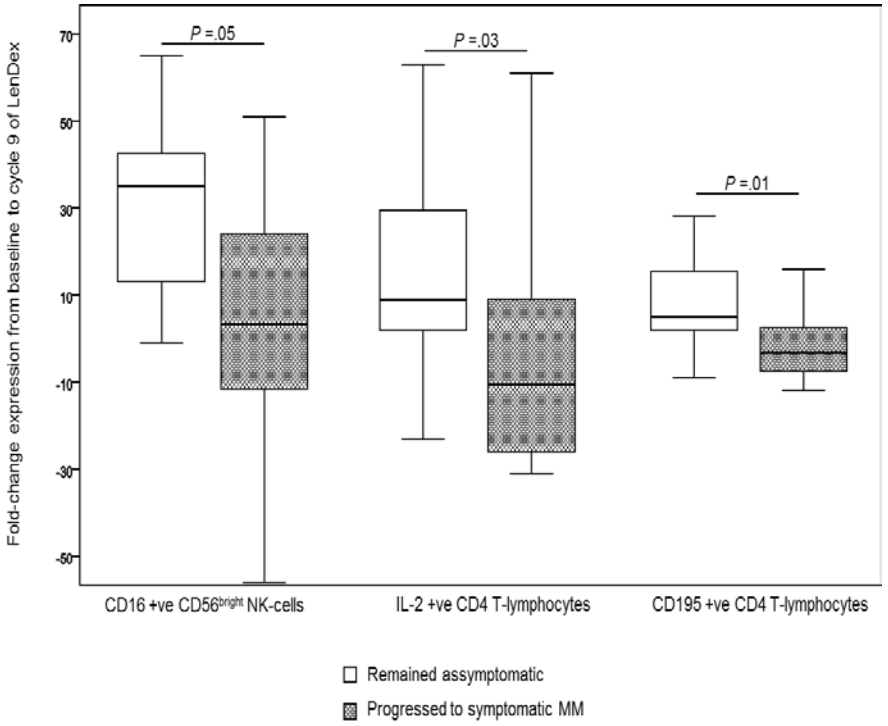


[1]Thomas DA, et al. Cancer Cell 2005; 8(5): 369-380; [2]Sze DM et al. Blood. 2001; 98(9):2817-27.[3]Brown RD et al. Leuk Lymphoma. 1998; 31(3-4):379-84.[4]Benson DM et al. Blood. 2010; 116(13):2286-94. [5]Paiva B et al. Leukemia 2015. 29(10):2110-13. [6]Pessoa de Magalhães RJ, et al. *Haematologica*. 2013;98(1):79-86

Therapeutic immunomodulation to delay the progression to active multiple myeloma: Lessons from QUIREDEX trial

Immunophenotypic expression profiling (IEP)



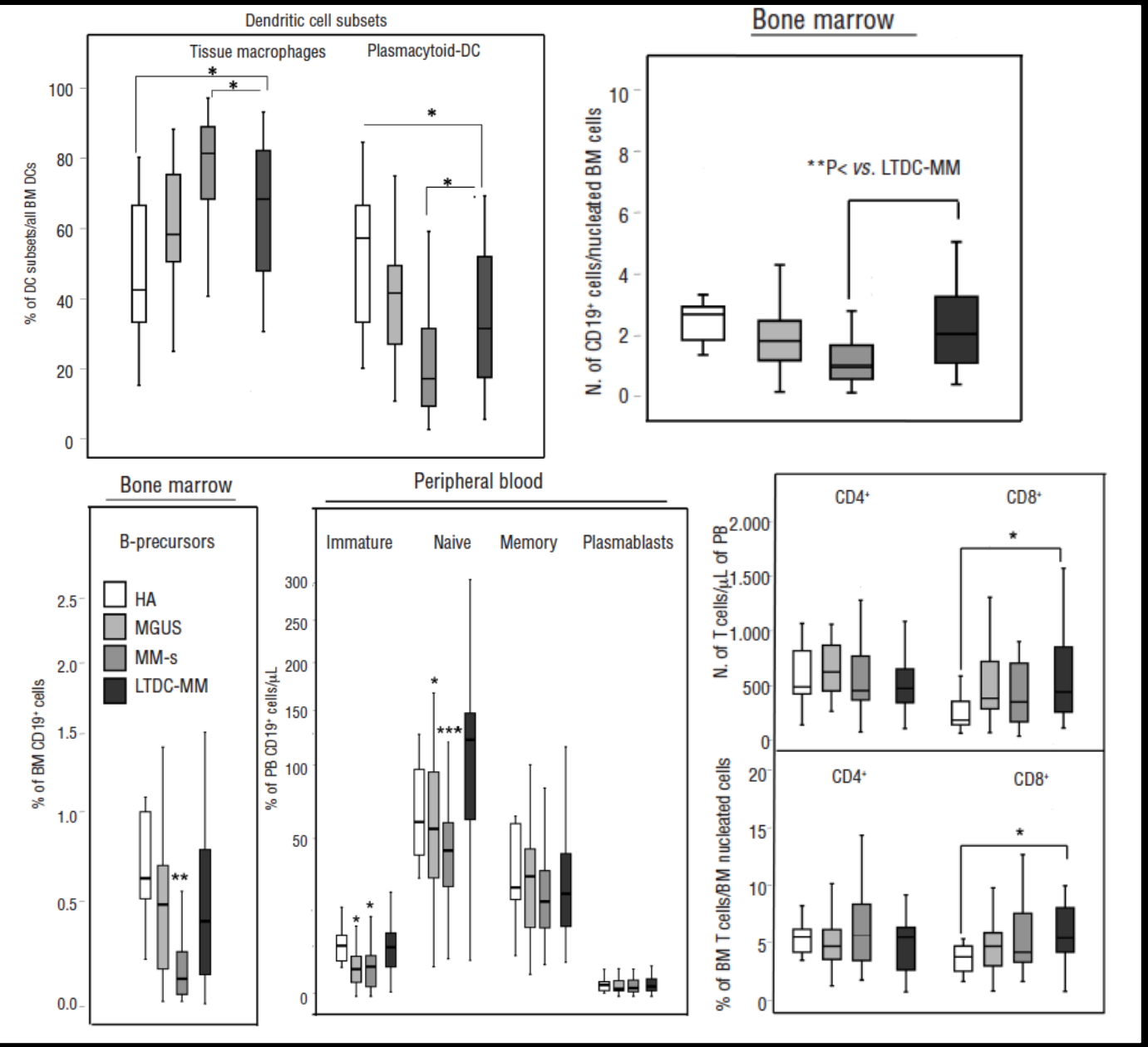


- **High risk SMM: decrease expression of activation, Th1 and proliferation related markers.**

- **IMID treatment restored this expression and induced shift in Tcell ad NK cell phenotype:**
  >*central memory Tcells & effector memory Tcells ; >expression of activation markers; >number of proliferating CD4 and CD8 T cells after treatment*

Paiva B, et al. Blood. 2015

Long-term MM survivors have unique immune changes suggesting *improve immune surveillance*



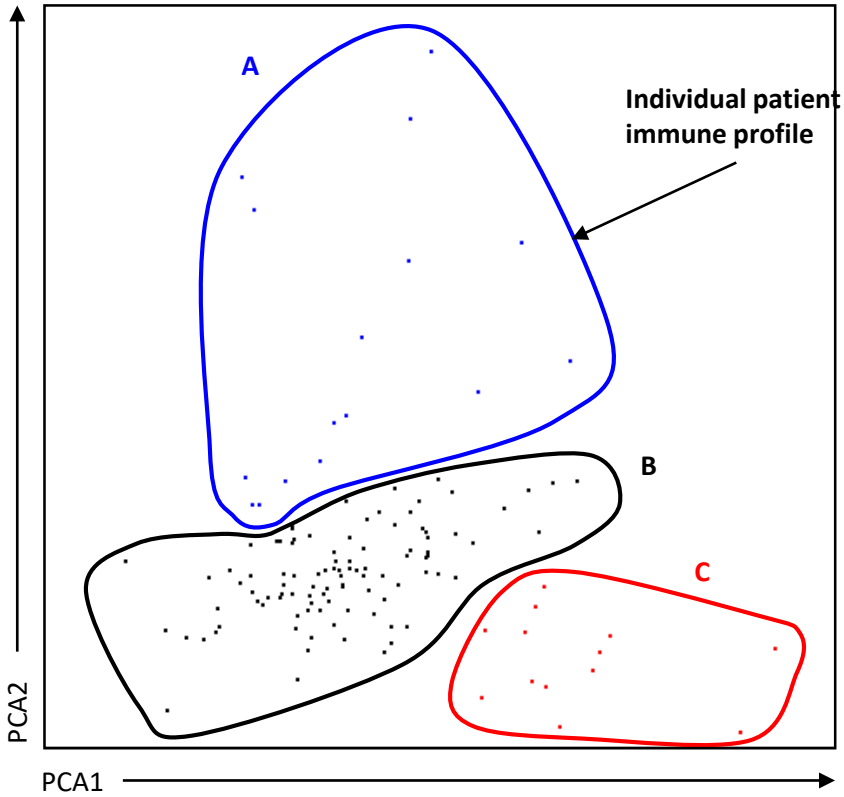
- Higher CD8+ effector cells
- Higher NK cells
- Higher B cells
- Higher normal PCs
- Higher dendritic cells
- Lower Tregs

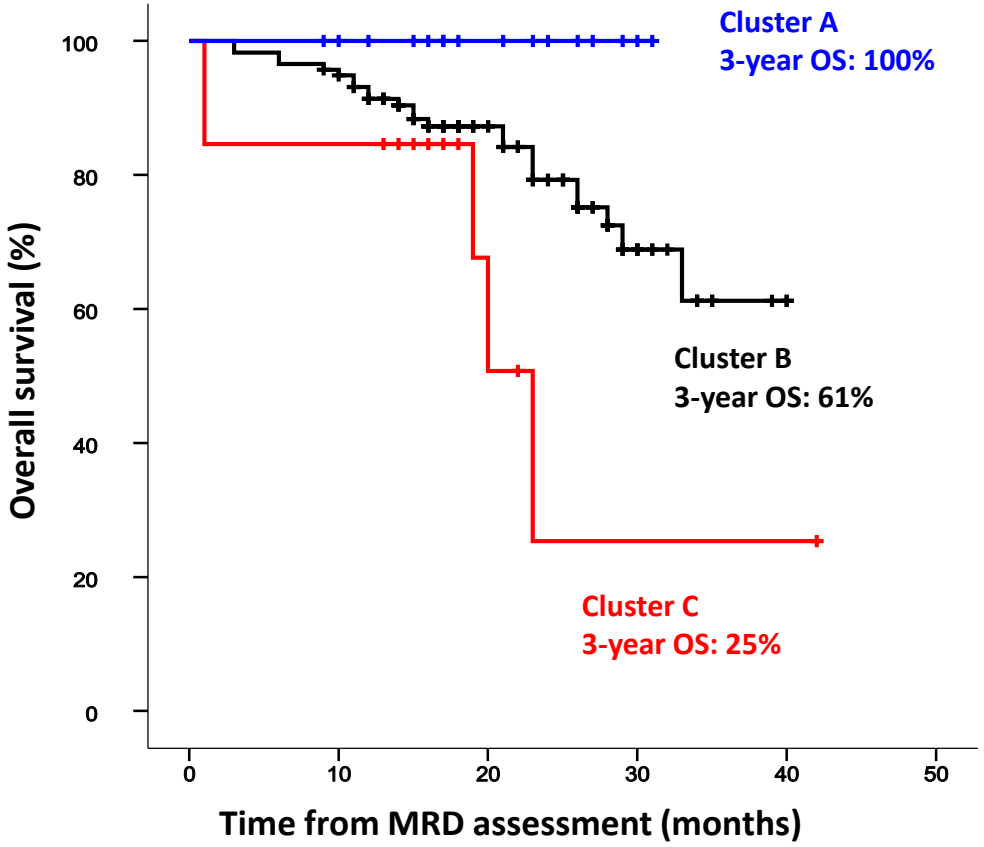
Improve immune surveillance

Pessoa de Magalhães RJ, et al. *Haematologica*. 2013;98(1):79-86.

Prognostic value of immune profiling during MRD monitoring

Immune signatures derived from Flow-MRD using a single 8-color MoAb combination

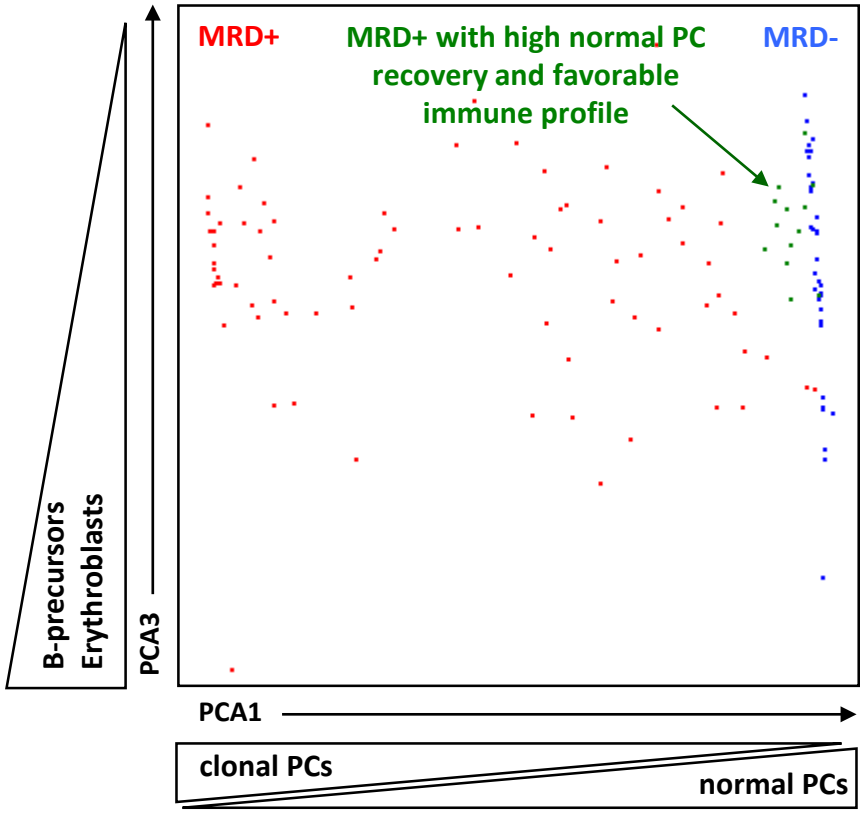


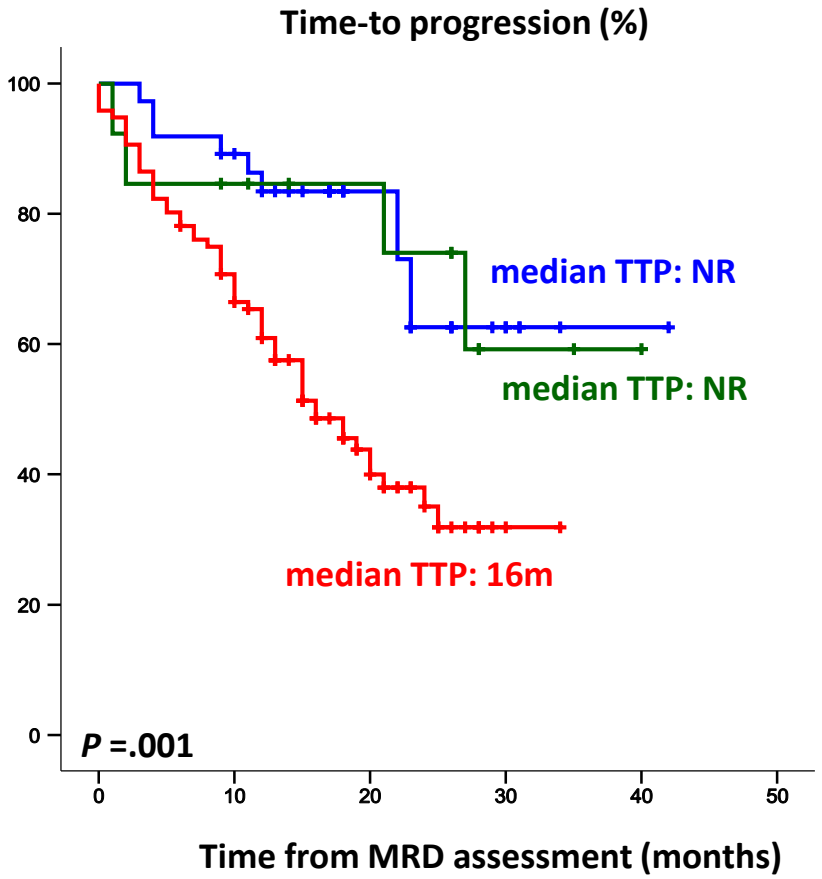


Recovery of B cells and neutrophils production…..good prognosis

Arana P, et al. Blood 2015 126:721

Identification of MRD+ve patients with favorable immune profile and superior outcome

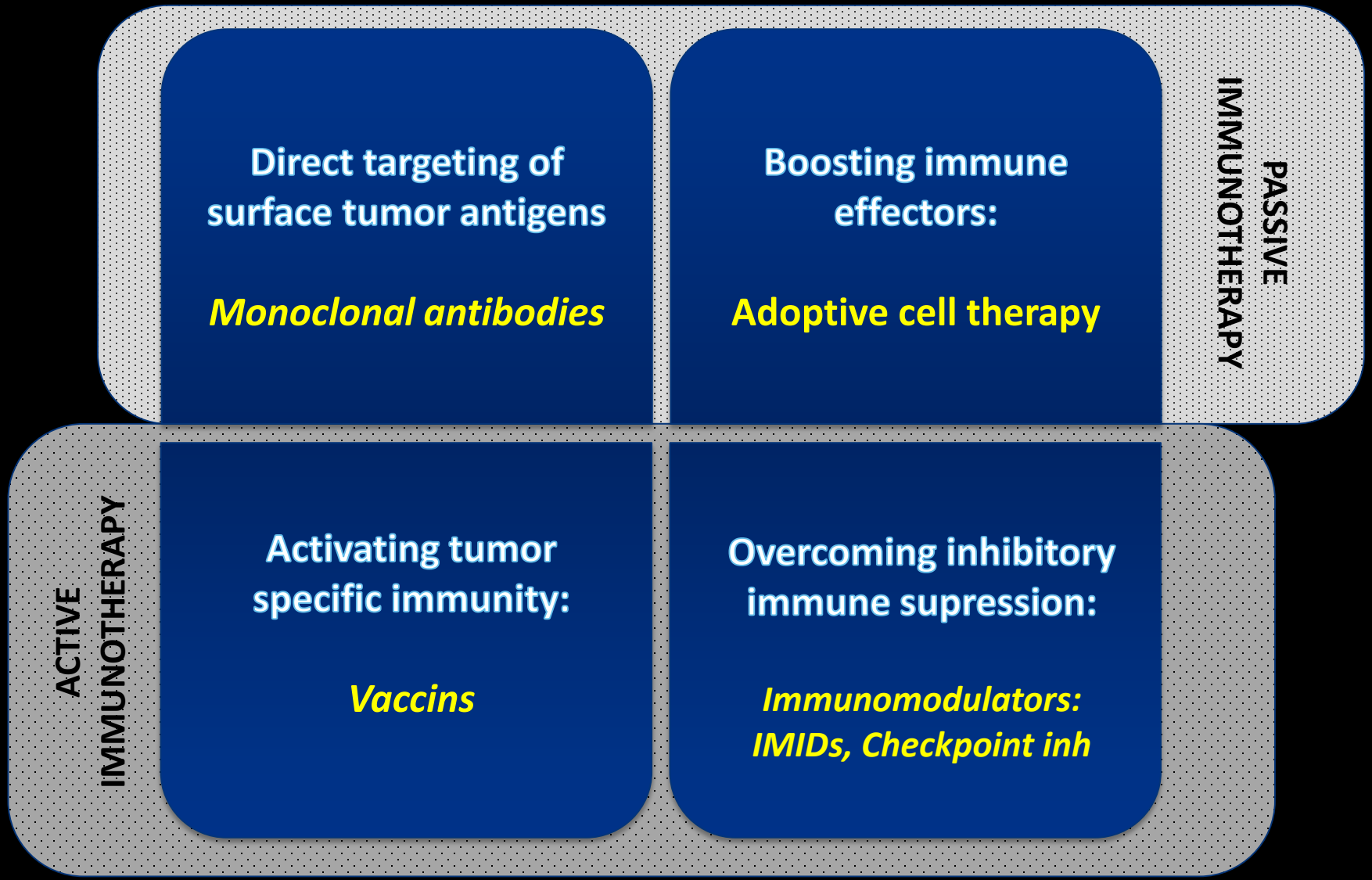




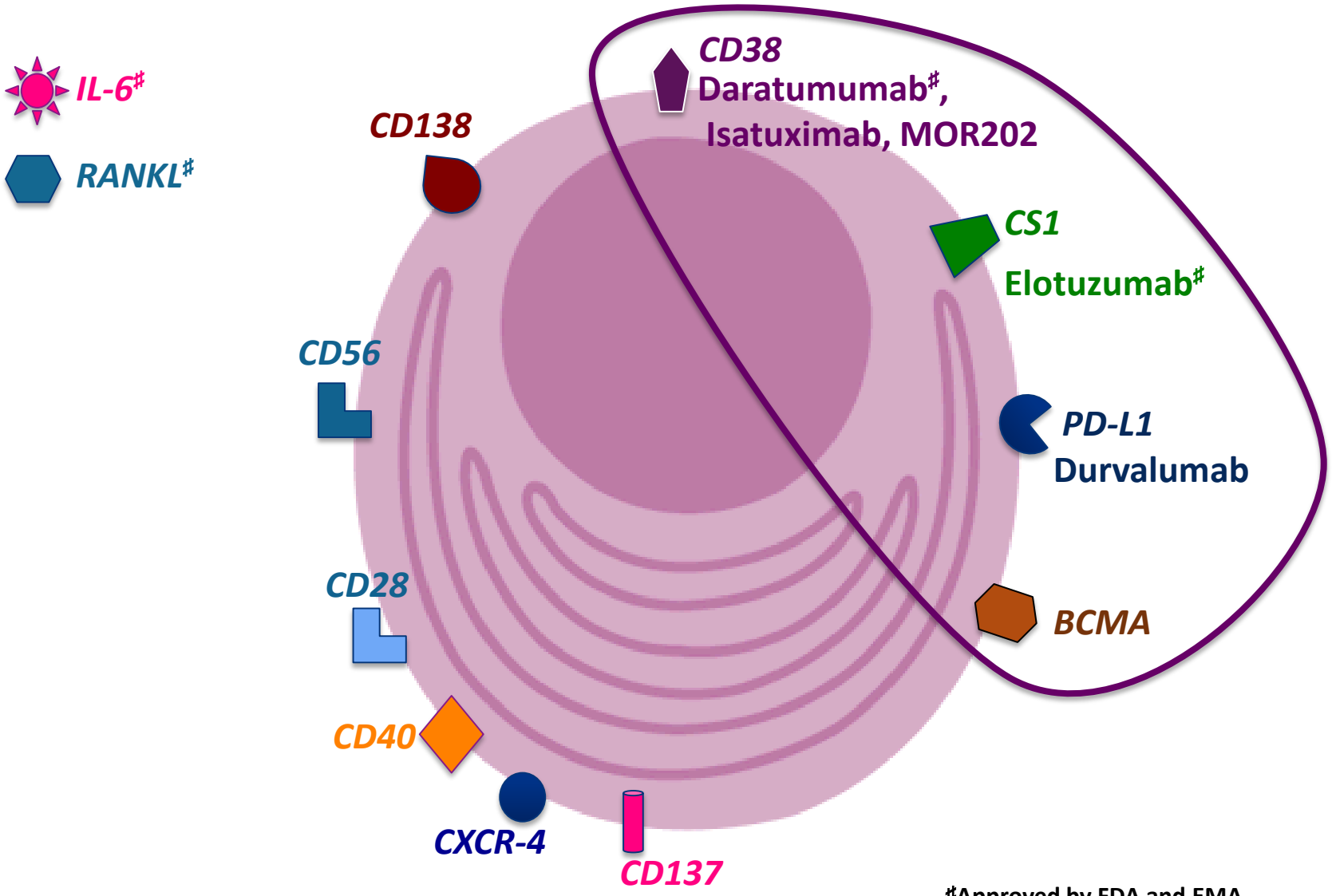
Multivariate analysis based on the distribution of 15 immune cell populations (including normal and clonal PCs) in the BM at the time of MRD assessment

