Multiple Myeloma: Changing and Emerging Treatment Paradigms

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- **Advisory Board:** Millennium-Takeda, Celgene,
- Gilead, Bristol Myers Squibb, Janssen
- **Scientific Founder:** Oncopep, C4 Therapeutics

Integration of Novel Therapy Into Myeloma Management

Proteasome inhibitors: Bortezomib, carfilzomib, ixazomib; **immunomodulatory drugs:** thalidomide, lenalidomide, pomalidomide; **HDAC inhibitor:** panobinostat; **monoclonal antibodies:** elotuzumab and daratumumab

Target MM in the BM microenvironment, alone and in combination, to overcome conventional drug resistance *in vitro* and *in vivo*

Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy

22 FDA approvals and median patient survival prolonged 3-4 fold, from 3 to at least 8-10 years, and MM is a chronic illness In many patients.

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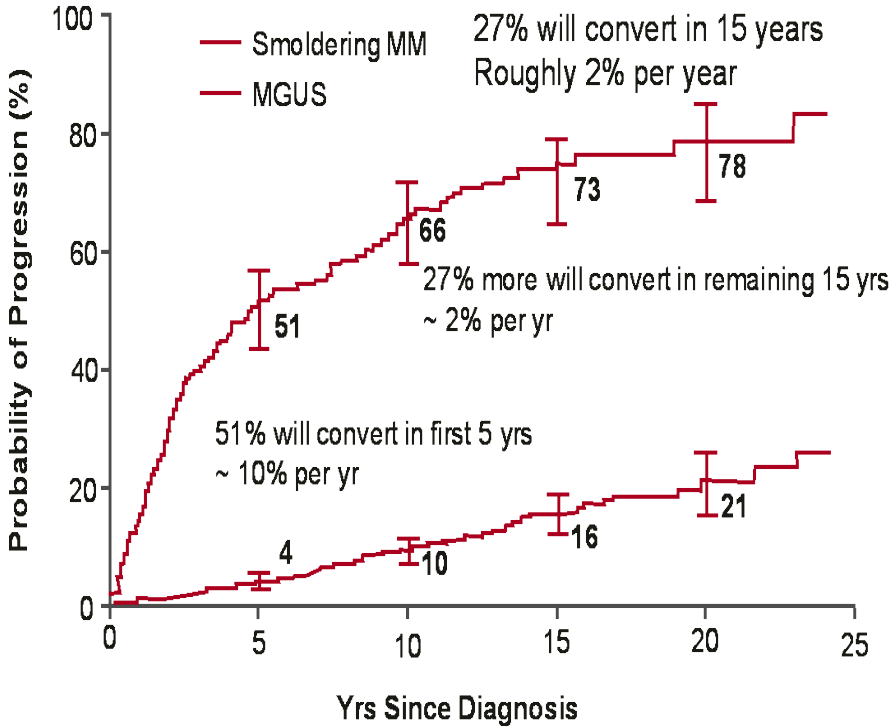
Progression from MGUS to MM



Kyle RA, et al. N Engl J Med. 2007;356:2582-2590. Greipp PR, et al. J Clin Oncol. 2005;23:3412-3420.

Diagnosis of Active MM (IMWG)

Even without CRAB features, the following define active MM:

Bone marrow plasmacytosis $\geq$ 60%

Abnormal FLC ratio $\geq$ 100 (involved kappa) or <0.01 (involved lambda)

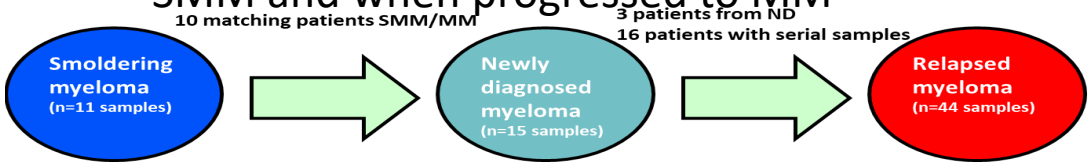
Focal bone marrow lesions on PET-CT and/or MRI

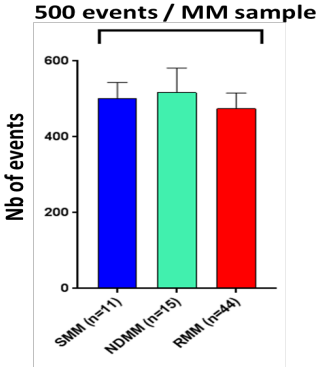
Protocols of novel agents/immune therapies to delay or prevent progression of smoldering to active MM.

Rajkumar et al. *Lancet Oncol* 2015; 12:e538-e548

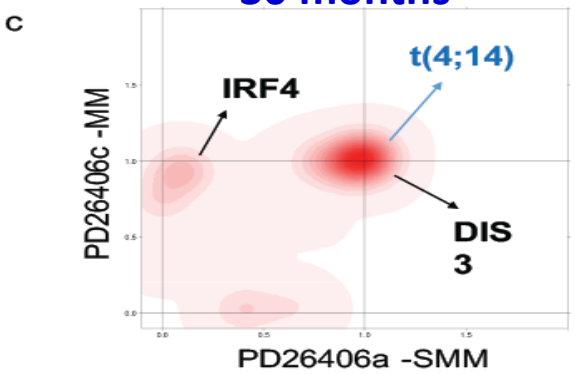
Define Genomic Changes With Progression of SMM to MM: Clinical Implications

11 matched paired samples from patients with SMM and when progressed to MM



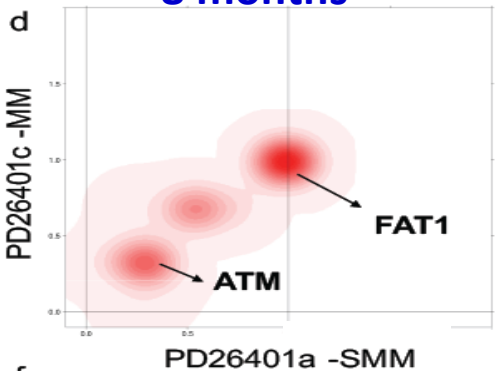


Progression 30 months

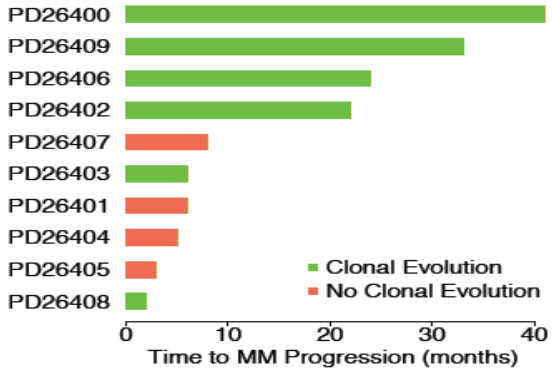


Branching evolution

Progression 8 months

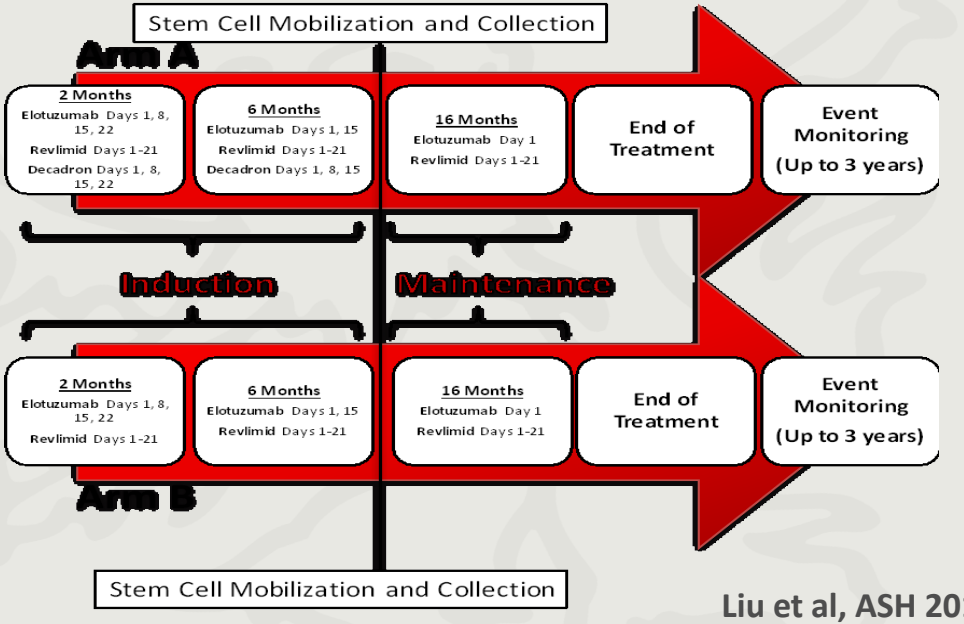


Limited Change in Clonal composition



Bolli et al:Nature Comm, 2018

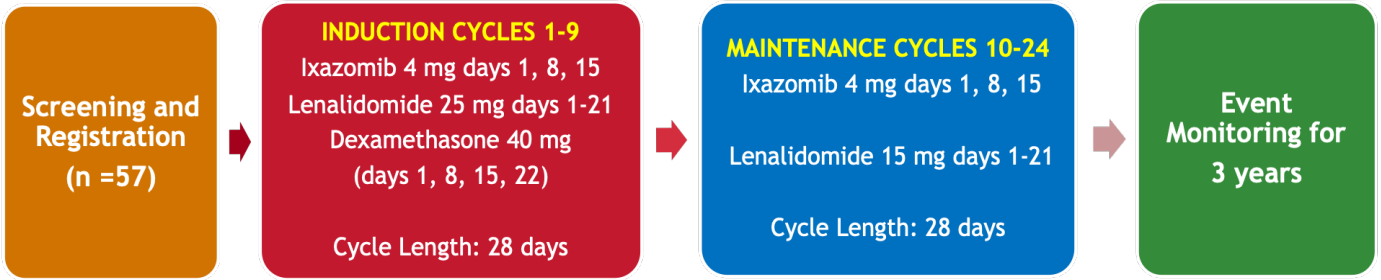
Phase II Trial of Combination of Elotuzumab, Lenalidomide, and Dexamethasone for High-Risk Smoldering Multiple Myeloma



Liu et al, ASH 2018