Arana P, et al. Blood 2015 126:721

Four major targets for cancer immunotherapy

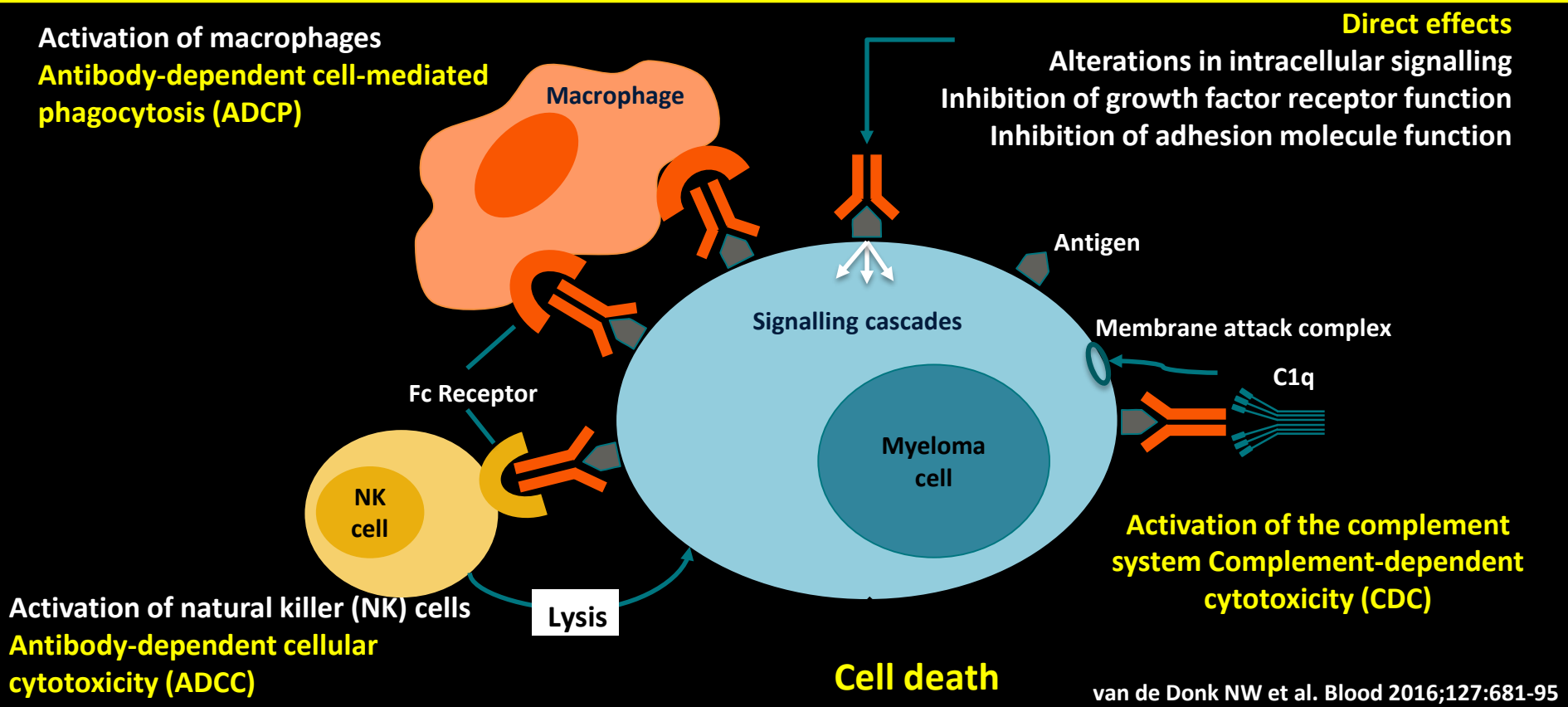


Surface antigens in clonal plasma cells



♯Approved by FDA and EMA

Monoclonal antibodies in Multiple Myeloma

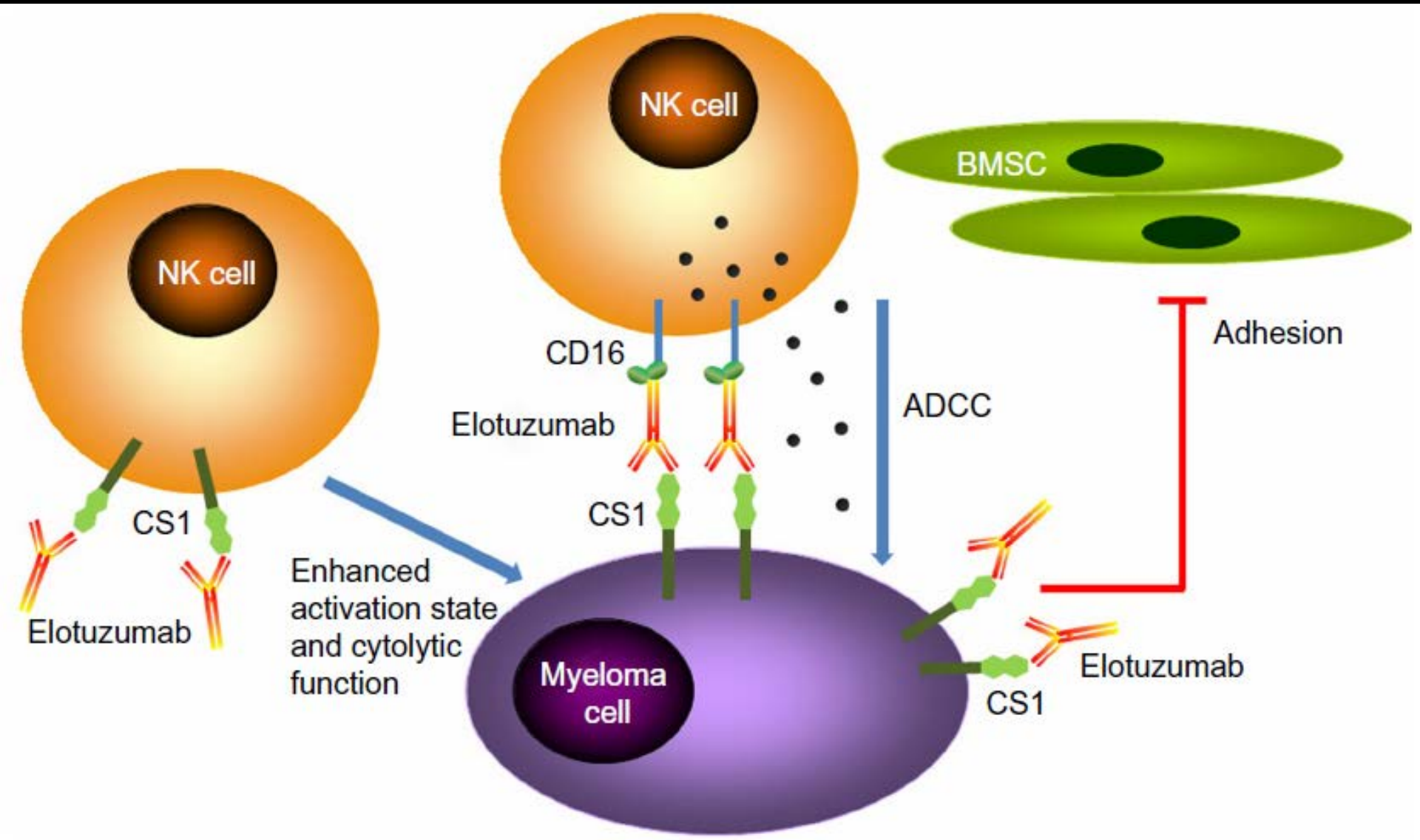


van de Donk NW et al. Blood 2016;127:681-95

- Elotuzumab (Anti-SLAMF7)
  - Single Agent[2]: 26% SD
  - Elo + Ld[3]: 92% ORR & 33m PFS[1]
  - Ld +/- ELO[1]: 19.4 vs 14.9 m[1]
- Anti-CD38: Daratumumab[4,5] & Isatuximab[6]
  - Single agent: 30-35% ORR, PFS 3.7m
  - + Len-Dex: 64-75% ORR (inc. Len ref.)

[1]*Lonial S, et al. NEJM 2015.* [2]*Zonder, Blood 2012.* [3]*Lonial, ASCO 2013. Abstract 854.* [4]Lokhorst HM et al. NEJM, 363:8, 2015. [5]Sagar Lonial, ASCO 2015, abstract 8512. [6]Martin et al. ASCO 2014; Abstract 8532

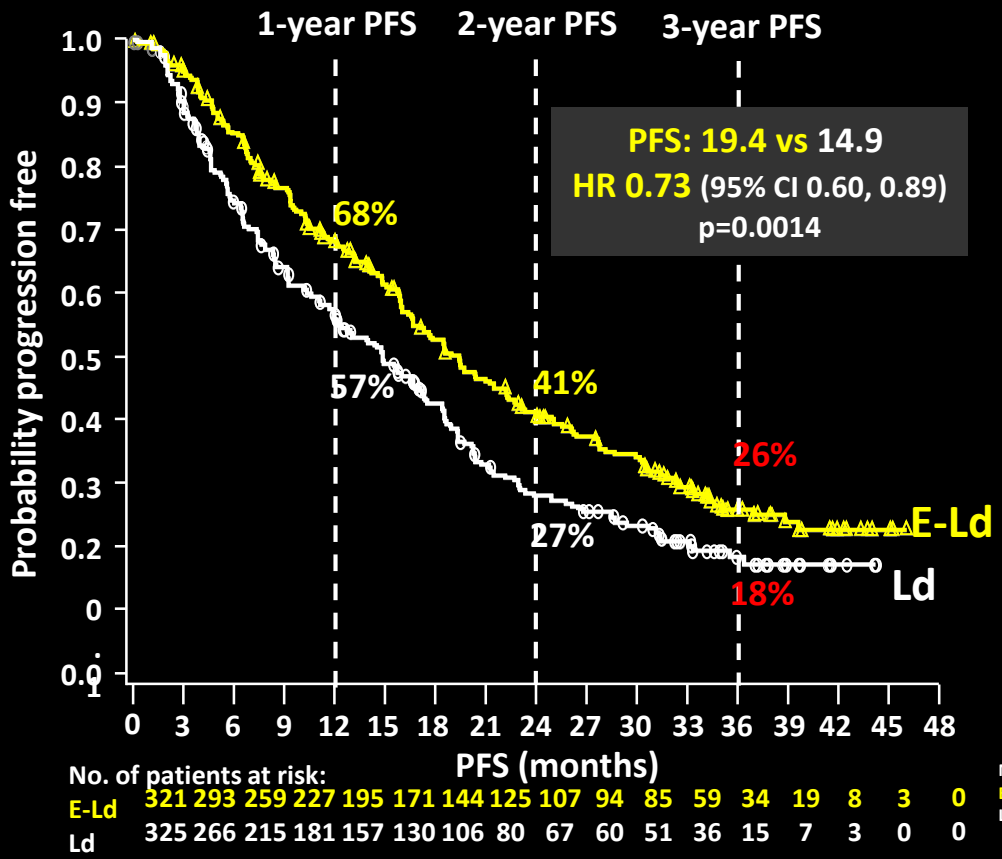
Elotuzumab (SLAMF7:Signaling Lymphocytic Activation Molecule F7: Anti-CS1)



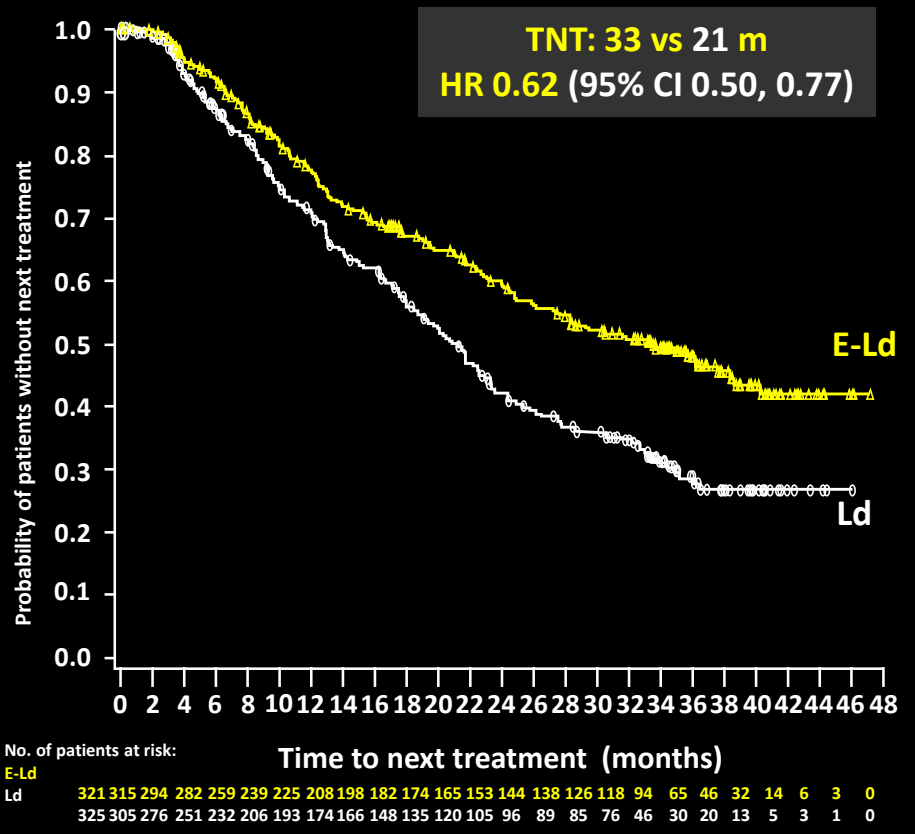
Eloquent-2 (Elo-Ld vs Ld): Extended PFS and TNT

ORR (ELd vs Ld): 79% vs 66%. ≥VGPR: 32.7% vs 27.9%

PFS (19.4 vs 14.9 m)



TNT (33 vs 21 m)

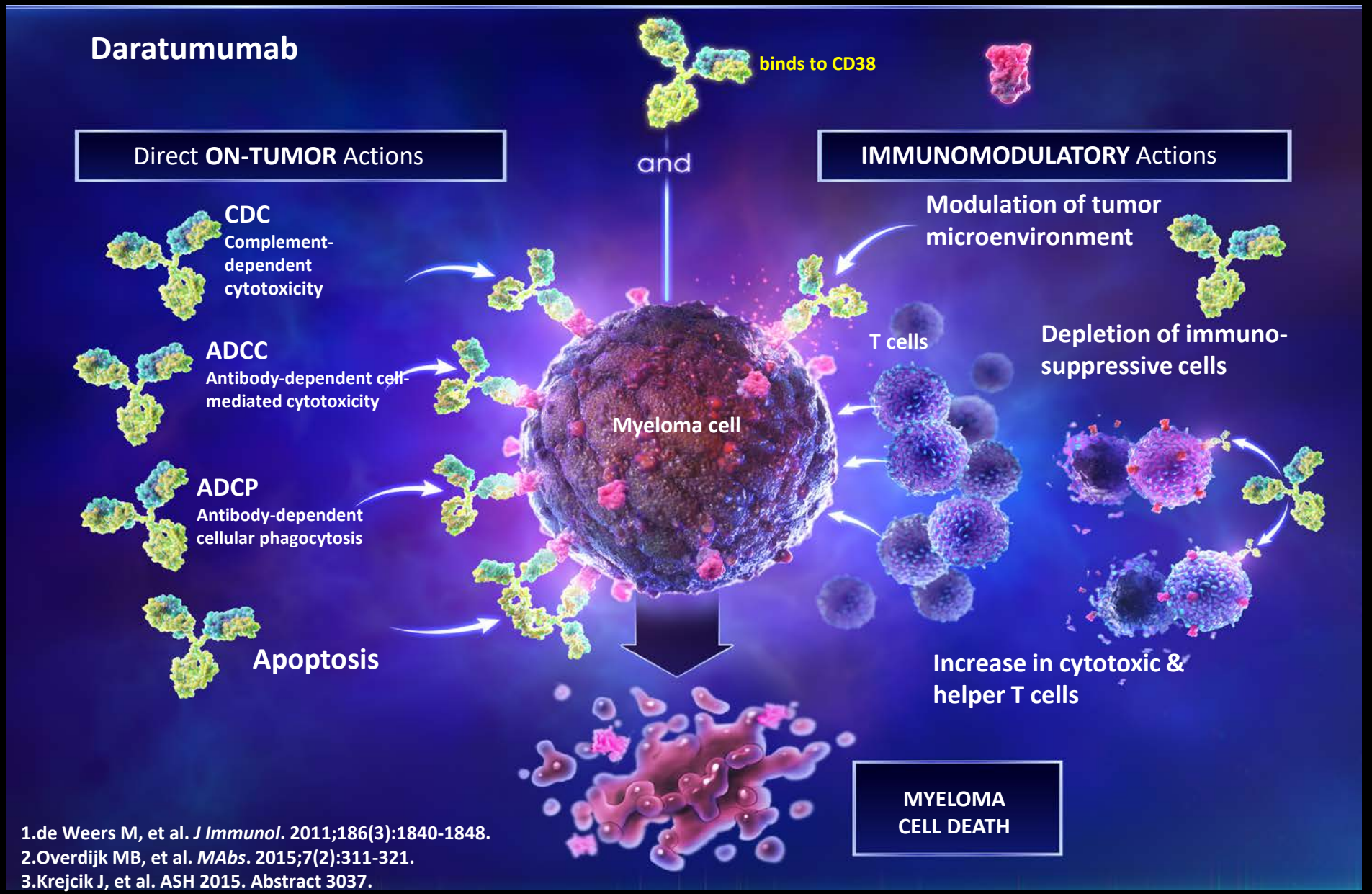


27% reduction in the risk of disease progression or death

Relative improvement in PFS of 44% at 3 years

Dimopoulos M, ASH 2015 Abst 28

Anti CD38 antibodies: Mechanisms of Action



1.de Weers M, et al. *J Immunol*. 2011;186(3):1840-1848.
2.Overdijk MB, et al. *MAbs*. 2015;7(2):311-321.
3.Krejcik J, et al. ASH 2015. Abstract 3037.

Anti CD38 in MM: single agent activity in RRMM

	Daratumumab	Isatuximab
Study details	3 studies: GEN501[1], SIRIUS[2] & combined analysis[4]	First in-human, phase 1 dose escalation[3]
Patients	Pts with rel/ref MM n=148 (SIRIUS n=42 and GEN501 n=106)	Pts with rel/ref MM N=97
Dose	16 mg/kg	Dose is not yet defined
Results	• **ORR 31%** ***(36% GEN501 & 29% SIRIUS)*** • **Median DOR: 7.6 m** • **1 year OS: 77% / 69%** • Median PFS: 5.6m , 3.7 m, Infusion-related reactions gr 1-2	• At ≥ 10 mg/kg: **24%** • Abnormal CA: 44% • Median DOR: 6.6 m • IARs: 49%, mostly grade ≤2, 94% during 1st infusion.

Dara/SAAR are CD38 MoAB showing activity as single agents in RRMM patients

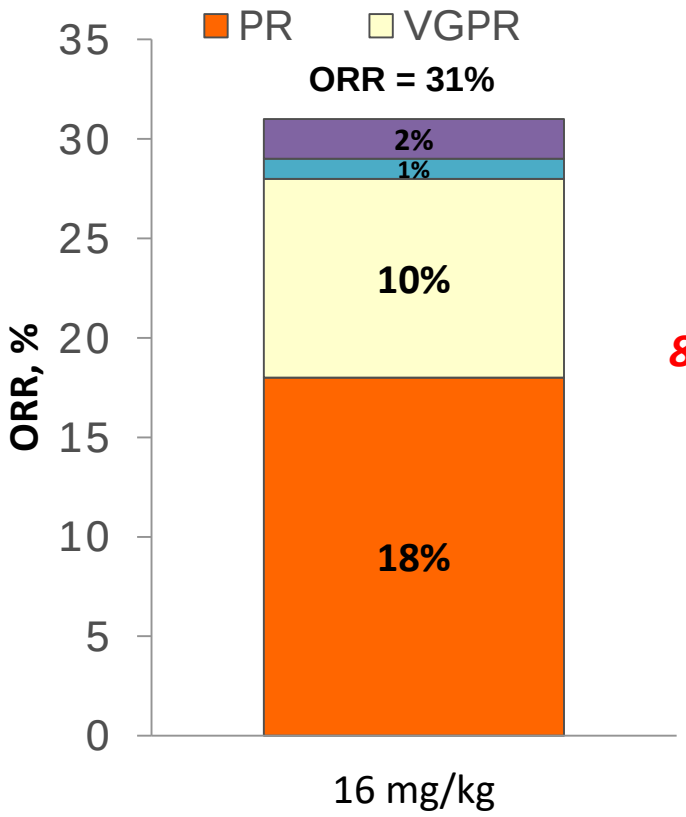
[1]Lokhorst HM et al, NEJM 2015, 363:8; [1]Lokhorst et al. ASCO 2014; Abstract 8513; Lonial S JCO 2015, [3]Martin et al. ASCO 2014; Abstract 8532; [4]Usmani S, et al ASH 2015 abstract 29, [5]Martin T, ASH 2015 abstract 509; Richter JR, et al. ASCO 2016; J Clin Oncol 34, 2016 (suppl; abstr 8005)

COMBINED ANALYSIS: Refractory status

	16 mg/kg		
Refractory to, n (%)	**GEN501, Part 2 n = 42**	**SIRIUS n = 106**	**Combined N = 148**
Last line of therapy	32 (76)	103 (97)	135 (91)
Both PI and IMiD PI only IMiD only	27 (64) 3 (7) 4 (10)	101 (95) 3 (3) 1 (1)	**128 (86)** 6 (4) 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. Blood 2016