- 84% ≥ PR, 43% ≥ VGPR, well tolerated
- At 3 years, 95% PFS for EloRd vs 77% for Rd
- Genomic and immune profiling ongoing

Phase II Trial of Ixazomib, Lenalidomide, and Dexamethasone in High-risk Smoldering Multiple Myeloma



- **ORR 93.1%, 56% CR or VGPR, well tolerated**

Bustoros et al ASH 2018

Therapy for Newly Diagnosed MM
Transplant Candidates (several cycles)

Triplets preferred: Lenalidomide (Len)/ Bortezomib (Bort)/ Dexamethasone (Dex) RVD

Cyclophosphamide (Cy)/Bort/Dex CyBorD

Carfilzomib RD if neuropathy KRD

Quadruplets RVD, KRD, RD with or without Dara under evaluation

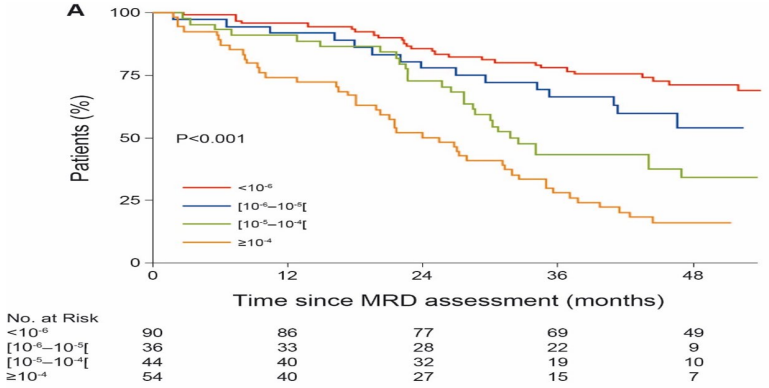
Doublets rarely used, ie Bort/Dex to improve renal dysfunction, then add Len