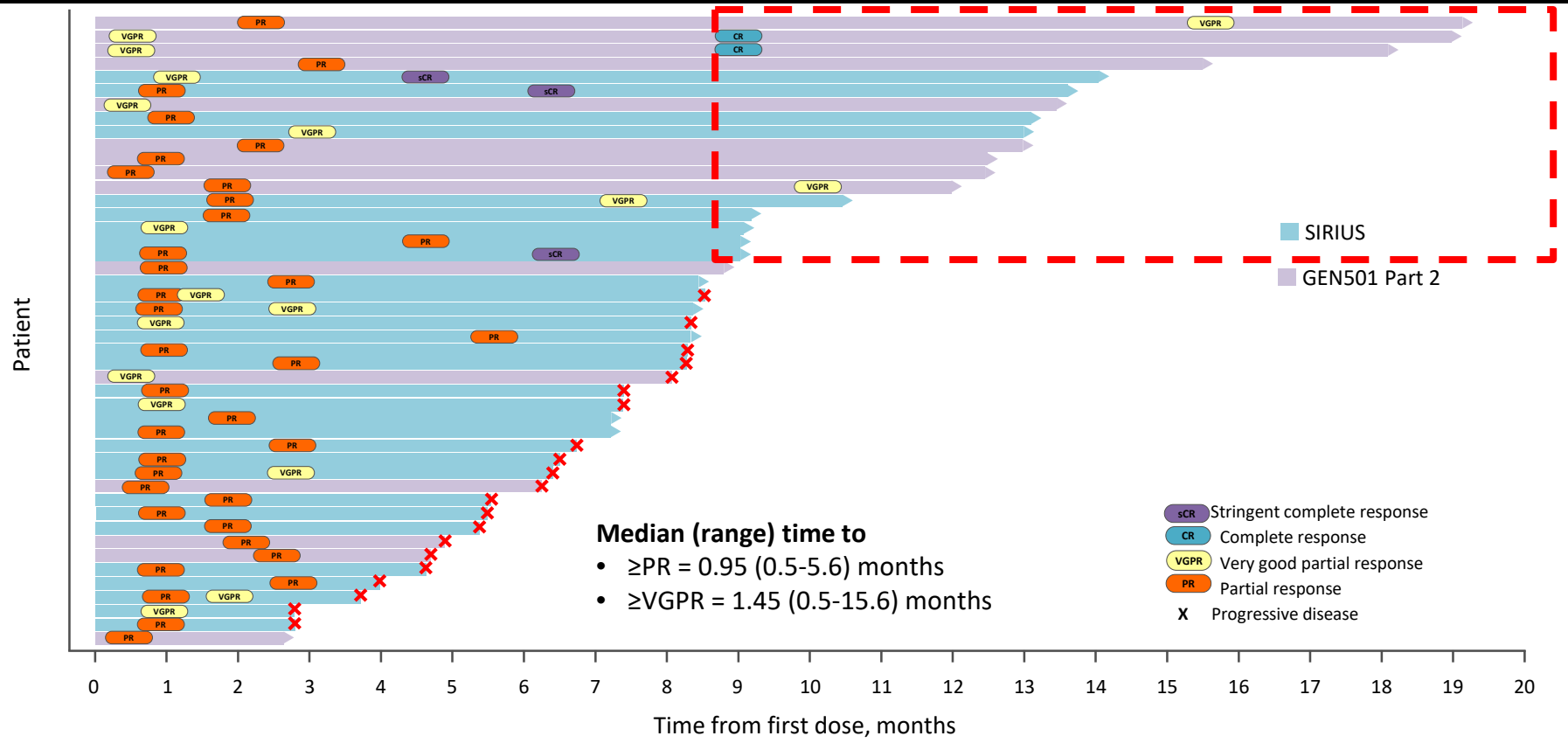
GEN502/SIRIUS: Overall response



83.1% of SD or better

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

GEN502/SIRIUS: Depth and DOR

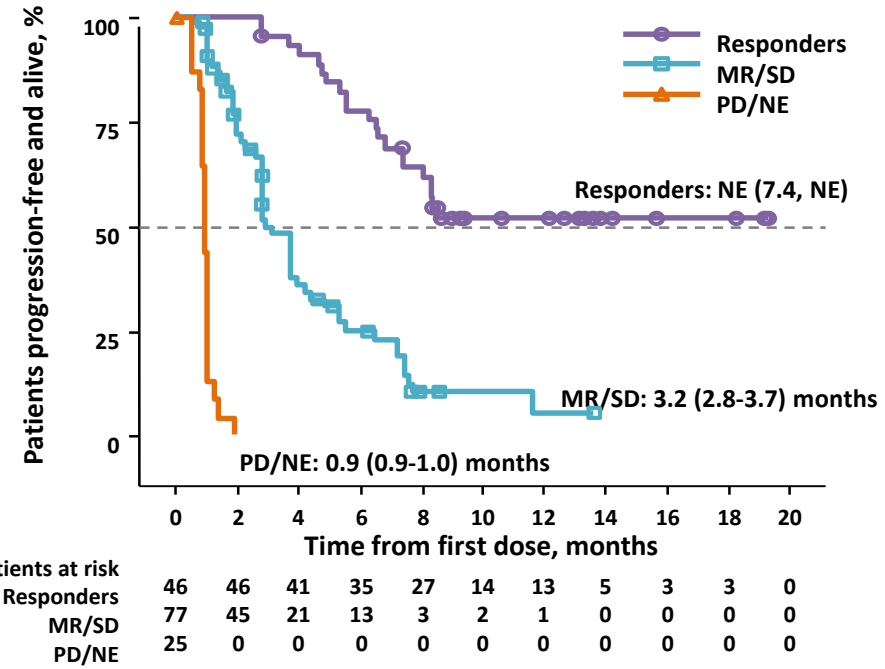


- In many patients, responses deepened with continued DARA treatment
- **Median DOR = 7.6 (95% CI, 5.6-NE) months**
- At a median follow-up of 14.8 m, 50% (95% CI, 33.6-63.9) of responders were progression-free at 12m

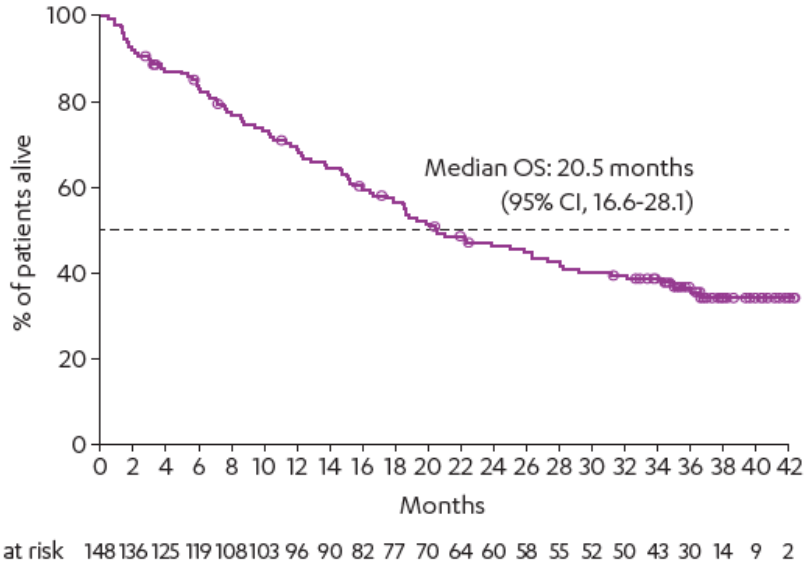
Combined analysis:

Two studies: GEN501 & SIRIUS – PFS and OS analysis

Progression-free survival



Overall Survival



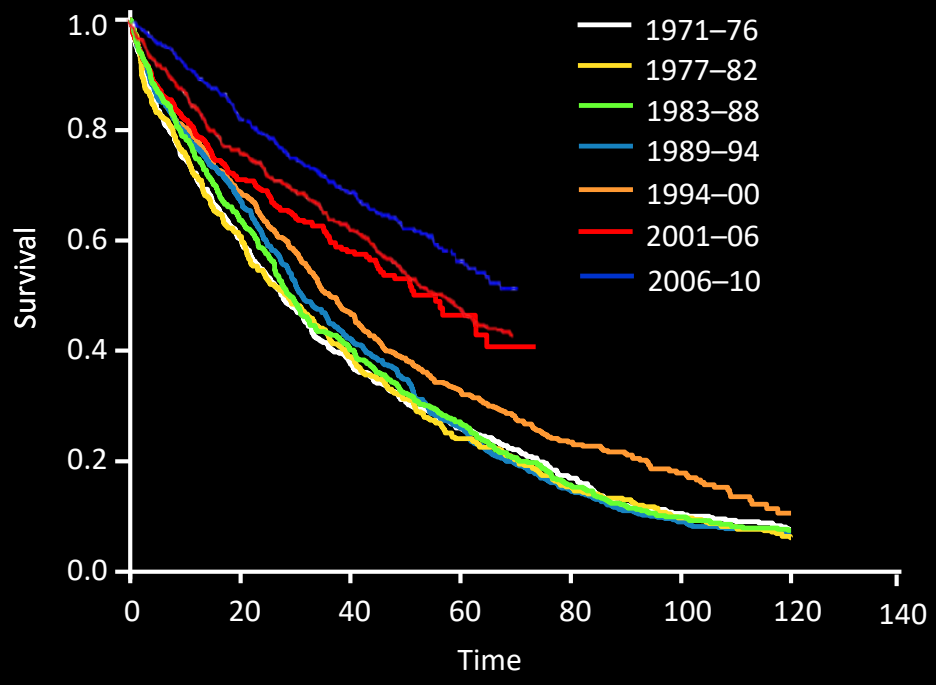
OS, overall survival; CI, confidence interval.

- **For the combined analysis, median OS = 20.5 months (95%IC, 16.6 – 28.1m)**
- **1-year overall survival rate = 69% (95% CI, 60.4-75.6)**

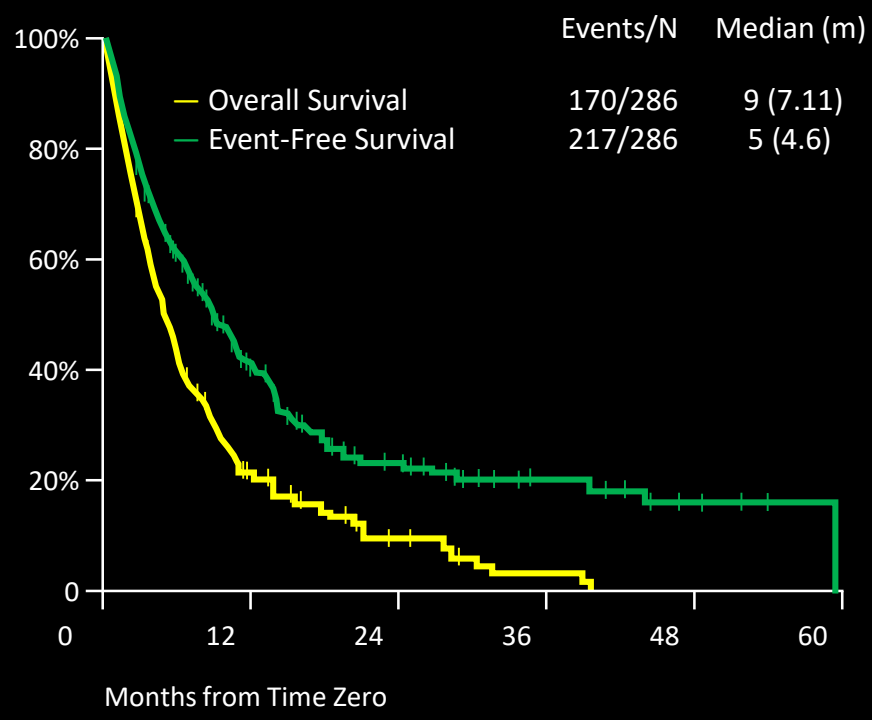
Usmani S, et al. Blood 2016. Usmani et al. ASH 2017. Poster presentation. #3107

Outcome in patients refractory to novel agents

Evolution of MM OS over the years



Outcome of pts refr to Btz & IMIDs*



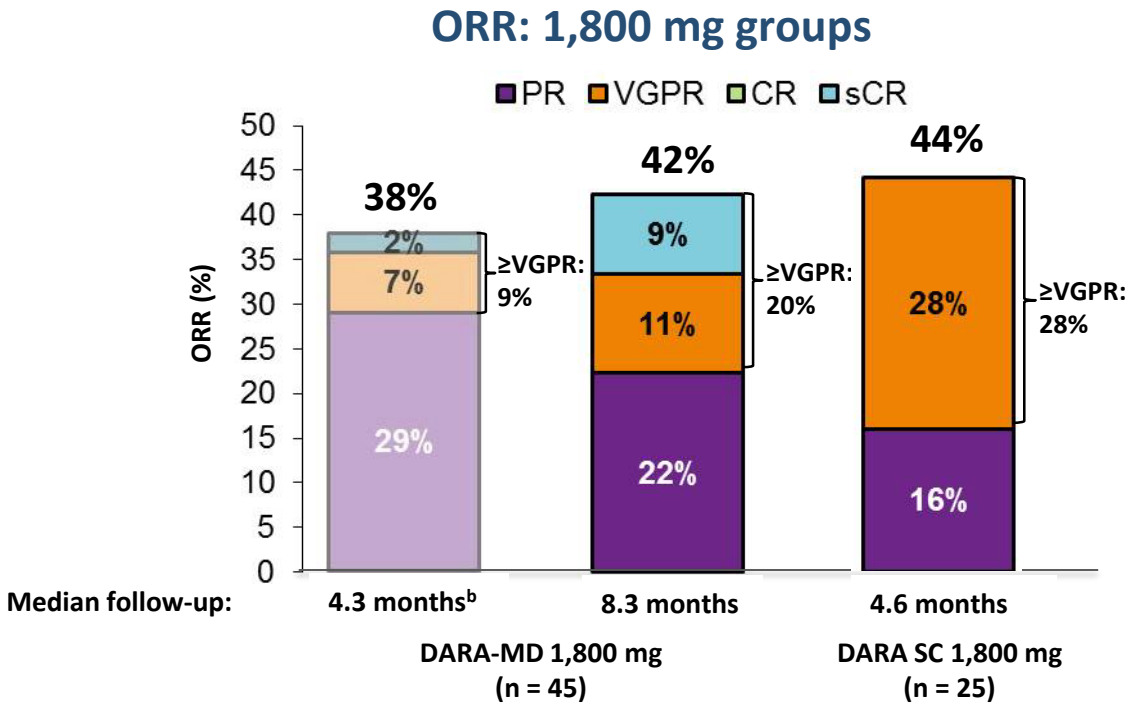
Despite the benefit observed with novel agents in the last years,
… other drugs are still needed for relapsed/refractory patients

** 286 pts refractory to BTZ and relapsed or refractory or ineligible to receive an IMiD*

Kumar, Blood 2008 *Kumar, Leukemia 2014* *Kumar, Leukemia 2012*

Daratumumab - Subcutaneous Formulation

PAVO – MMY1004 phase I trial



SAFETY PROFILE:

- **Treatment related AEs**: 48% all grade TEAEs.
  - Grade 3-4 hematologic AEs: 4% anemia and 8% thrombocytopenia
  - Grade 3-4 non-hematologic AEs: 4% fatigue, 4% hypertension
- **IRR**: 12%
- **Injection site reactions**: 20% erythema, 4% induration.

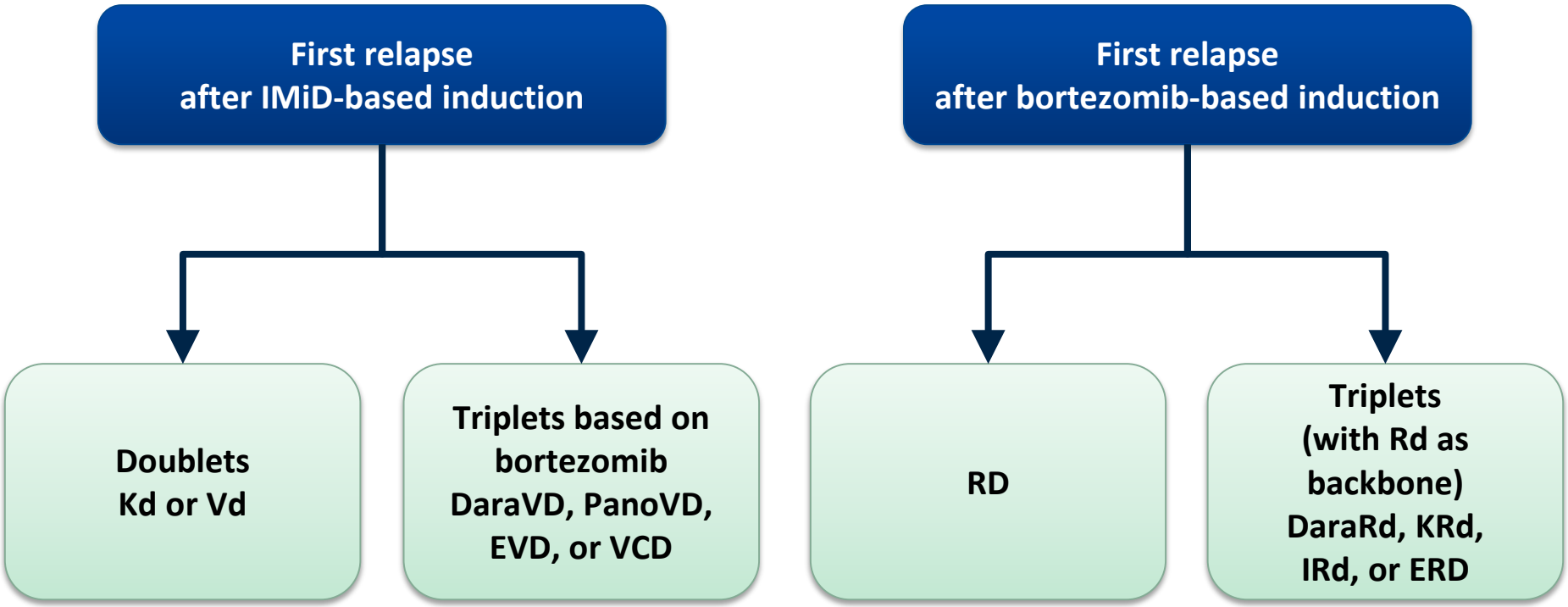
Chari et al. ASH 2017. Oral presentation

Anti-CD38 MoAb plus IMIDs in relapse or RRMM

		Study population	Results
AntiCD38 + LEN + Dex	POLLUX trial DaraRD vs Rd Phase III	Relapse MM >1 prior lines Len-Sensitive	ORR: 93% vs 76% CR rate: 46% vs 20% PFS: NR vs 17.5 m HR for PFS: 0.41 (p<0.0001)
	Phase Ib Isatuximab + Rd	RRMM 84% refractory to IMIDs	ORR 58% (6% sCR, 23% VGPR, 29% PR) PFS 6.2 months
AntiCD38 + POM + Dex	Phase I Dara-Pom-Dex	>2 prior lines PI & IMID exposed	ORR = 71% (9% CR/sCR). 67% double- ref.
	Phase I Isa-Pom-Dex	>2 prior lines PI & IMID exposed	ORR 64% Len-ref. ORR 67% (10mg/kg 2QW)

San Miguel JF, et al. IMWG 2017; **Chari A, ASH 2015 Abst 508; Richardson P et al. IMWG 2017;** Martin et al. ASH 2014 (Abstract 83).

Therapeutic options for patients with relapsed/refractory multiple myeloma

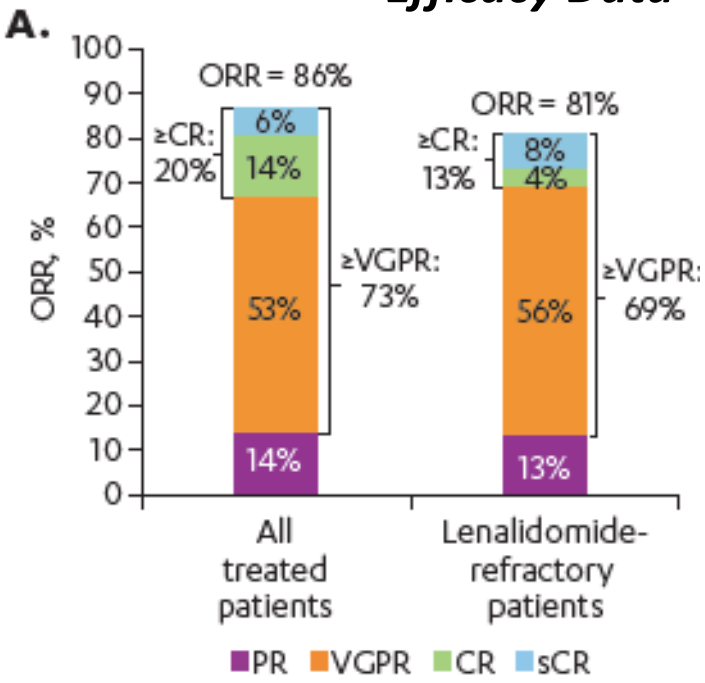


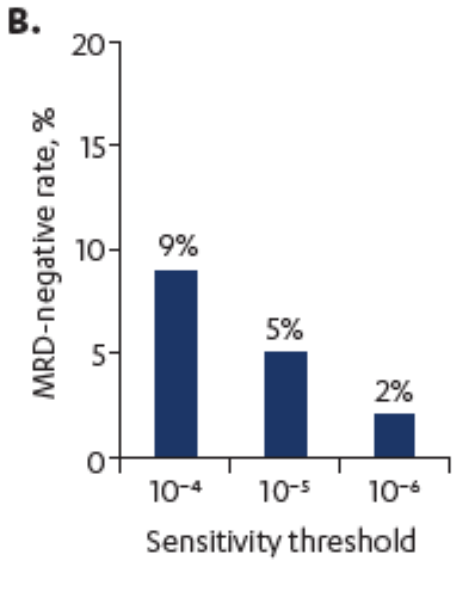
Dara, daratumumab; ERD, elotuzumab, lenalidomide, dexamethasone; IRd, isatuximab, Rd; KRd, carfilzomib, Rd; Pano, panobinostat.

Moreau P, et al. Ann Oncol. 2017;28 Suppl 4:iv52-61.

Novel combinations
Dara + KD (phase I MMY1001 trial)

Efficacy Data

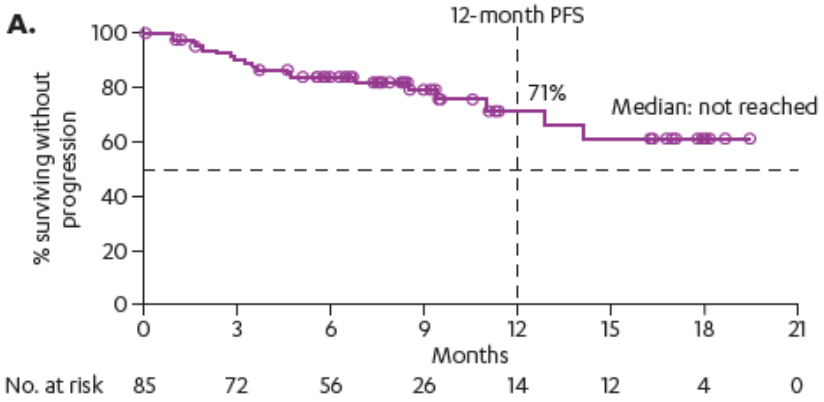




- Median duration of response was not reached (95% CI, 13.1 months-not estimable)
- Median PFS was not reached (95% CI, 12.9 months-not estimable;
  - 12-month PFS rate was 71% (95% CI, 55-83)
- In lenalidomide-refractory patients, median PFS was 14.1 (95% CI, 9.4-not estimable) months
  - 12-month PFS rate was 69% (95% CI, 49-82)

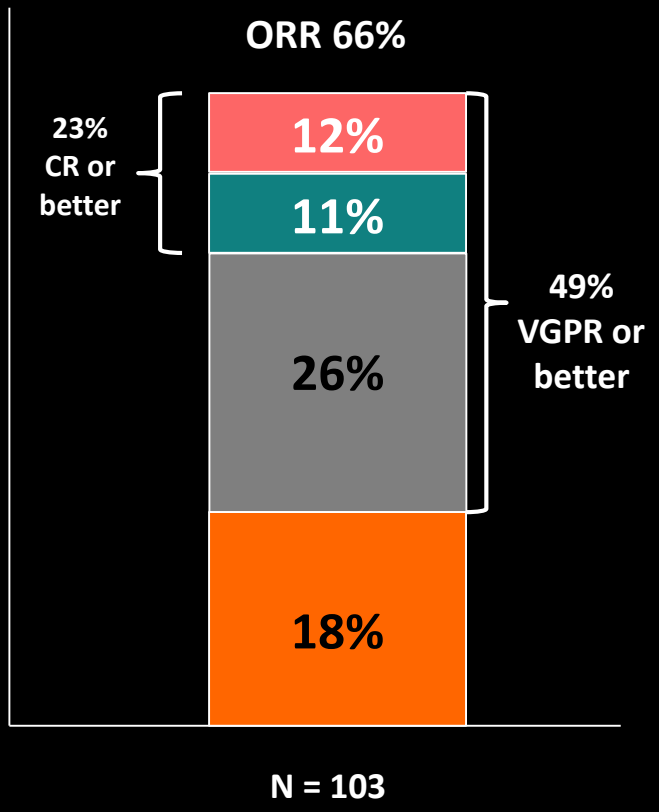
Safety profile

- Most frequent AEs: thrombocytopenia (64%)
- 38% asthenia
- IRR 60% in the single dose group and 40% split dose.
- Adequate safety profile.



Lonial S, et al. ASH 2017. Poster. Abstract 1869

Daratumumab + Pomalidomide + Dex
Phase 1 data



- Median nº of prior lines: 4 (1 – 13)
- 52% had > 3 prior lines
- **Median DOR: 21.4 m**
- **Median PFS: 9.9 m**
- **Median OS: 25.1 m.**
- *Rates of grade ≥3 AEs were similar to those observed with POM-D alone*

Facon T, et al. ASH 2017. Blood 2017; 130:1824

Similar results with Isatuximab-Pd

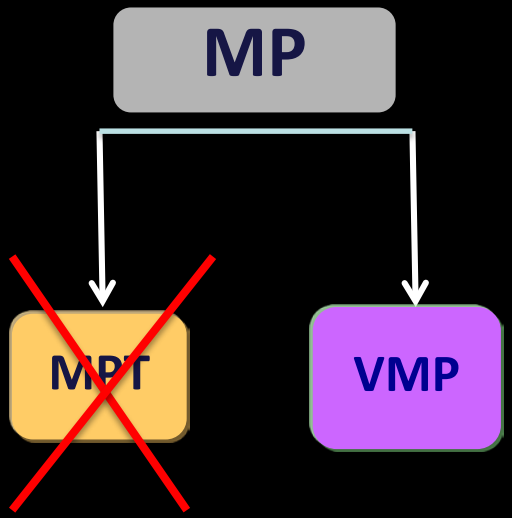
ORR 56%. Len-refractory: 58%

Richardson PG et al. ASH 2017.

Moving to the frontline setting

New standards of care for elderly MM patients

Alkylators-based regimens



Six randomized trials:

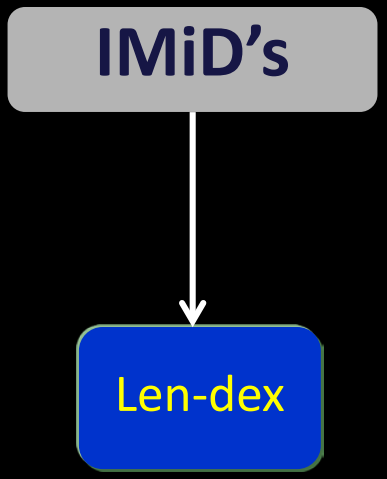
Benefit in PFS&OS...6m

One randomized trial:

Benefit in PFS...8m

OS...13m

Alkylators-free regimens



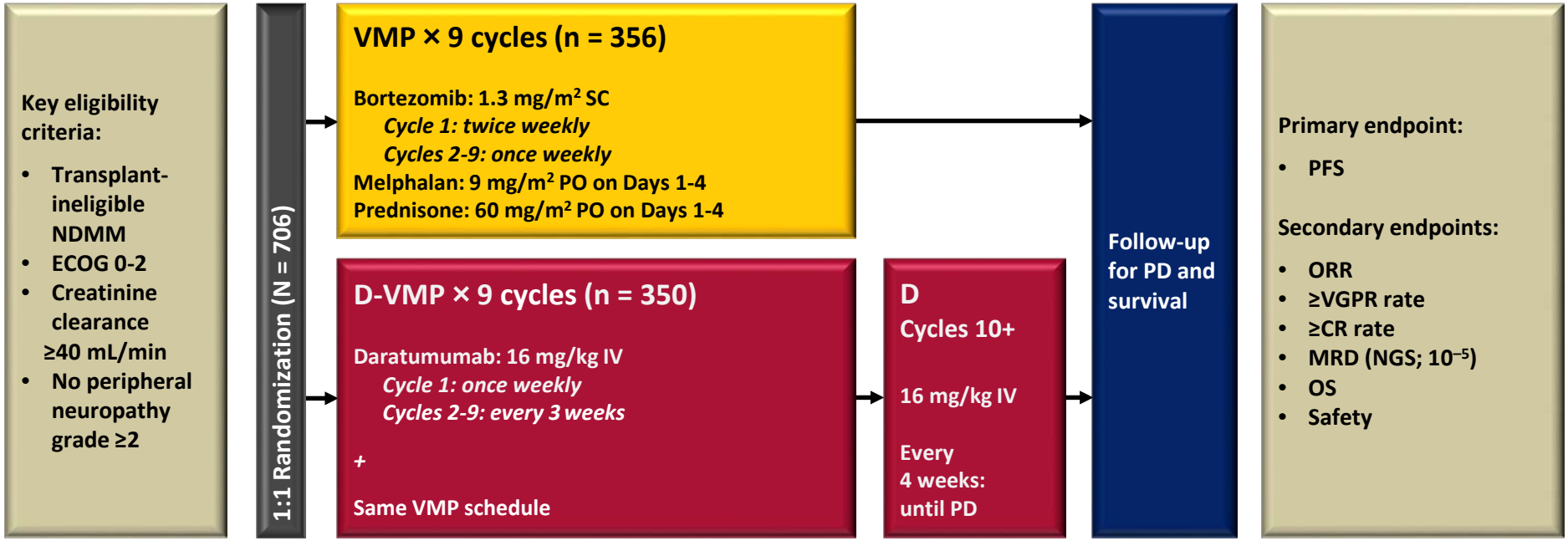
One randomized trial:

Benefit in PFS&OS vs MPT

Fayers PM et al. Blood 2011; 118(5): 1239-47
San Miguel. N Engl J Med 2008;359:906-17
San Miguel . J Clin Oncol. 2013; 31: 448-55

Benboubker L, et al. NEJM 2014; 371: 906-17

Moving to the frontline setting
Dara + VMP (ALCYONE phase III trial)



Stratification factors
- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

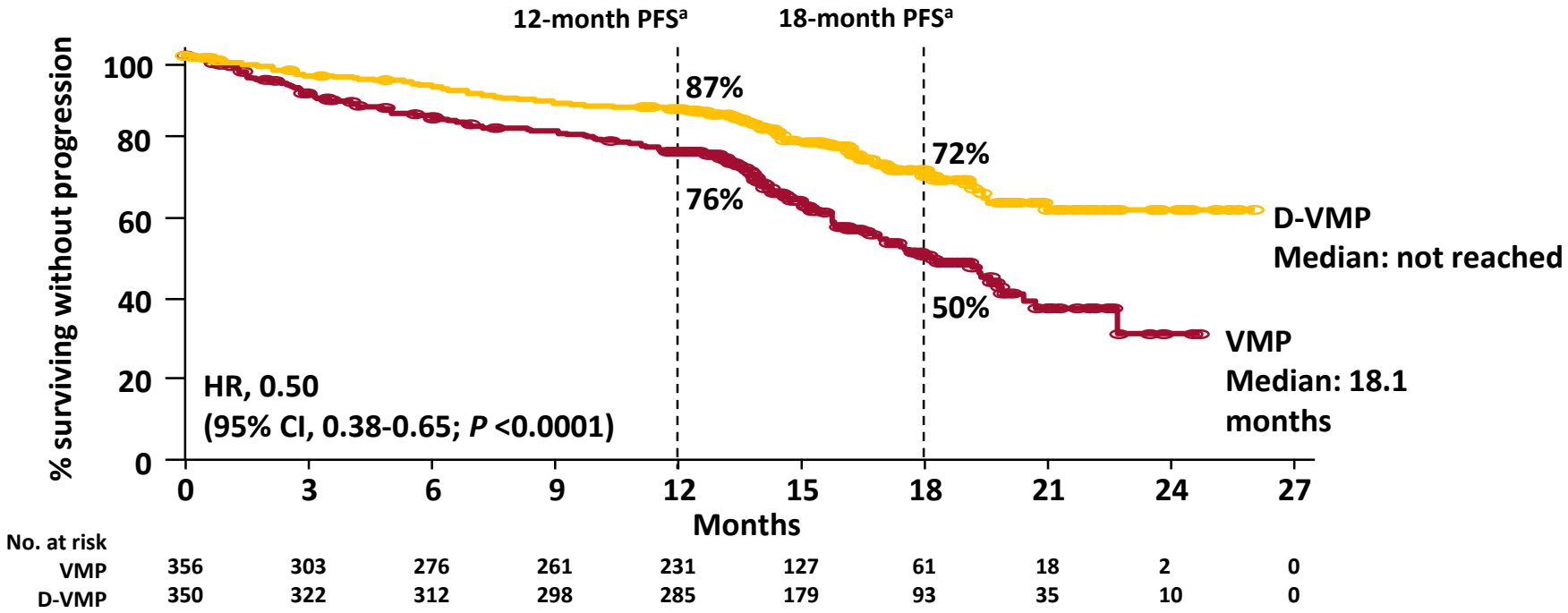
Statistical analyses
- 360 PFS events: 85% power for 8-month PFS improvement
- Interim analysis: ~216 PFS events

Mateos MV, et al. Presented at ASH 2017 (Abstract LBA-4). Mateos MV, et al. NEJM 2018.

Dara-VMP (ALCYONE phase III trial
Responses and PFS

ORR D-VMP vs VMP: 91% vs 74%. **CR rates: 43% vs 24%.**

- Median (range) follow-up: 16.5 (0.1-28.1) months



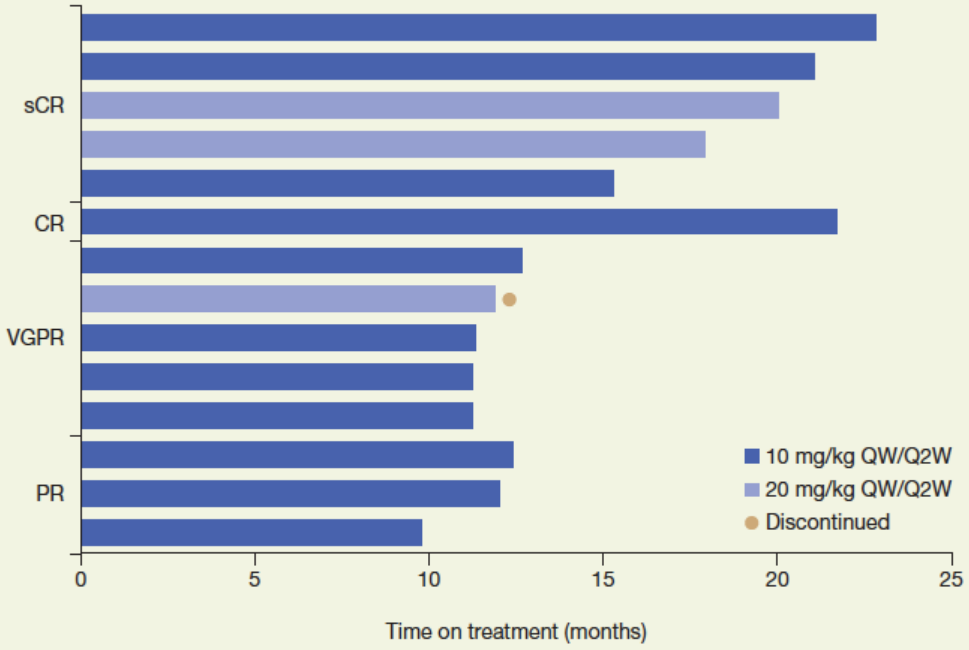
50% reduction in the risk of progression or death in patients receiving D-VMP

Mateos MV, et al. Presented at ASH 2017 (Abstract LBA-4). Mateos MV, et al. NEJM 2018.

Isatuximab – CyBORDex Phase I trial
ORR

ORR: 93.3%
sCR: 33%
Median DOR: 10 months

n, (%)	Isatuximab dose (mg/kg) and schedule		
	10 QW/Q2W (n=12)	20 QW/Q2W (n=3)	All (n=15)
ORR	11 (91.7)	3 (100)	14 (93.3)
sCR	3 (25.0)	2 (66.7)	5 (33.3)
CR	1 (8.3)	0	1 (6.7)
VGPR	4 (33.3)	1 (33.3)	5 (33.3)
PR	3 (25.0)	0	3 (20.0)



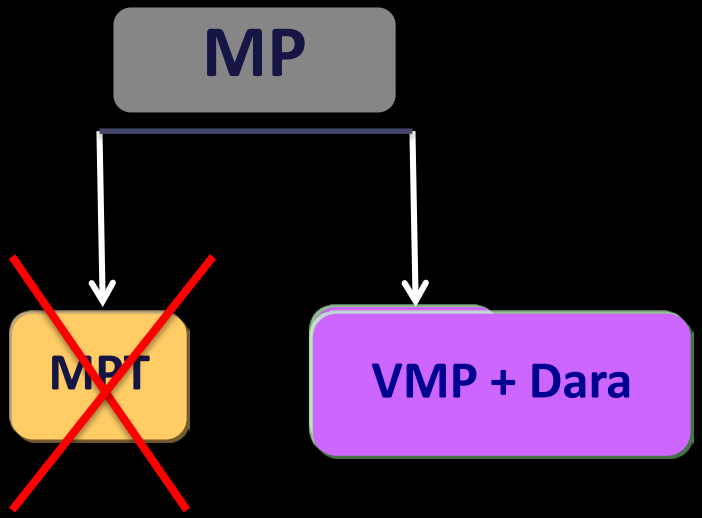
- Incidence of AEs with this combination is generally consistent with the known safety profiles of the individual agents.
- IARs were generally Gr 1/2 in severity and all occurred during the first infusion.

Ocio EM, et al. ASH 2017. Poster presentation. Abstract 3160.

Moving to the frontline setting

New standards of care for elderly MM patients

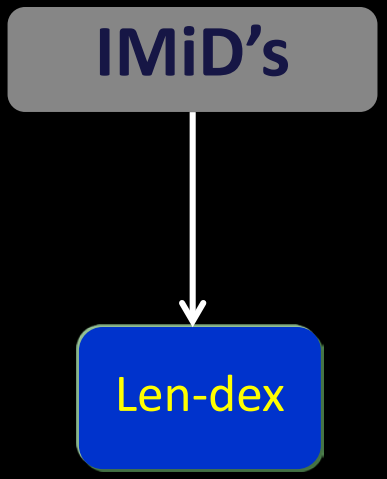
Alkylators-based regimens



Six randomized trials:
Benefit in PFS&OS...6m

One randomized trial:
Benefit in PFS...8m
OS...13m

Alkylators-free regimens

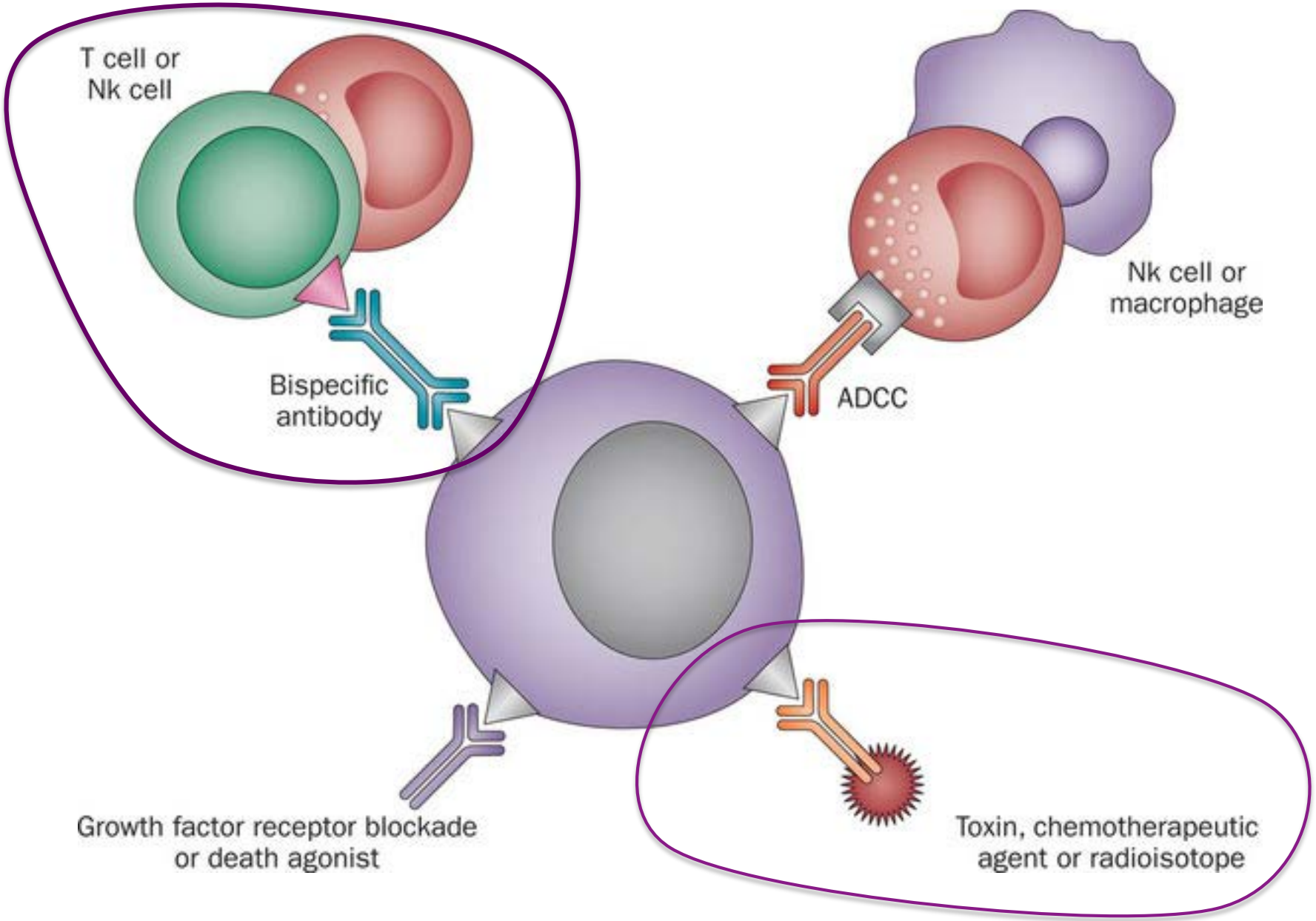


One randomized trial:
Benefit in PFS&OS vs MPT

Fayers PM et al. Blood 2011; 118(5): 1239-47
San Miguel. N Engl J Med 2008;359:906-17
San Miguel . J Clin Oncol. 2013; 31: 448-55

Benboubker L, et al. NEJM 2014; 371: 906-17

MoAbs: Futures perspectives



BCMA – MMAF for RRMM (GSK2857916) – Conjugated MoAb

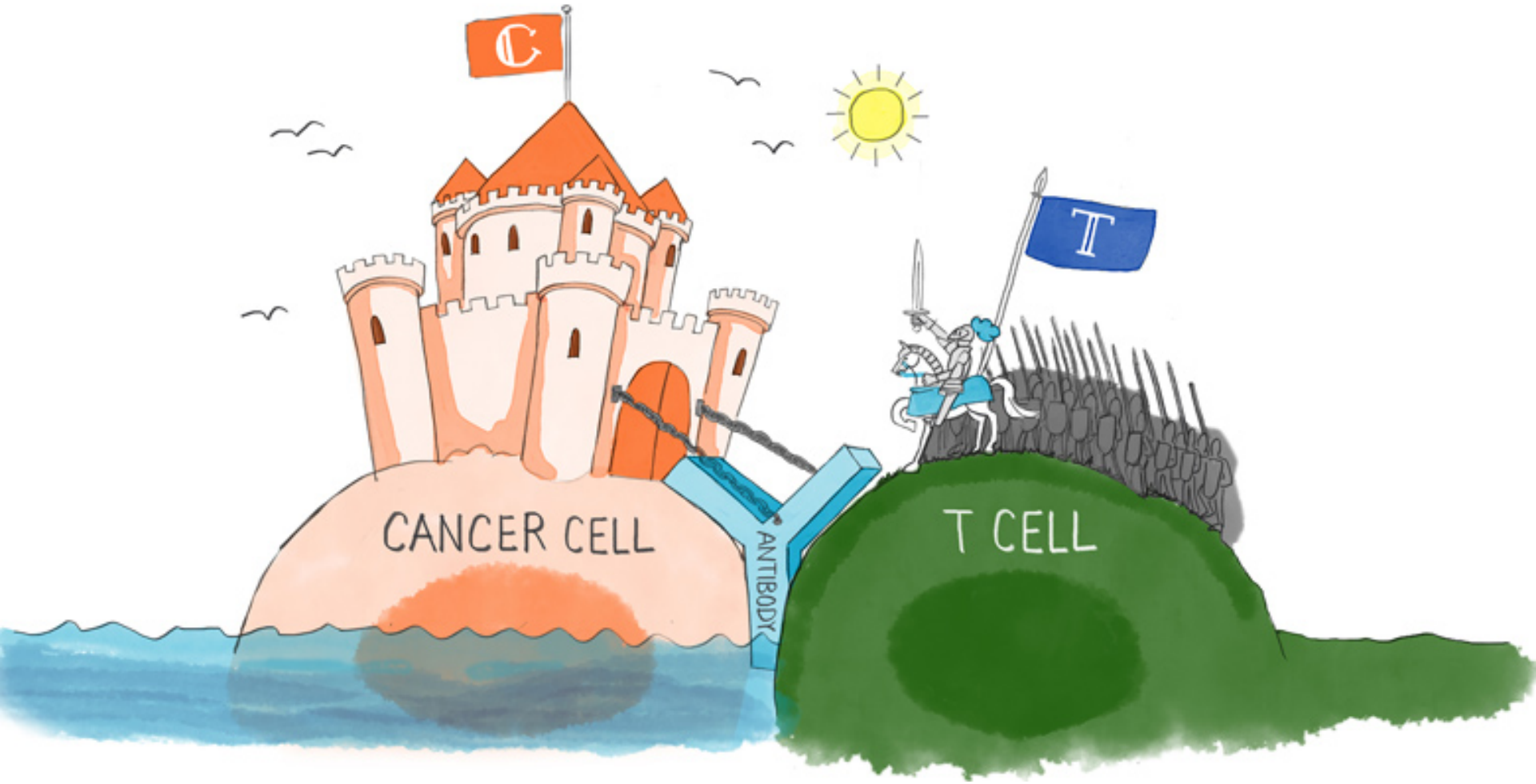
Phase I dose escalation trial (n=73)

- Recommended phase 2 dose: 3.4 mg/kg.
- No DLT.
- 97% PI refractory. 91% IMID-refractory
- 57% with ≥ 5 prior lines of therapy

	Part 1 (n=38)	Part 2 (n=35) 3.4 mg/kg /3 wks until PD.
Efficacy data	**ORR 27% (8/30)** 1 sCR, 3 VGPR, 4 PR.	**ORR 60% (21/35)** 1 sCR, 2 CR, 15 VGPR, 3 PR ORR in Dara-treated: 43%
Safety data (all grade AEs)	63% corneal events (mostly grade 1-2) Thrombocytopenia: 57% Anemia 29%	

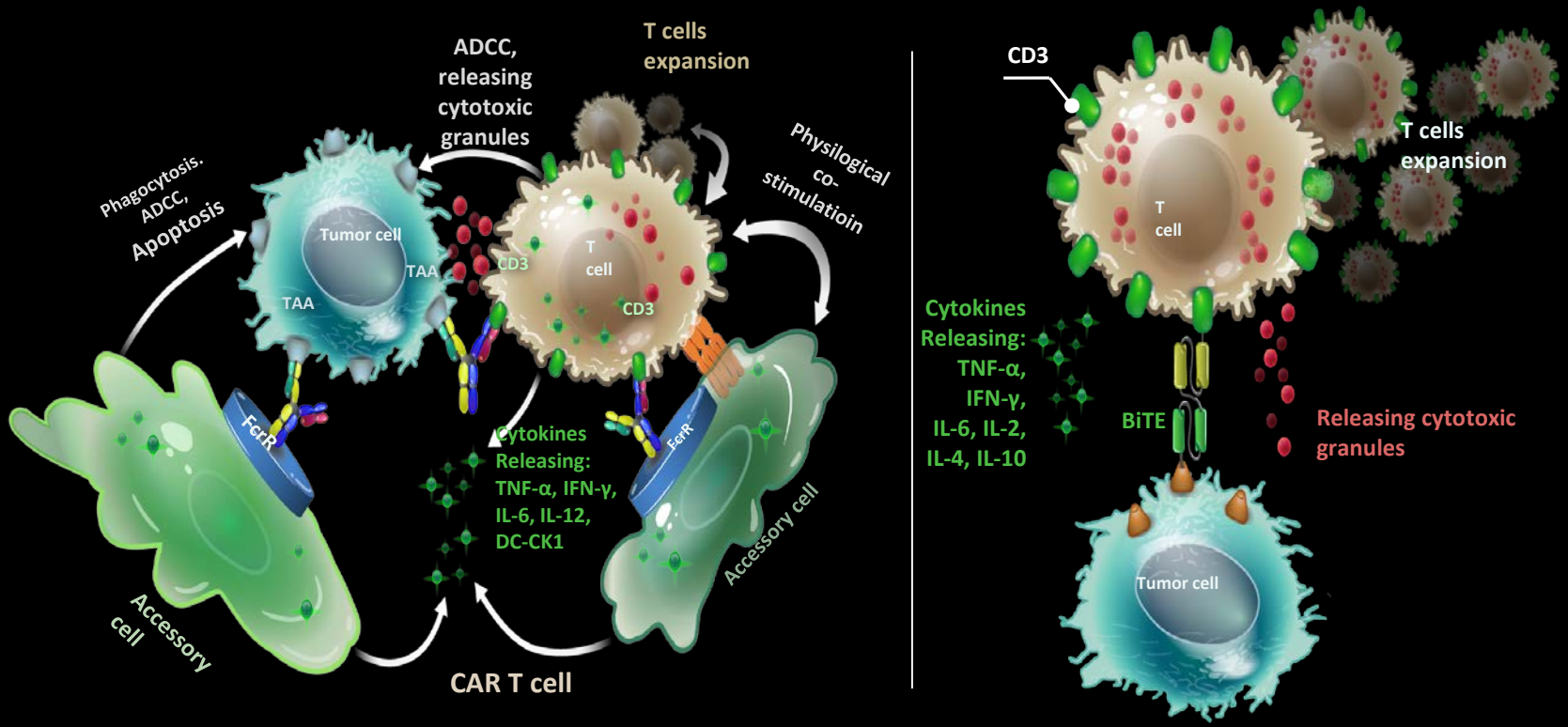
Trudel S et al, ASH 2017, Abs#741

Bispecific Antibodies



Bispecific antibodies - Different platforms

May overcome the limitations of an immunosuppresivetumor microenvironment by linking CTLs with the tumor cell.