Maintenance Len in standard risk, Bort or Len Bort in high risk

Role of Transplant and Minimal Residual Disease (MRD) in Multiple Myeloma

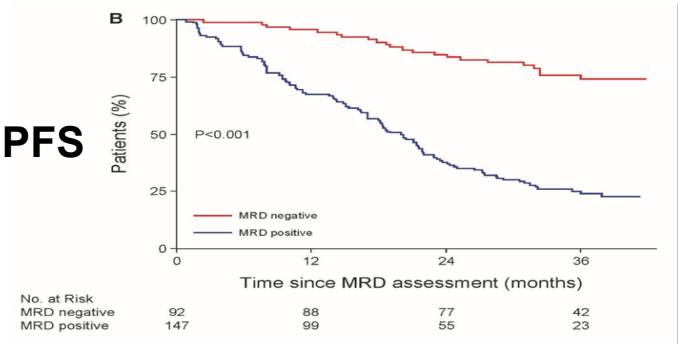
	RVD arm N=350	Transplant arm N=350	p-value
CR	49%	59%	
VGPR	29%	29%	0.02
PR	20%	11%	
<PR	2%	1%	
At least VGPR	78%	88%	0.001
Neg MRD by FCM , n (%)	228 (65%)	280 (80%)	0.001

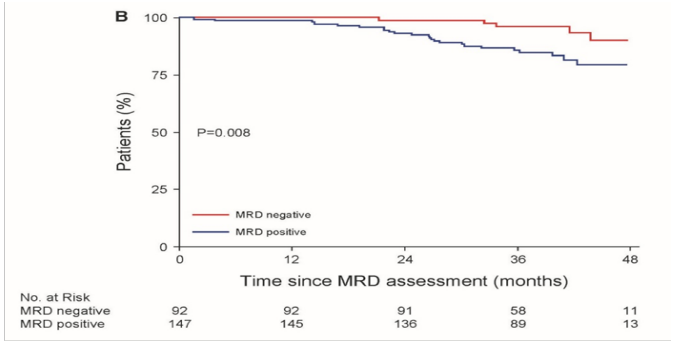
Attal et al NEJM 2017; 376: 1311-20



Defined the Sensitivity of the Test

PFS



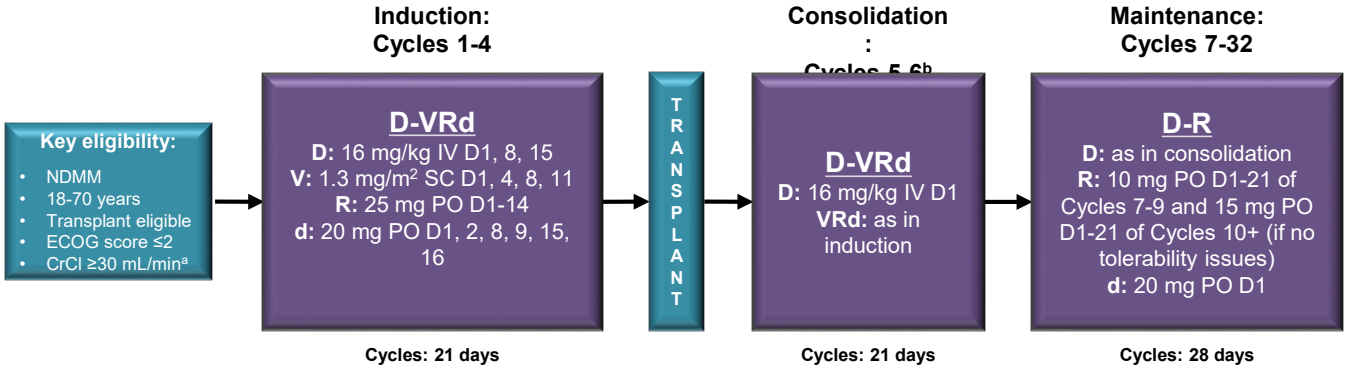


OS

Validated Clinical Impact of MRD Negativity

Perrot A et al Blood 2018

GRIFFIN :Daratumumab (DARA), Bortezomib (V), Lenalidomide (R), Dexamethasone (d; DARA-VRd) vs. VRd in NDMM Eligible for (ASCT)*