IgG Like

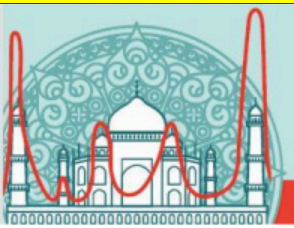
- Longer serum half-life
- Retain Fc function

Non IgG Like

- Better tissue penetrance
- Better access to epitopes

Adapted from Fan G, et al. *J Hematol Oncol*. 2015;8:130.

Bispecific antibodies - Different platforms



16TH INTERNATIONAL Myeloma Workshop

NEW DELHI, INDIA • MARCH 1-4, 2017

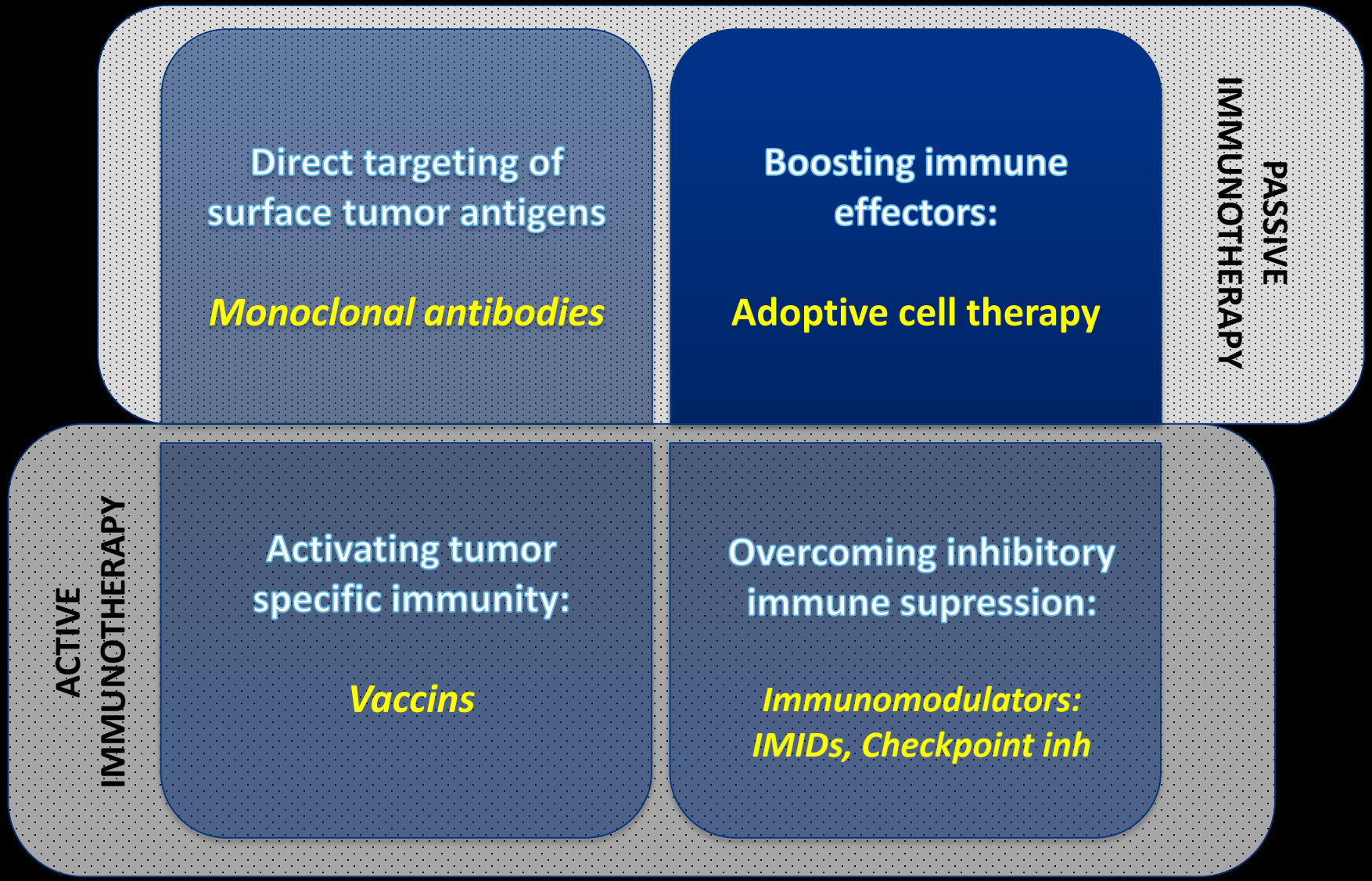
BCMA Bispecific Antibodies in Myeloma

- BCMA (B-cell maturation antigen, CD269) plasma cell antigen
- IgG like bispecific antibody
  - anti-BCMAxCD3 (Pfizer)[1]
  - Ab-957 (Genmab DuoBody/Janssen)[2]
  - EM901 (EngMab/Celgene)[3]
  - Bi-Fab[4]
- Non-IgG like BiTE
  - BI 836909 (AMG420, Amgen)[5]

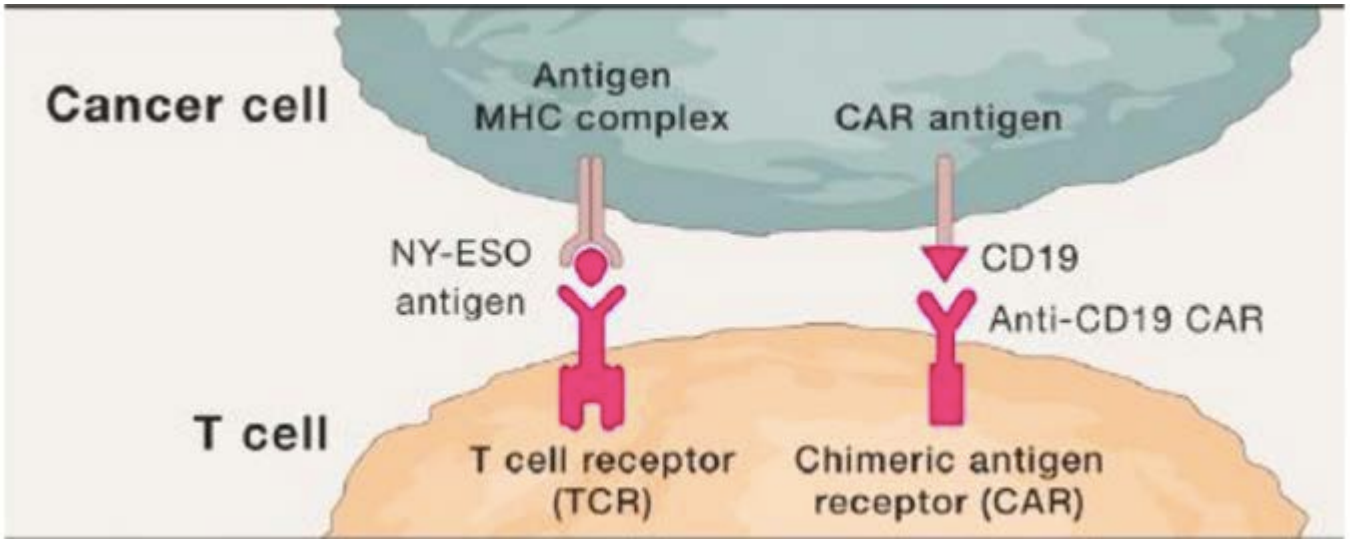
Phase I clinical trials ongoing
No data yet available

1. Panowski SH et al. Blood. 2016. 128:383.
2. Pillarisetti K et al. Blood. 2016. 128:2116.
3. Moreno L et al. Blood. 2016. 128:2096.
4. Ramadoss NS et al. J Am Chem Soc. 2015. 137:5288-5291.
5. Hipp S et al. Leukemia. 2017. 1-9.

Four major targets for cancer immunotherapy



Adoptive Cell Therapy – Genetically-modified T cell therapy

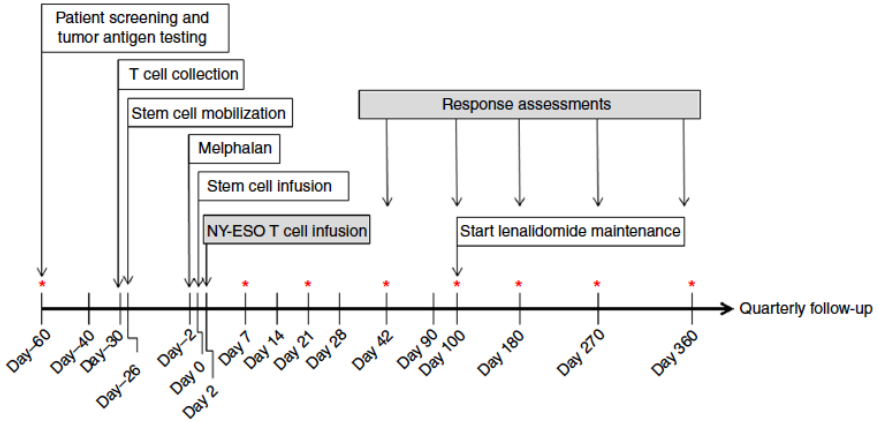


TCR engineered T cells	CAR T cells
HLA - restricted.	Antigen recognition is independent of MHC molecule.
Potential recognition of intracellular antigens	Only extracellular proteins can be recognized (like MoAb)
TCR-mediated activation.	Possibility to insert other genes

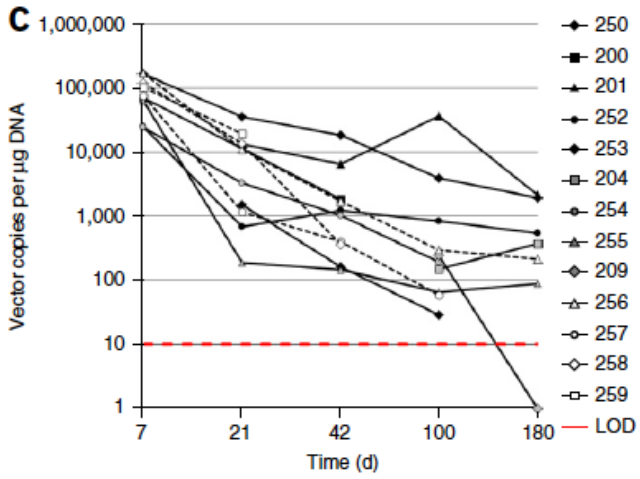
Lim and June, *Cancer Cell* 2017

NY-ESO-1-specific TCR-engineered T cells in MM

- **N= 20**
- 25% prior ASCT
- 60% CA (35% HR)



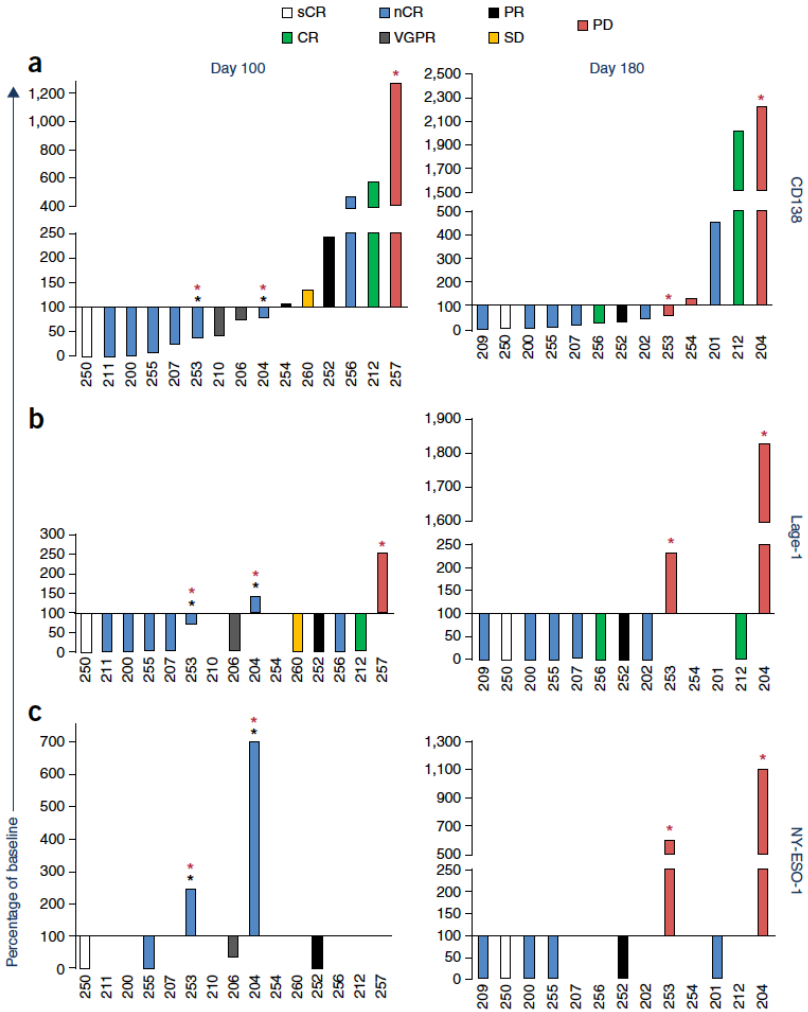
TCR-T cells were detected from day 7 - 180



Median PFS: 19.1 m (8.5 – NR).

PD in 25%: loss of TCR-cells or neg-clone

70% nCR or better



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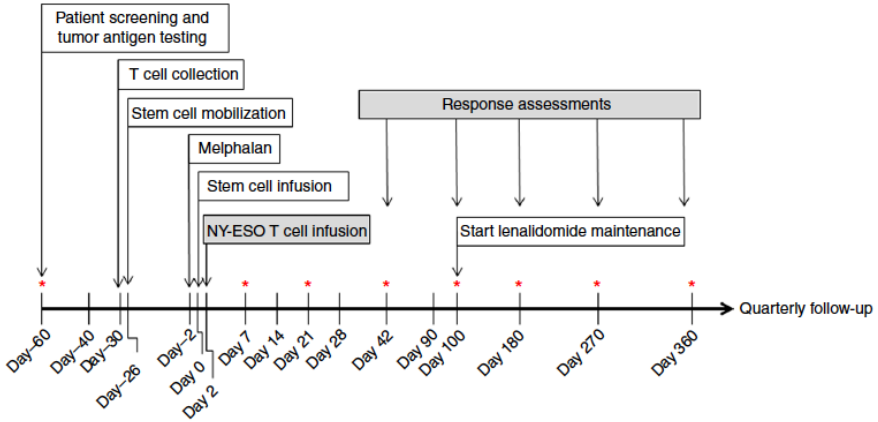

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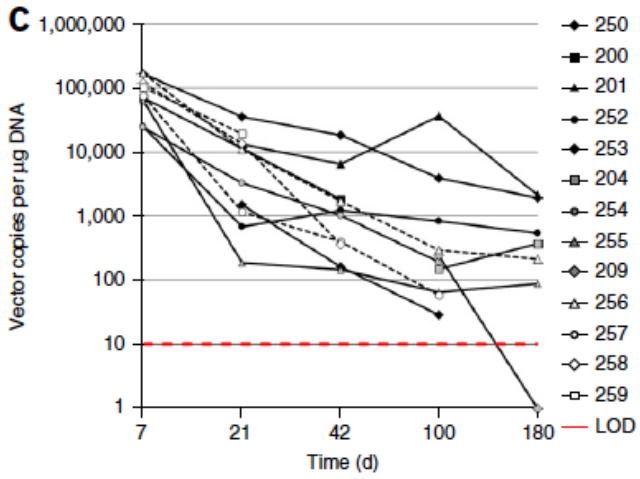

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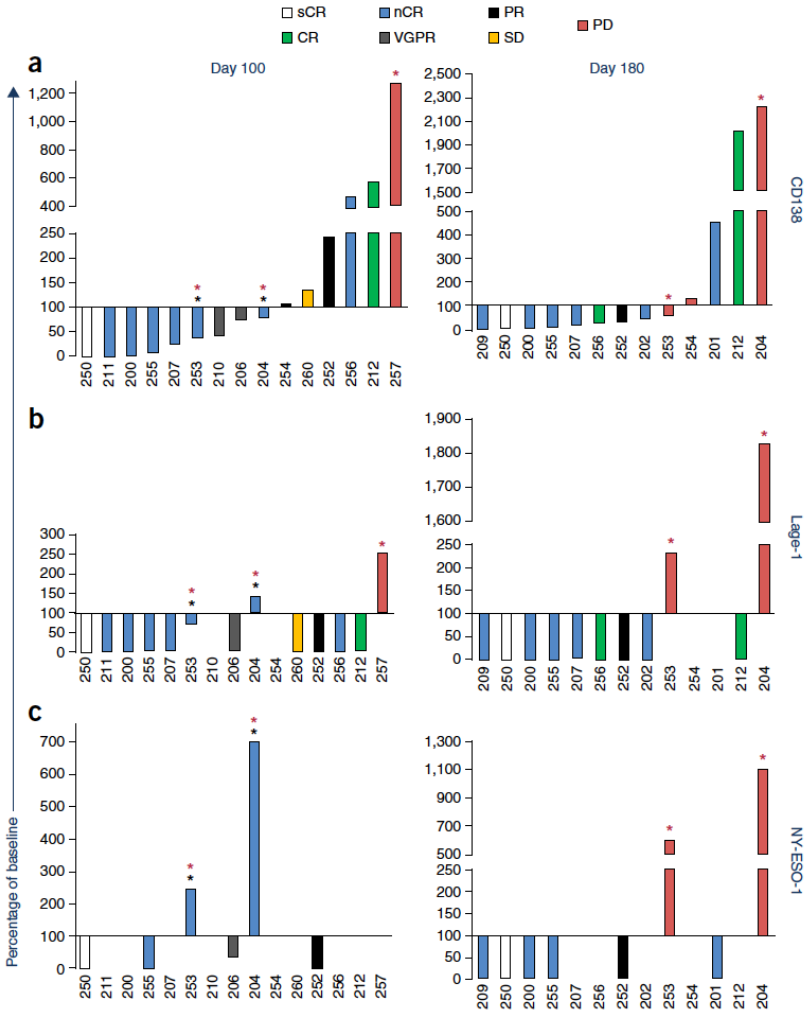
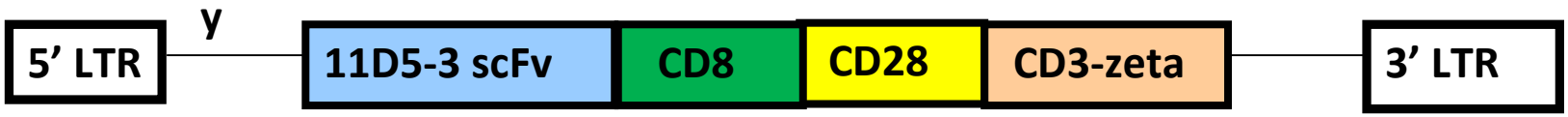


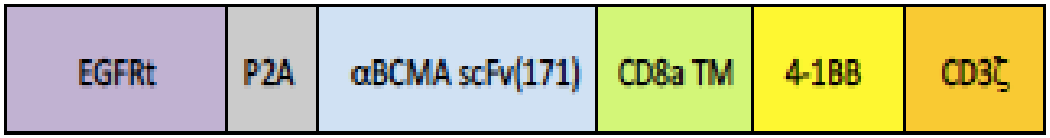
BCMA CAR-T cells in MM

NOVARTIS/UPenn[1]

NIH[2]



MSK/Juno[3]



Legen Biotech[4]

Construct unknown. 4-1BB costimulatory domain. BCMA target

BB2121/Celgene[5]

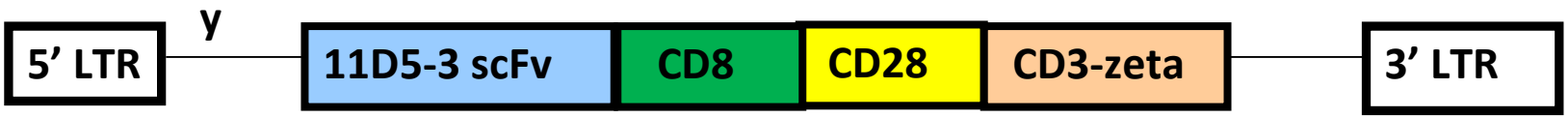
[1]Cohen et al. ASH 2017· [2]Ali et al. *Blood* 2016; [3]Smith et al, ASH 2017. [4]Aili He et al, EHA 2017. [5]Berdeja J et al, ASH 2017

B-cell Maturation Antigen (BCMA)-specific chimeric antigen receptor T cells (CART-BCMA) for MM

	Anti-BCMA CAR (1) NCT02215967	Bb2121 (2) NCT02658929	LCAR-B38M (3) NCT03090659	CART-BCMA (4) NCT02546167
Group/Company	NIH	Bluebird/Celgene/ NCI	Nanjing Legend Biotech	Novartis/UPenn
Binder/ costimulatory	Murine/CD3 & CD28	Murine/CD3 & 41-BB	Murine/CD3 & 41-BB	Fully human/CD3 & 41-BB
Transfection	Gamma-retroviral	Lentiviral	Lentiviral	Lentiviral
BCMA expression required?	Yes	Yes	Yes	No
Median prior lines of therapy	7	5 (1 – 16)	3	7 (3 – 11)
Reported Efficacy	16 patients at 9x106/kg dose level. ORR 14/16 (81%) 11/14 (79%) MRD- Median EFS: 31 w	21 patients (18 evaluable) 89% ≥VGPR (56% sCR)	35 patients: 19 CRs 9 VGPR 2PRs	3 cohorts 21 pts (9/5/7) #1: 67% (1sCR,1VGPR) #2: (40%) 1 PR, 1 MR both PD #3: (83%) 1CR, 3PR, 1MR
Safety Data	Substantial but reversible	1 death, cardiopulmonary arrest (unrelated) CRS gr1-2: 71%	Transient CRS No neurotoxicity	CRS: 17 pts (gr3: 6) Neurotox: 3 (2 gr 4) 1 death – PD candidaemia

1. Ali S et al, Blood 2016 2. Yi Lin EHA 2017 3. Aili He EHA 2017 4. Cohen A, et al. ASH 2017. Abs#505

BCMA-CAR T cells in MM – Phase I data – NIH



Cyclophosphamide 300 mg/m^2
Fludarabine 30 mg/m^2
QD for 3 days

→ CAR-BCMA T cells*
Single infusion

*Dose escalation of CAR+ T cells/kg
0.3×10^6
1.0×10^6
3.0×10^6
9.0×10^6

Key inclusion criteria:

- ≥ 3 prior lines of therapy
- Clear, uniform expression of BCMA (flow/IHQ)

N=26 patients // 16 on the highest dose level.

Patients characteristics:

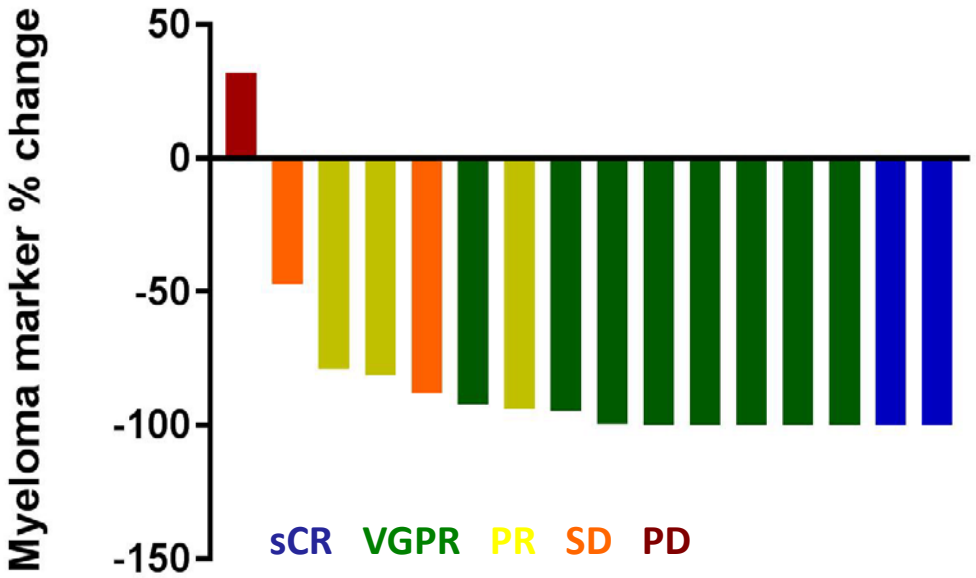
- Median number of prior lines: 10
- 6/16 patients (38%) with HR CA, 5/16 (31%) patients with del(17p)
- 8/16 patients (50%) refractory to last treatment regimen
- Last 14 patients were required to have low disease burden (< 30% PC in BM)

Ali et al, ASH 2015. LBA 1.

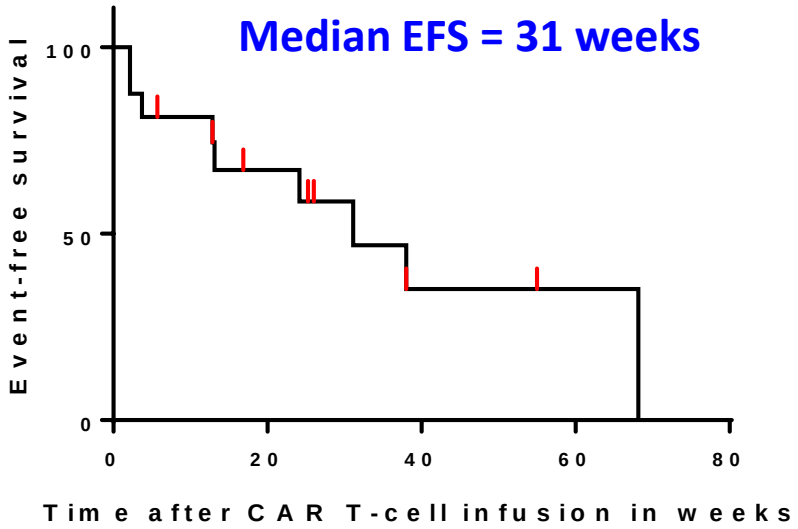
BCMA-CAR T cells in MM – Phase I NIH – Efficacy

ORR: 14/16 (81%) at 9x106/kg dose level

11/14 (79%) evaluable patients at 9x10^6/kg achieved MRD negative status



Median EFS = 31 weeks



CRS minimal at lower doses but substantial at 9x10^6/kg

- 6 patients grade 3-4 CRS
- 10 patients grade 1-2 CRS
- 5 pts (31%) received Tocilizumab
- 19% received steroids.

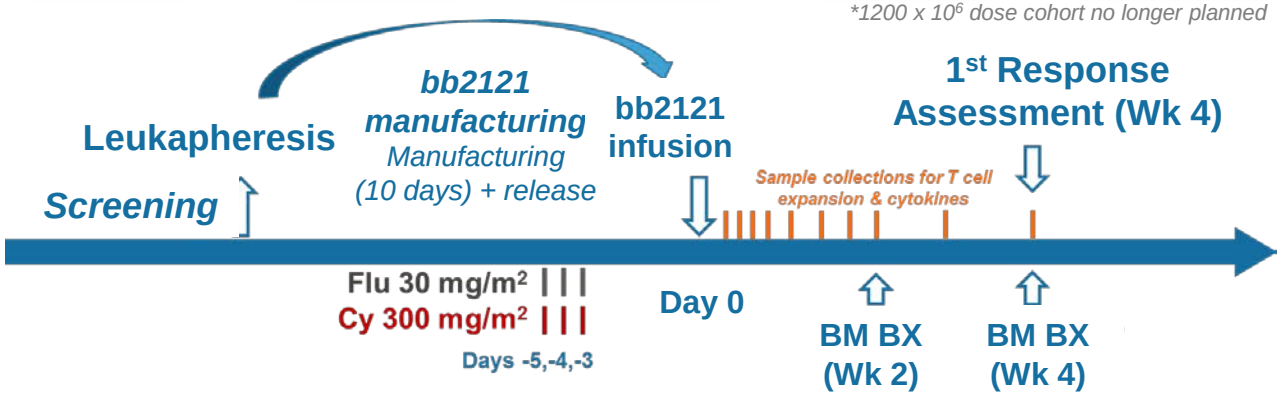
Ali et al, ASH 2015. LBA 1.

BCMA-CAR T cells – Phase 1 bb2121

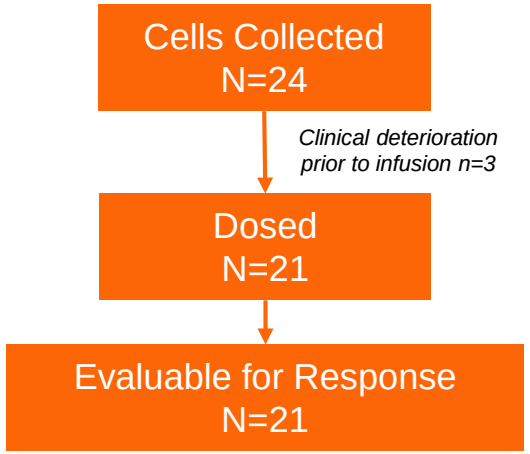
3 + 3 Dose Escalation of CAR+ T Cells

50 x 10^6 → 150 x 10^6 → 450 x 10^6 → 800 x 10^6 → 1200 x 10^{6*}

*1200 x 10^6 dose cohort no longer planned



Study Status (Escalation Phase)



Manufacturing success rate of 100%

Expansion Cohort Initiated in August 2017

- 12 additional patients have been collected and dosed in the Expansion Cohort as of 02 Nov 2017

N=50 patients

Key inclusion:

- **RRMM with ≥ 3 prior lines of therapy (including PI and IMiD), or double refractory**
- **≥ 50% BCMA expression**

Berdeja et al. ASH 2017, abs #740

BCMA-CAR T cells – Phase 1 bb2121 - Efficacy

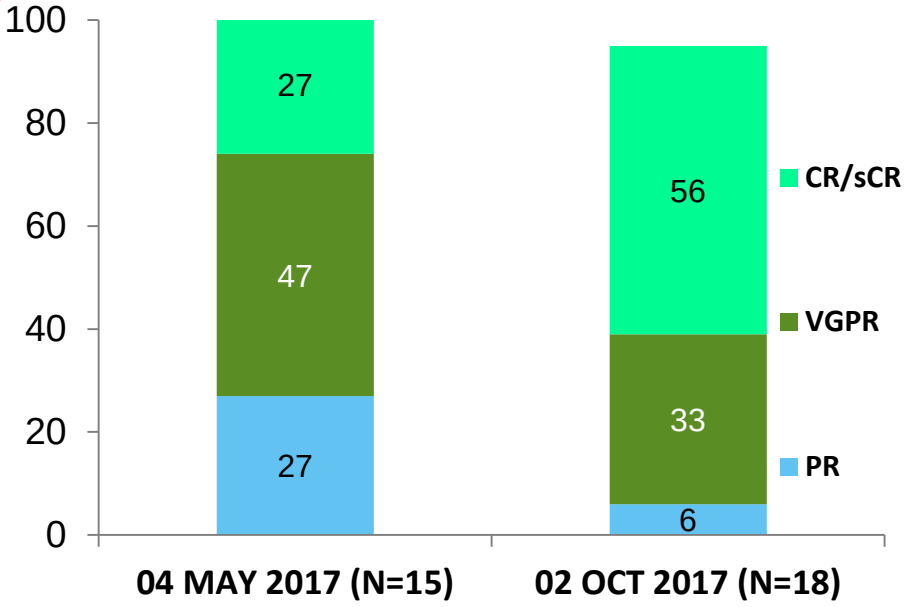
- N=21 patients (18 evaluable)
- Median number of prior lines: 7
- **29% penta-refractory**

Dose Escalation: Cohorts ≥150 × 10^6 CAR+ T Cells (N=18)

Median duration of follow up 40 weeks (min, max: 6.6, 69.1)

Efficacy Parameter	Statistic	Result
Time (months) to First Response	Median (min, max)	1.02 (0.5, 3.0)
Time (months) to Best Response	Median (min, max)	3.74 (0.5, 13.7)
Time (months) to Complete Response	Median (min, max)	3.84 (0.5, 13.7)
Duration of Response	Median (min, max)	NR
Progression free survival	Median (min, max)	NR
Progression free survival rate @ 6 mos	%	81%
Progression free survival rate @ 9 mos	%	71%

Objective Response Rate Subjects Treated in Escalation – Cohorts ≥150 × 10^6



Note: Objective Response defined as attaining Stringent Complete Response, Complete Response, Very Good Partial Response, or Partial Response. Including unconfirmed responses.

- ORR 89% // **ORR 100% with 150 x 10^6 CAR-T cell infusion**

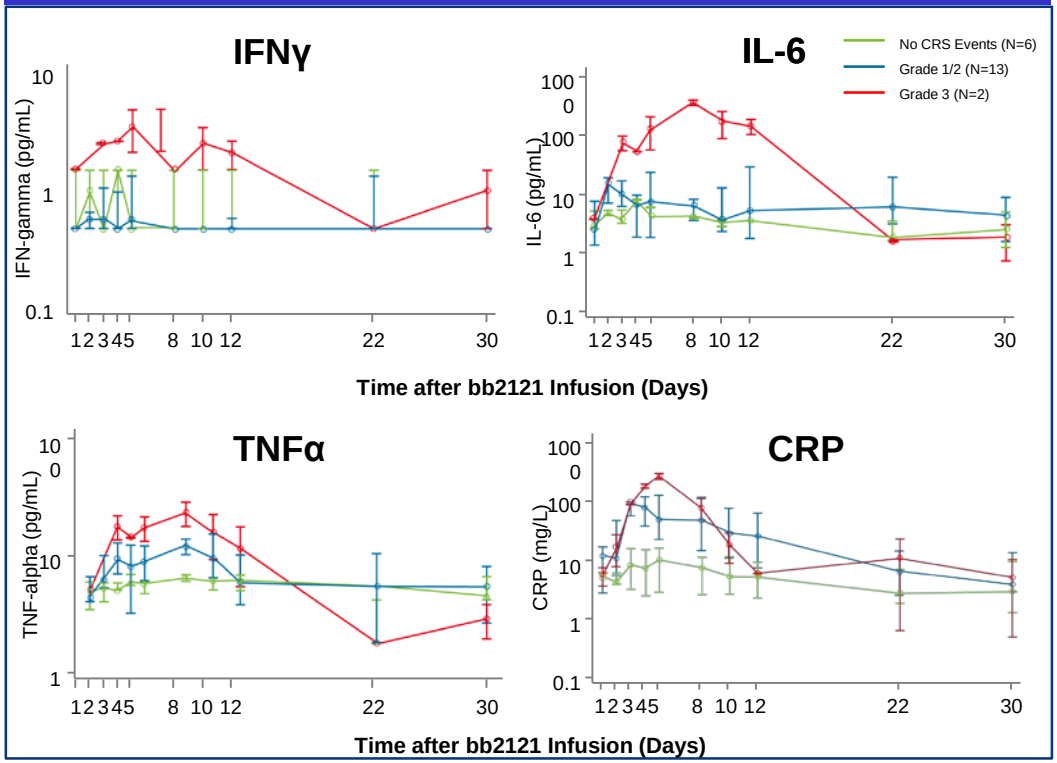
- **CRS: 71% (gr 1-2), 2 pts grade 3. No DLTs, No grade 3 toxicity.**

Berdeja et al. ASH 2017, abs #740

BCMA-CAR T cells – Phase 1 bb2121 – Safety

Parameter	Statistic	Dosed Patients (N = 21)
Patients with a CRS event	n (%)	15 (71)
Time (days) to onset of first CRS	Median (min, max)	2 (1,19)
Duration (days) of CRS	Median (min, max)	7 (1, 11)
Time (days) to onset of grade ≥3 CRS	Median (min, max)	5 (4, 6)
Duration (days) of grade ≥3 CRS	Median (min, max)	2 (2, 2)

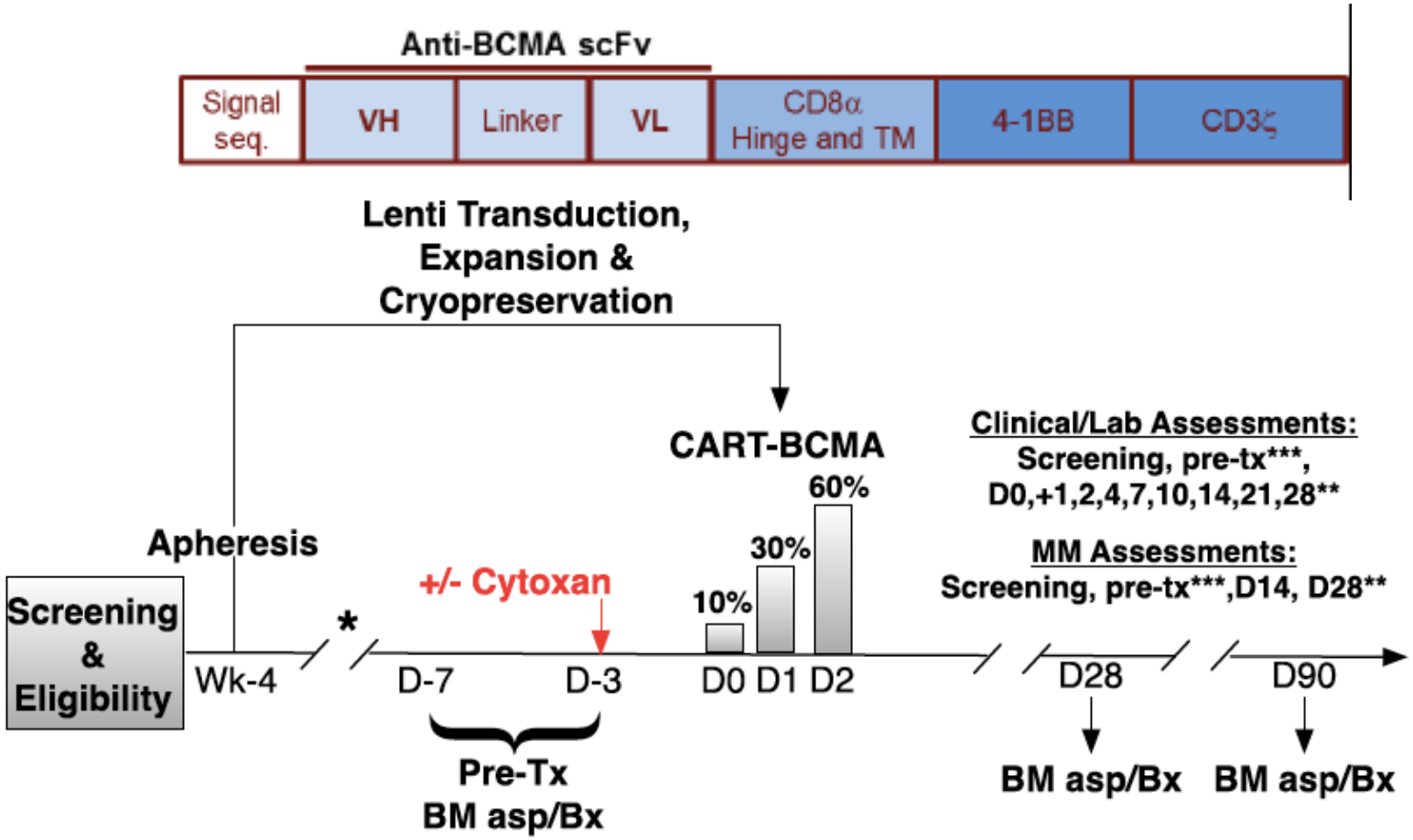
Median (Q1, Q3) Over Time by CRS Grade Subjects Treated in Escalation



- CRS: 71% (gr 1-2), 2 pts grade 3.
- No DLTs.
- No grade 3 toxicity.
- 4 patientes received Tocilizumab

Berdeja et al. ASH 2017, abs #740

BCMA-CAR T cells in MM Upenn/Novartis – Phase I data



* Patients may receive therapy during manufacturing to maintain disease control
** After first 28 days, follow-up is q4 wks up to 6 mos., then q3 mos. up to 2 years
*** Pre-tx = pre-treatment, 3 to 7 days before CAR T cell infusion

Key inclusion: ≥ 3 prior lines, RRMM or doble refractory disease

Cohen et al. ASH 2017 Abstract 505

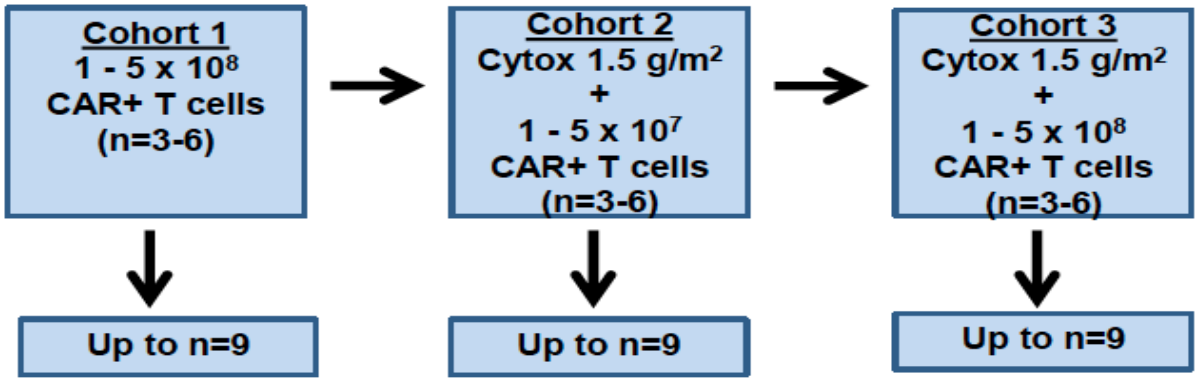
BCMA-CAR T cells in MM Upenn/Novartis – Phase I data

33 enrolled, 28 eligible (4 awaiting infusion, 3 never treated due to rapid PD)

21 treated patients

Median number of prior lines: 7 (3 – 11)

- **100% IMID and PI refractory**
- **67% refractory to Dara.**
- **95% high-risk cytogenetics (67% del17p or *TP53* mutation)**



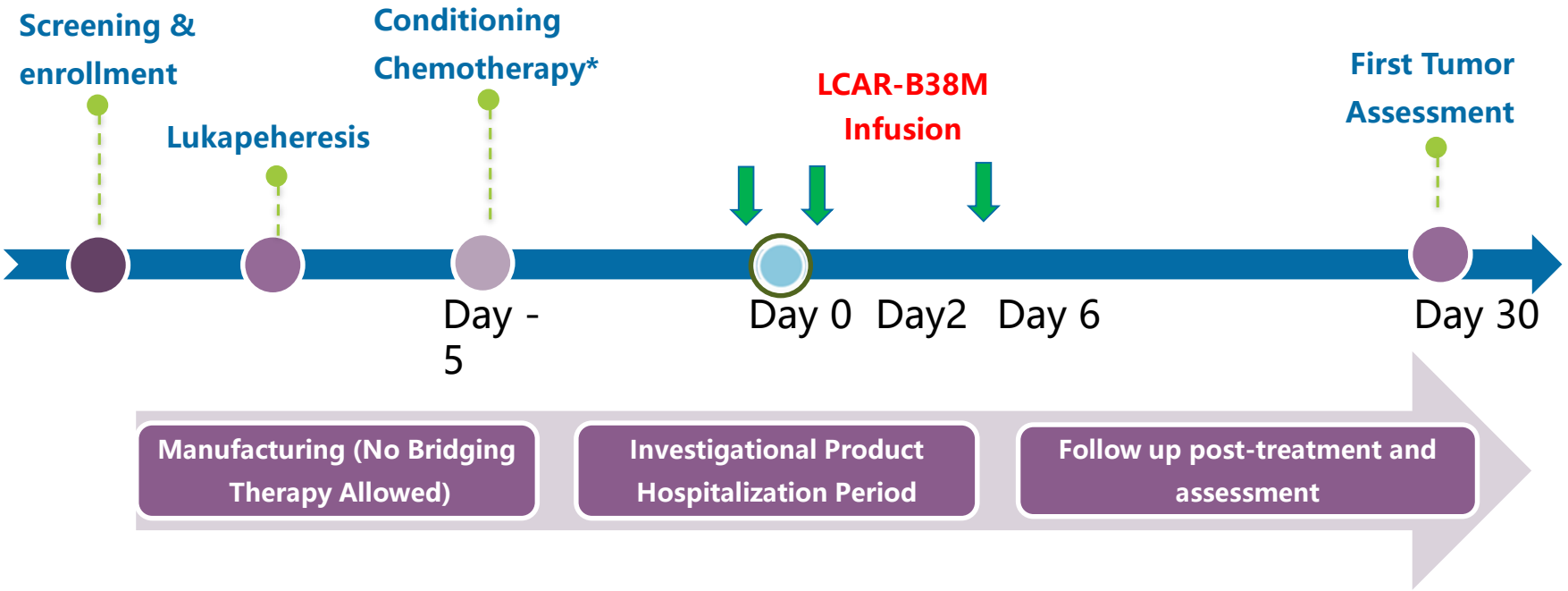
N	9	5	7
Efficacy	**ORR 67%** 1sCR, 2 VGPR, 1 PR, 2MR 1 ongoing sCR at 21m	**ORR: 40%** 1 PR, 1 MR 2 PD: 4 and 2 months	**ORR 83%** Only 1 month FUP 1 CR, 3 PR, 1 MR
Safety	CRS: 8 pts (3 grade 3/4) Neurotox: 2 pts (2 gr 4)	CRS: 9 pts (3 grade 3) Neurotox: 1 patient	

Cohen et al. ASH 2017 Abstract 505

BCMA CAR-T Legenf Biotech – Phase I - Design

Lentiviral vector based + 4-1BB co-stimulatory domain

BCMA catching domain target two different epitope simultaneously

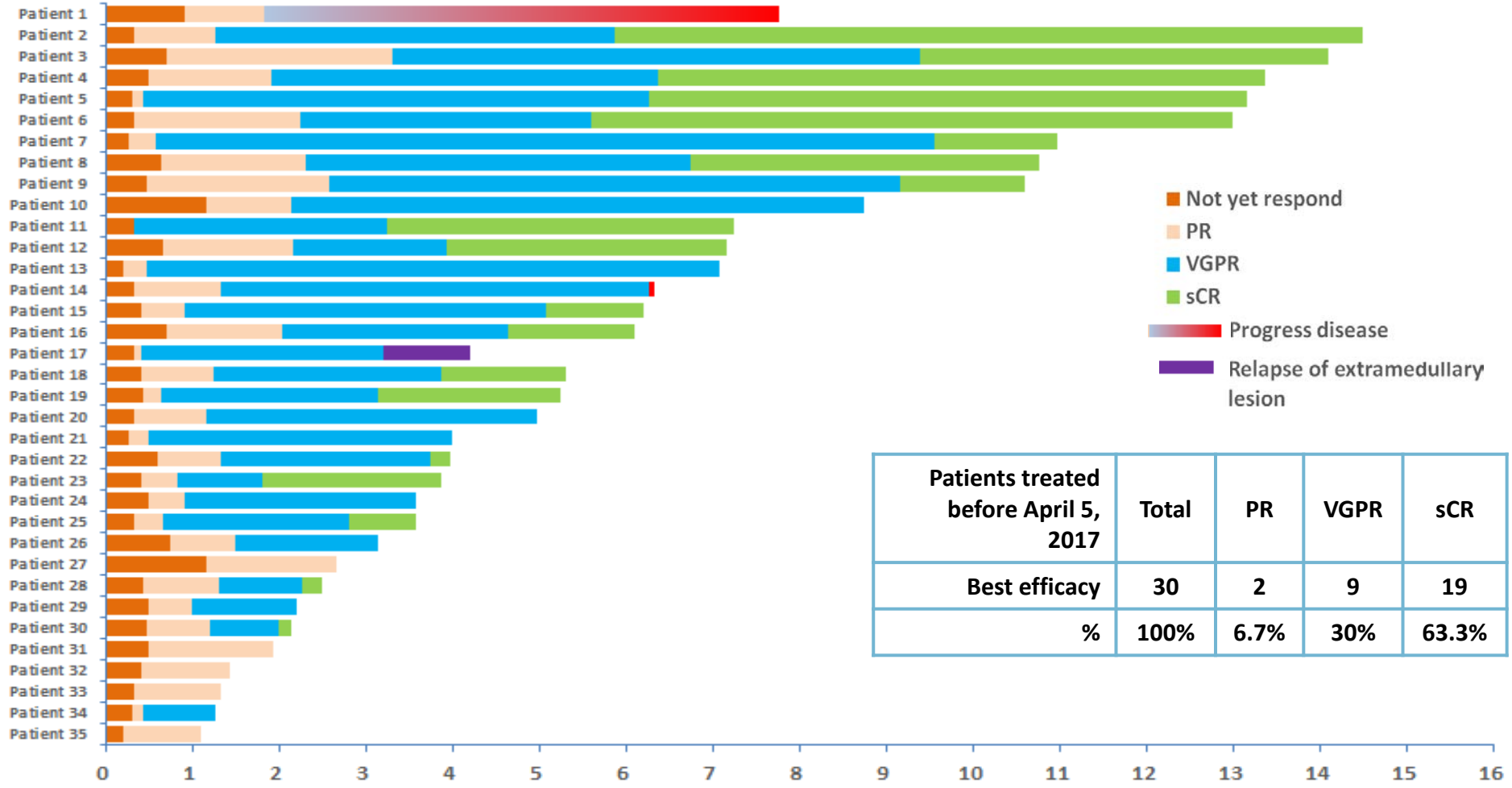


Key inclusion: **resistant to > 3 prior lines, BCMA expression in >10% clonal PCs**

N=35 patients

Aili He et al. EHA 2017

BCMA CAR-T Legenf Biotech – Phase I – Efficacy & Safety

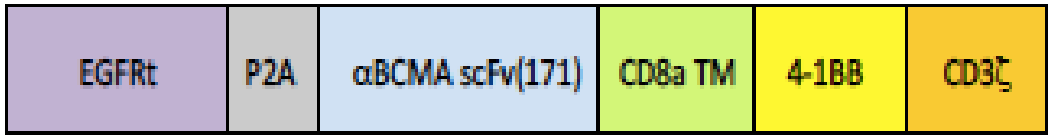


Patients treated before April 5, 2017	Total	PR	VGPR	sCR
Best efficacy	30	2	9	19
%	100%	6.7%	30%	63.3%

- **CRS was mild.**
- **Only 5.7% AEs grade 3 or higher.**
- **No neurotoxicity**

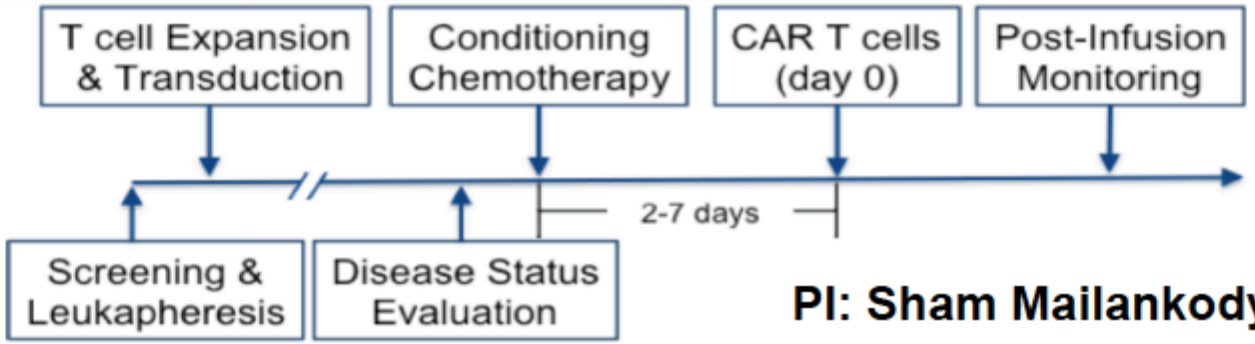
Aili He et al. EHA 2017

BCMA CAR-T *Memorial Sloan Ketering* – Ph I – MCARH171



Dose Level	Conditioning Chemotherapy	CAR+ T cell dose (mean given)	Pts
1	Cy 3g/m^2 x1	72 x 10^6	3
2	Cy 300mg/m^2 x3 Flu 30mg/m^2 x3	137 x 10^6	3
3	Cy 300mg/m^2 x3 Flu 30mg/m^2 x3	450 x 10^6 (planned)	2-6
4	Cy 300mg/m^2 x3 Flu 30mg/m^2 x3	800 x 10^6 (planned)	2-6

BCMA+ (any) by flow or ICH 100% qualified



PI: Sham Mailankody

Memorial Sloan Kettering Cancer Center

Efficacy: not yet mature

Toxicity: CRS grade 1=2; grade 2=1.

Smith EL W et al. ASH 2017

Co-Infusion BCMA + CD19 CAR T cells in RRMM – Ph I trial

T-cells + anti-BCMA scFv + anti-CD19 scFv + cytopl. portion of OX40 + CD28 + Cd3z

Fludarabine 30mg/m2 x 3days
Cyclophosphamide 300mg/m2 x 3d

CART-19 ($1x10^7$ kg) d0 +
CART-BCMA (40% d1 and 60% d2)

8 patients (2 allo for BCMA-CAR T due to previous autologus BCMA-CART treatment)

Safety:
100% CRS. No neurotoxicity.
No TRM.

Efficacy (5 pts with FUP > 1m):
ORR: 80% (1sCR, 1 VGPR, 2 PR)

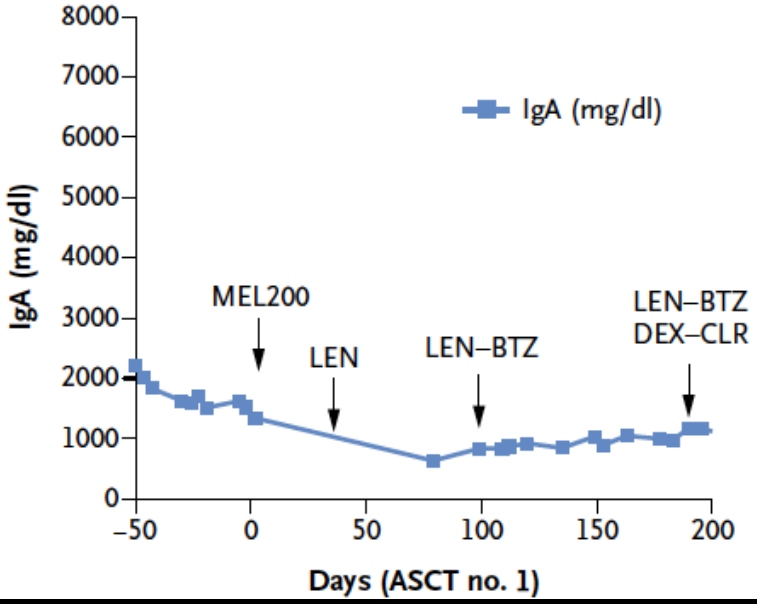
Pt.	Age,Sex /Isotype	NO. Prior lines	BCMA% on myeloma cells	CART-BCMA T cells infused (per kg)#	Peak CART expansion in blood: qPCR (cells/ml)	CRS stage	Response (duration, wks)
01	M64 /IgG κ	4	91.5	8.2×10^7	1.92×10^5	2	VGPR (20+)
02	M43 /IgG κ	3	54.2	4.5×10^7	1.88×10^5	2	sCR (7+)
03	M57 /IgG κ	2	81.6	3×10^7	1.49×10^6	2	PR (7+)
04	F60 /IgG κ	7	55.7	6.8×10^7	7.22×10^5	2	SD (7+)
05	M58 /IgA κ	5	94.6	4.75×10^7	5.71×10^5	2	PR (4+)
06	F47 /IgG λ	4	69.7	2.5×10^7	2.25×10^6	1	NE
07	M69 /IgG λ	2	96.9	2.5×10^7	1.53×10^6	1	NE
08	M60 /IgD λ	3	80.8	6.2×10^7	3.05×10^6	3	NE

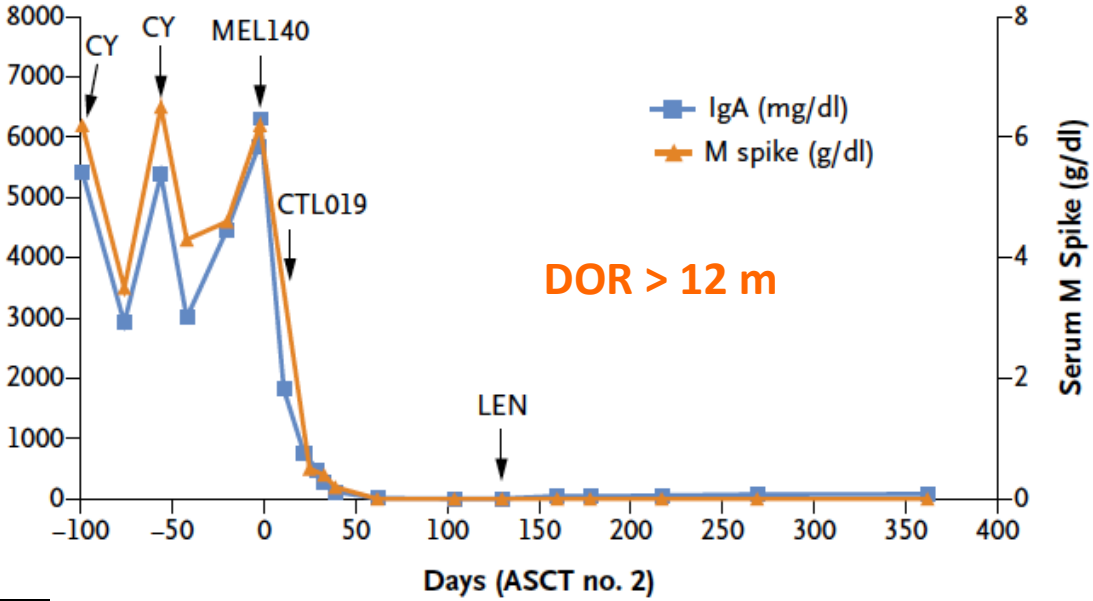
#: Before infusion CART-BCMA T cells, all patients had already received CD19 specific CART cells (1×10^7/kg)

NE: No Evaluation

Yan L. ASH 2017 Abstract #506

CD19-CAR T cells in MM – First patient treated

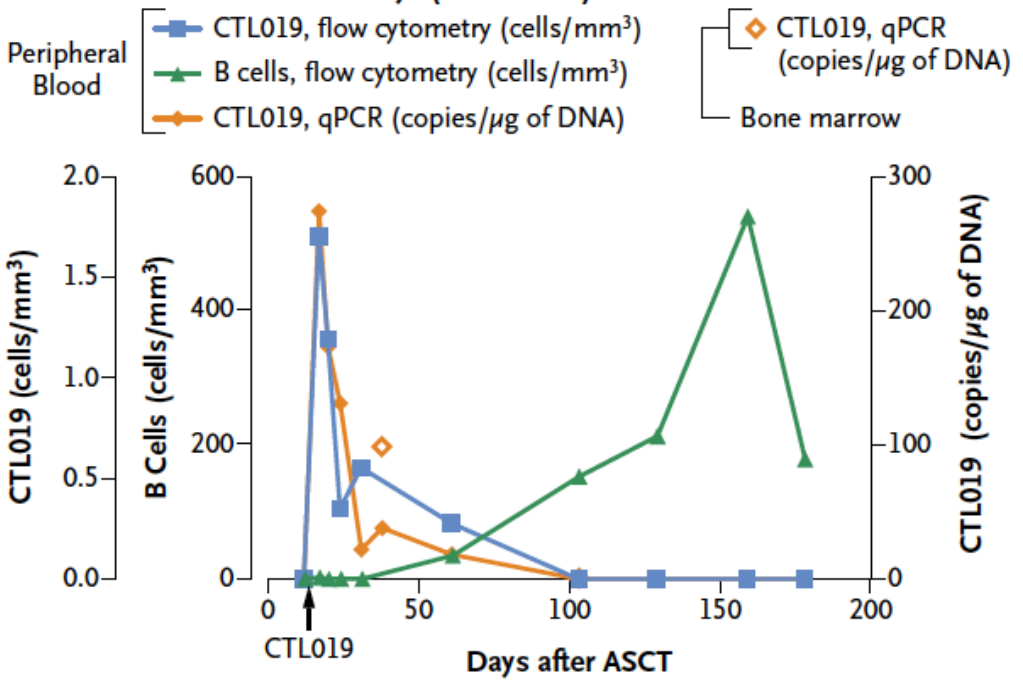




DOR > 12 m

- **RRMM**
- ***Rationale: Minor component of the MM clone that is drug-resistant and has disease proagating properties has a B-cell origin .***
- **CD19-CAR after Mel140.**
- **CD19 was negative in 99.95% PC.**

Stadtmauer E, et al. NEJM 2015



CD19-CAR T cells in MM

Study Design

Eligibility Criteria
- Multiple Myeloma
- Progression within one year of prior ASCT
- Age <70
- Fit for 2nd ASCT

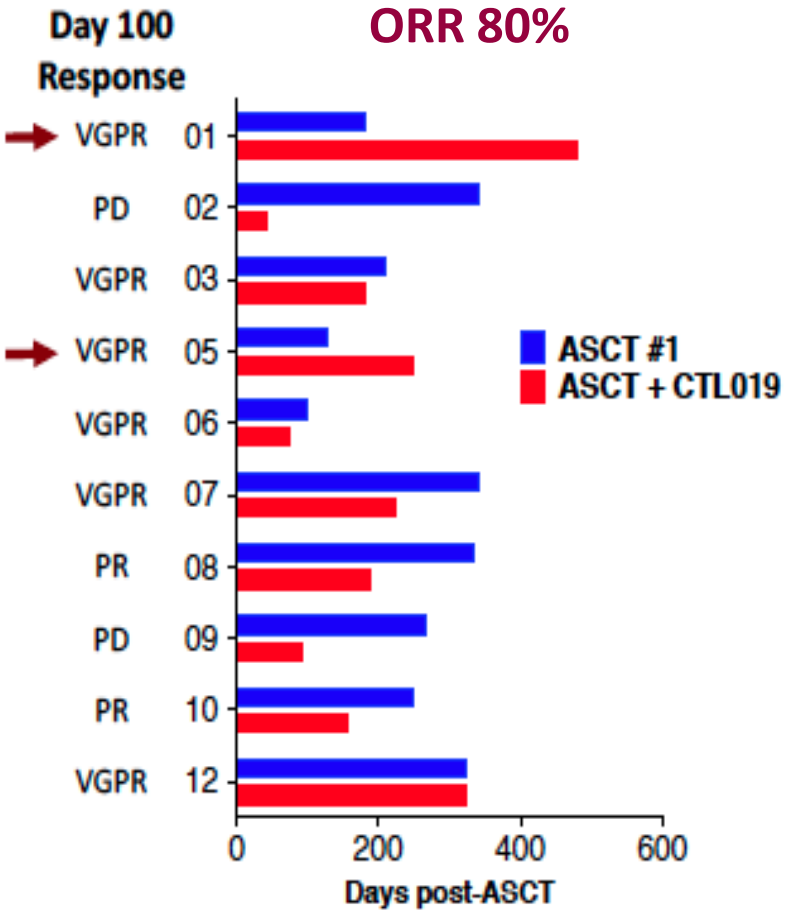
Salvage High-dose Melphalan + Auto-SCT → 12-14 DAYS → CTL019 5 x 10^7 cells → FOLLOW FOR PFS

Primary Endpoints
- Safety (CRS, neurotoxicity)
- Feasibility (manufacturing success)

Secondary Endpoints
- CTL019 engraftment and B cell aplasia
- Day 42 and day 100 response
- Progression-free survival (vs. last ASCT)
- Correlation of response to CD19 expression

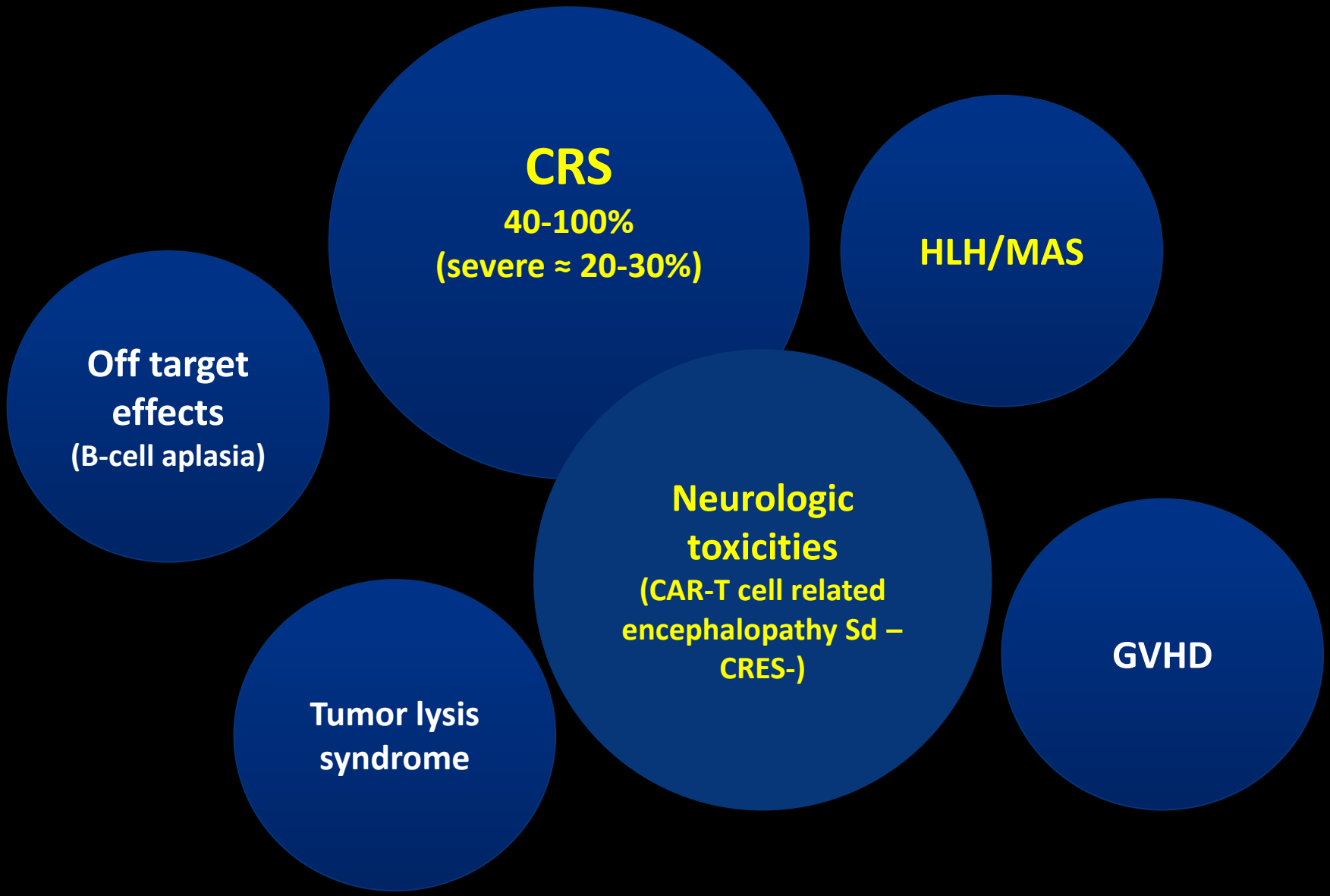
Efficacy

ORR 80%

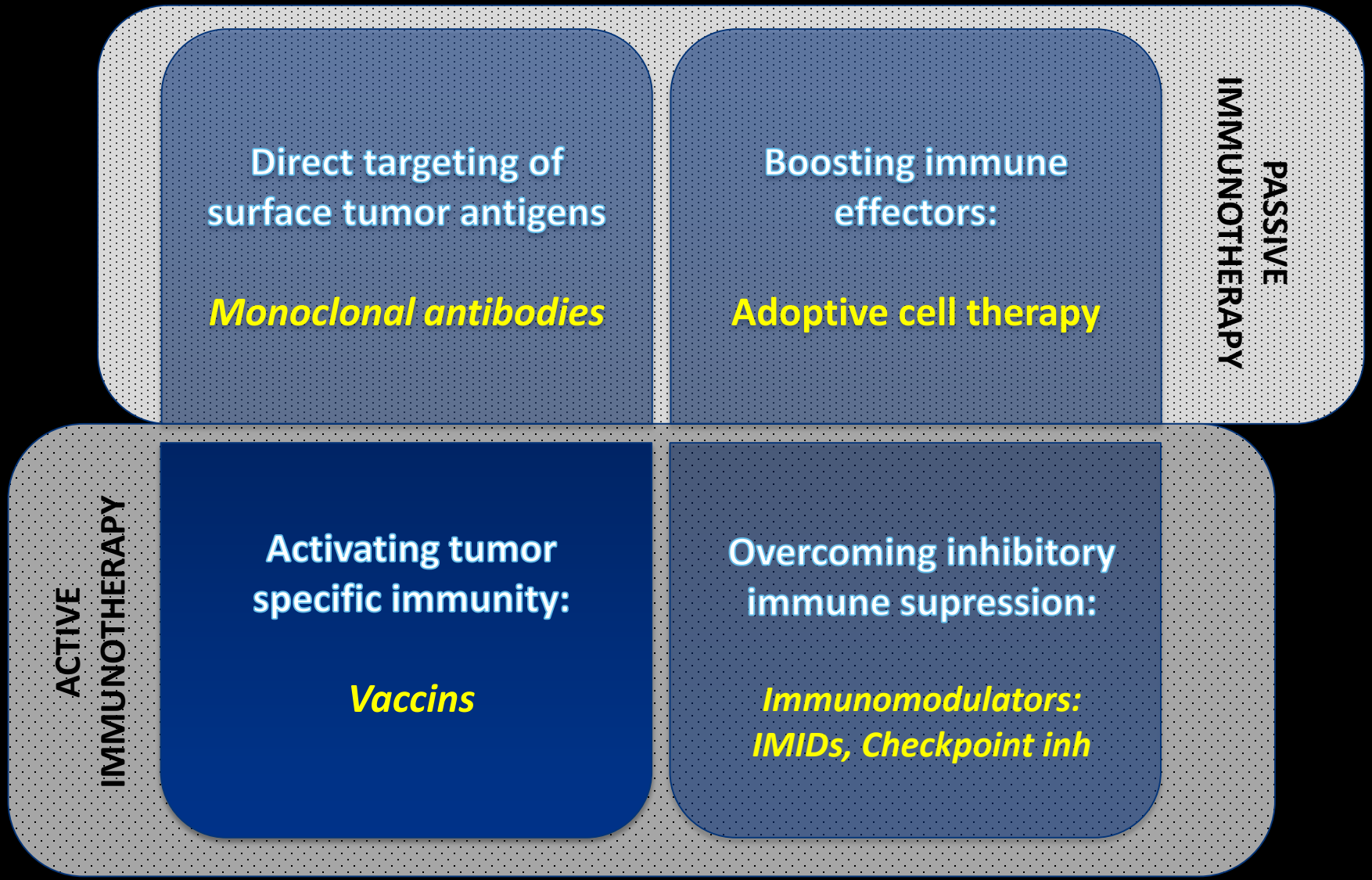


Garfall et al. ASH 2016 Abstract 974

Safety concerns regarding CAR T cell therapy



Four major targets for cancer immunotherapy

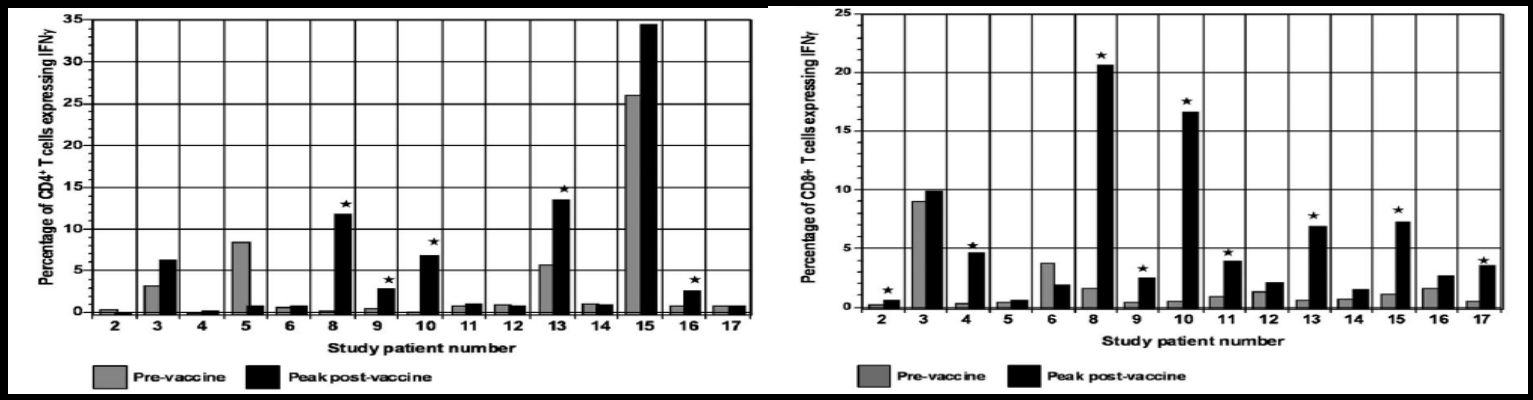


Dendritic cell vaccines in Multiple Myeloma

- Vaccination combining different antigen formats and adjuvants has been investigated in MM (Rosenblatt et al., 2013),

- but active vaccine strategies are hampered by the insufficient numbers of induced T cells, their poor homing to tumor sites, and the immunosuppressive tumor microenvironment.

- Two separate vaccinations approaches: peptide-based (NY-ESO-1, MAGE-AE, WT-1, XBP-1) and dendritic cell fused vaccines (➔ broad spectrum of MM antiges are presented in the context of dendritic cell mediated costimulation) .

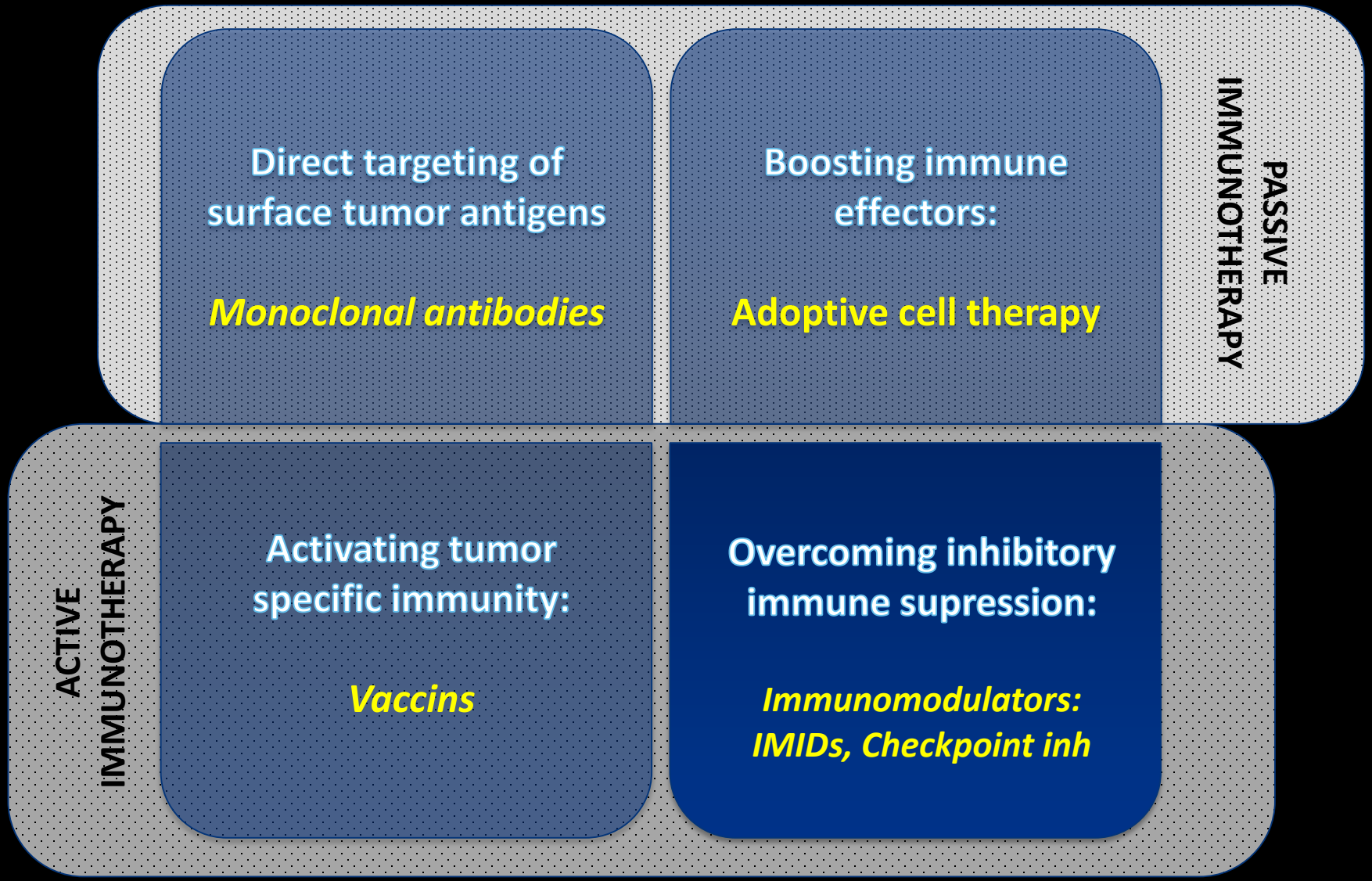


- Phase I: RRMM. n=16 patients. Median of prior lines: 4. Well tolerated.
- ORR: 11/16: ***Stable disease***. Several patients with SD lasting for 12 to 41 months.

- Phase II trial in the context of ASCT: CR/VGPR rate 78% early after ASCT. 24% of patients that improve responses.

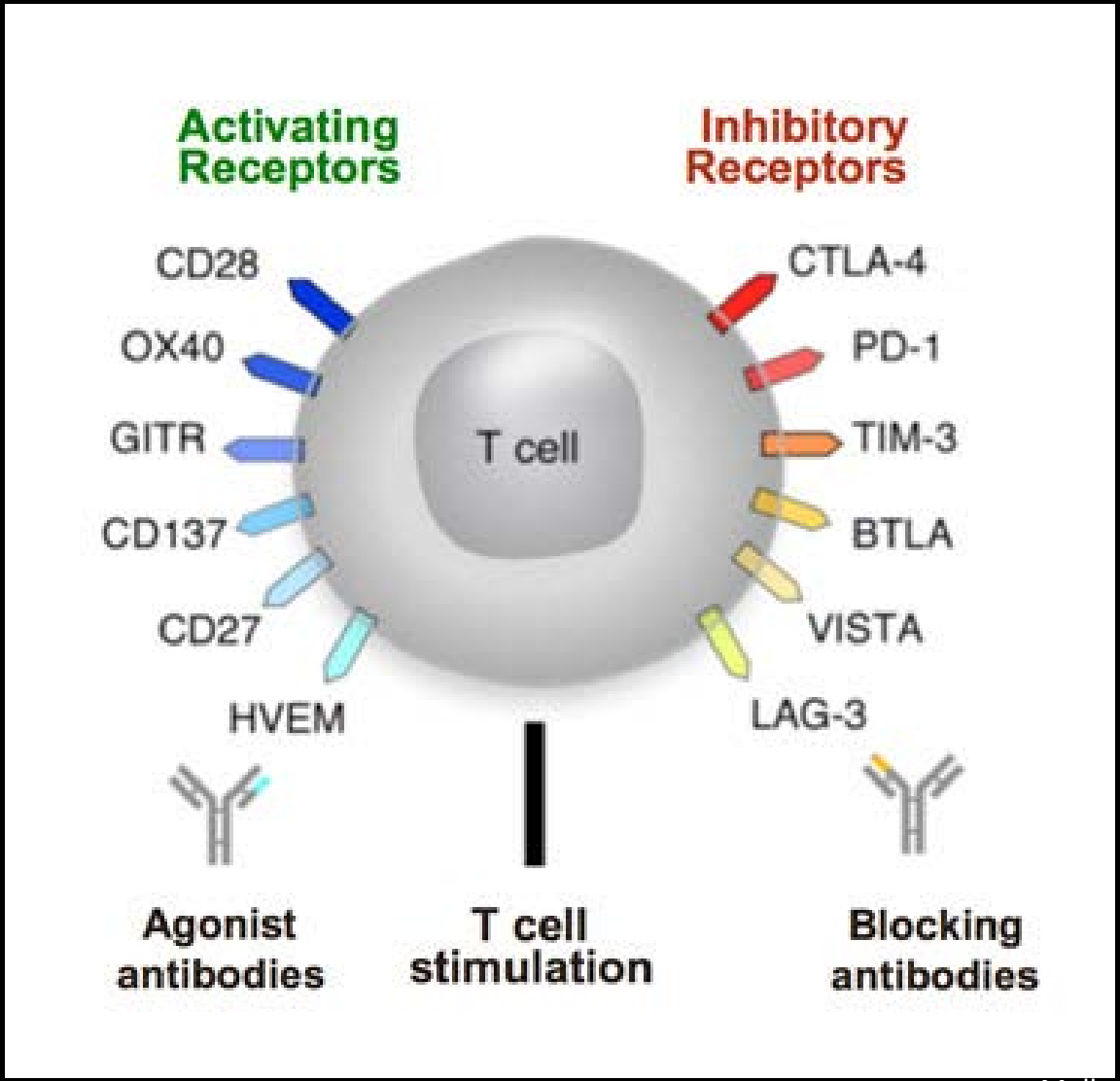
Rosenblatt J et al, *Blood* 2011

Four major targets for cancer immunotherapy



Immune Checkpoints

Press the gas pedal *Release the brakes*



Mellman I, et al. *Nature* 2011

PD-1/ PD-L1: Programmed Death Receptor *(releasing the brakes)*
Pembrolizumab treatment in RRMM – Phase I data

	KEYNOTE-023 (PhI): PEMBRO-LEN-DEX[1]	Ph I/II: PEMBRO – POMA –DEX[2]
Study design	PEMBRO 200mg/2QW LEN 25mg 1-21 DEX 40mg weekly	PEMBRO 200mg/2QW POMA 4mg 1-21 DEX 40mg weekly
Patient population	- > 2 prior lines - PI & IMID exposure	- >2 prior lines - RRMM - PI & IMID exposure
Refractory status	75.8% Len-refractory 66.1% double/triple/cuadruple refractory	89% Len-refractory 82% Bort-refractory 73% double-refractory
ORR	Global (n= 50): 44% Len-refr (n=37): 35.1% Median PFS all 7.2 m / Len-R: 6.3m Median OS: all NR vs 26.3m in Len-R	Total (n=48): ORR: 60% Double refractory (n=35): 68% Median PFS 17.4m
Safety	AEs consistent with individual drug safety profiles for approved indications IRAEs: no pneumonitis. No colitis. 65% AEs grade 3-5, 33% neutropenia	Good safety profile irAEs: 38% Pneumonitis: 14%

[1]Rodriguez-Otero P et al. EHA 2017, oral presentation; [2]Badros et al, Blood 2017 prepub May

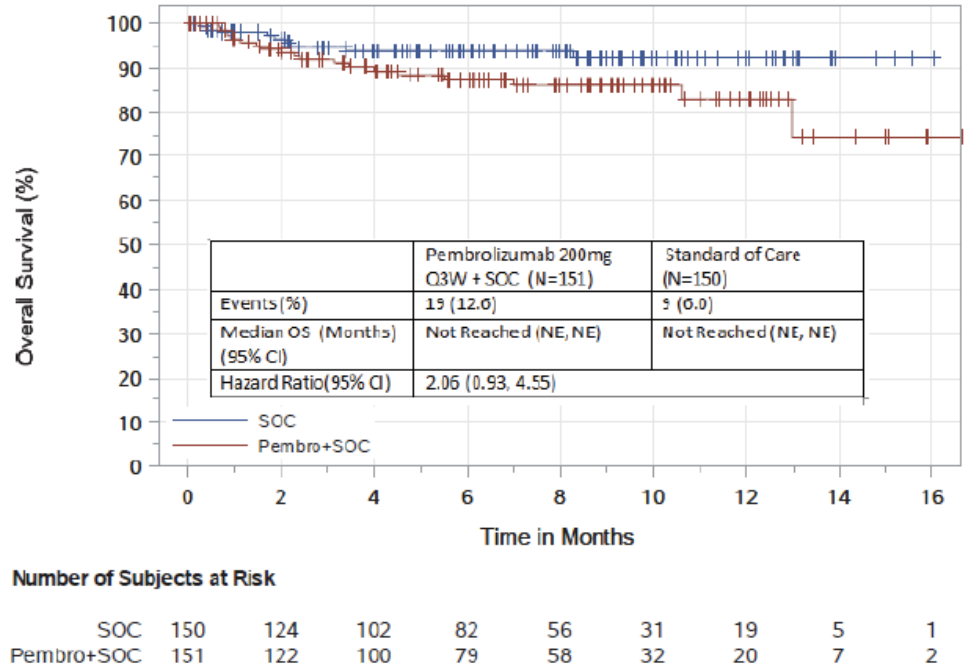
Pembrolizumab results in phase III trials

Keynote-185: NDMM non-TE. RD vs RD + Pembro (n=301)

ORR: PembroRD 64% vs 62% Rd

Overall Survival

HR 2.06 (95% CI: 0.93, 4.55)



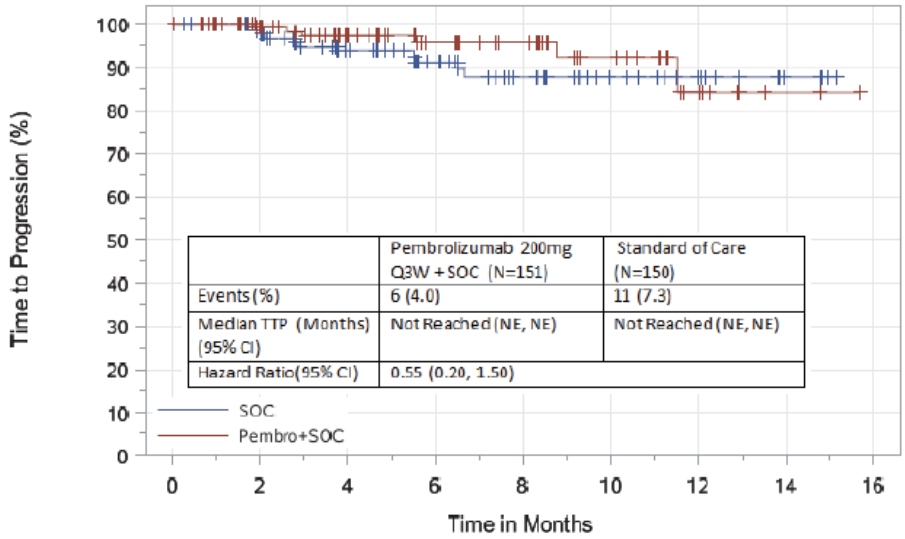
	Pembrolizumab 200mg Q3W + SOC (N=151)	Standard of Care (N=150)
Events (%)	19 (12.6)	9 (6.0)
Median OS (Months) (95% CI)	Not Reached (NE, NE)	Not Reached (NE, NE)
Hazard Ratio (95% CI)	2.06 (0.93, 4.55)	

Number of Subjects at Risk

SOC	150	124	102	82	56	31	19	5	1
Pembro+SOC	151	122	100	79	58	32	20	7	2

TTP

HR 0.55 (95% CI: 0.20, 1.50)



	Pembrolizumab 200mg Q3W + SOC (N=151)	Standard of Care (N=150)
Events (%)	6 (4.0)	11 (7.3)
Median TTP (Months) (95% CI)	Not Reached (NE, NE)	Not Reached (NE, NE)
Hazard Ratio (95% CI)	0.55 (0.20, 1.50)	

Number of Subjects at Risk

SOC	150	114	82	59	38	20	12	4	0
Pembro+SOC	151	108	80	57	45	19	8	2	0

Safety:

- 22% increase in gr 3-5 toxicity (72% vs 50%)
- Incidence of SAEs: 54% in PemRd vs 39% in Rd

Data cutoff date: June 2, 2017

Median FUP: 6.6 months

FDA Safety communication, 31-August-2017

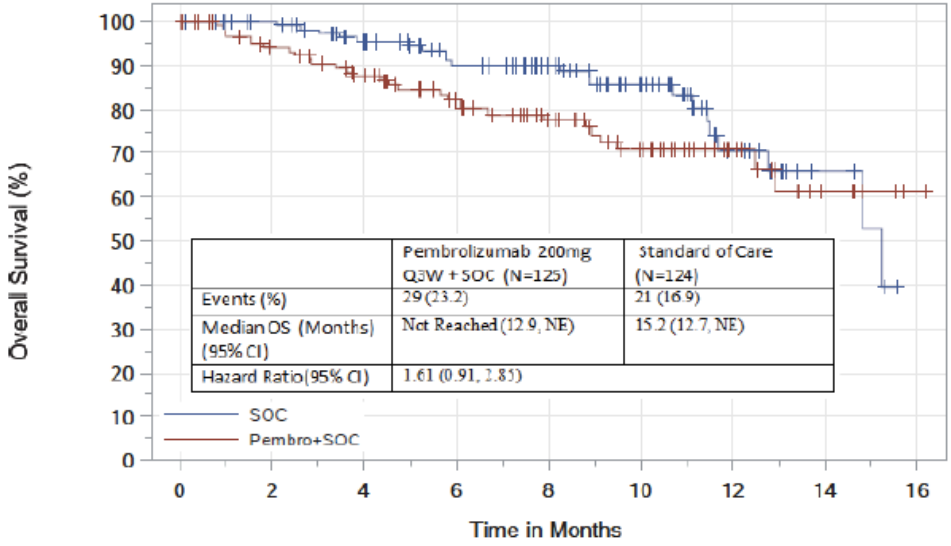
Pembrolizumab results in phase III trials

Keynote-183: RRMM. Pom-Dex vs Pom-dex + Pembro (n=249)

ORR: PembroPomD 34% vs 40% PomDex

Overall Survival

HR 1.61 (95% CI: 0.91, 2.85)



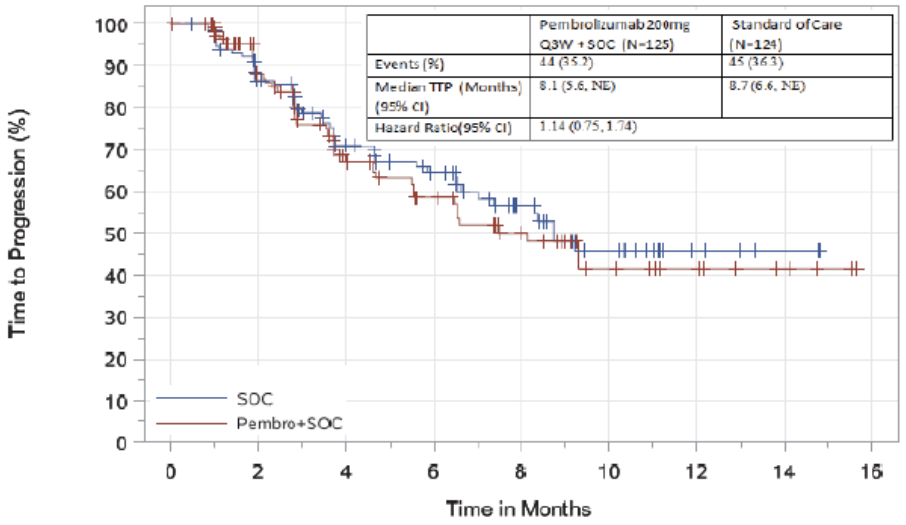
	Pembrolizumab 200mg Q3W + SOC (N=125)	Standard of Care (N=124)
Events (%)	29 (23.2)	21 (16.9)
Median OS (Months) (95% CI)	Not Reached (12.9, NE)	15.2 (12.7, NE)
Hazard Ratio (95% CI)	1.61 (0.91, 2.85)	

Number of Subjects at Risk

SOC	124	115	99	83	67	42	18	6	0
Pembro+SOC	125	105	91	73	53	37	18	7	1

TTP

HR 1.14 (95% CI: 0.75, 1.74)



	Pembrolizumab 200mg Q3W + SOC (N=125)	Standard of Care (N=124)
Events (%)	44 (35.2)	45 (36.3)
Median TTP (Months) (95% CI)	8.1 (5.6, NE)	8.7 (6.6, NE)
Hazard Ratio (95% CI)	1.14 (0.75, 1.74)	

Number of Subjects at Risk

SOC	124	91	61	46	29	17	5	2	0
Pembro+SOC	125	81	50	37	24	12	8	4	0

Safety:

- 18% increase in gr 3-5 toxicity (83% vs 65%)
- Incidence of SAEs: 63% in PemRd vs 46% in Rd

Data cutoff date: June 2, 2017

Median FUP: 8.1 months

FDA Safety communication, 31-August-2017

Summary

- Monoclonal antibodies are already a reality in the treatment of MM patients both at relapse and in the frontline setting. Still, there are some points that need further clarification,
  - Is it possible to retreat
  - Is there cross-resistance between antiCD38 MoAb
  - Mechanisms of resistance to MoAb

- Further development in the field of monoclonal antibodies (Bispecific, cojugates…) hold promise for relapse and refractory patients.

- Adoptive cell therapy has shown outstanding results in early phase trials but follow-up is still short and relapses continue to be an issue.

- Despite initial encouraging results with checkpoint inhibitors in MM, recent results showing an increased risk of early deaths among patients receiving PD-1 inhibitors have paused the development of these drugs in the field of MM, and now its use in this disease remains controversial.

Thank you for your attention

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