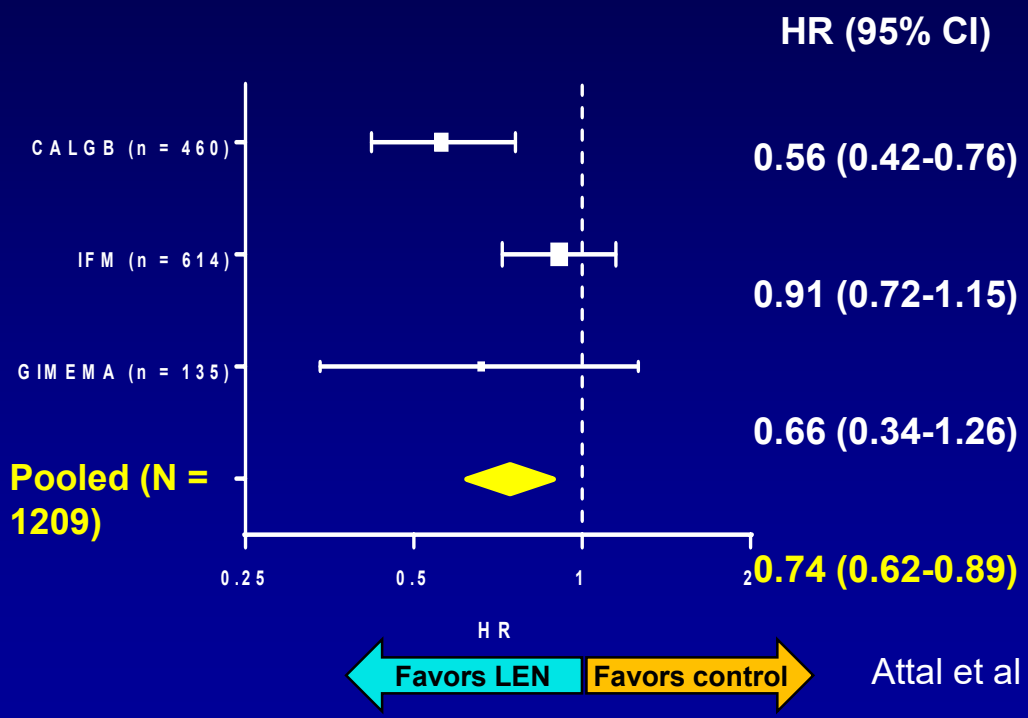
- Patients who complete maintenance cycles 7-32 may continue single-agent lenalidomide thereafter

Safety run-in phase in 16 patients to assess dose-limiting toxicities during 1 Cycle of D-VRd:

Well tolerated, 50% MRD negative post consolidation; randomized trial (n-222 D-RVd vs RVd fully enrolled

Voorhees et al ASH 2018

Lenalidomide Maintenance After High-Dose Melphalan and Autologous Stem Cell Transplant in Multiple Myeloma: A Meta-Analysis of Overall Survival Leading to FDA Approval



Attal et al ASCO 2016

- The size of the box is related to the size of the individual study. The confidence interval is a function of the overall sample size. HR, hazard ratio.

Survival Analysis of Lenalidomide Maintenance Therapy in NDMM Post-ASCT Adjusted for Crossover (Alliance 100104)

- Appropriate analysis of crossover studies is vital to enable assessment of therapy value and is recommended by health technology assessment bodies like NICE[6]
- Not adjusting for crossover can underestimate survival benefit
- **This updated crossover analysis found LEN maintenance therapy was associated with an OS gain of more than 3 years (40 months) versus placebo**
- The results provide further insight into the survival benefit of LEN maintenance post-ASCT, and support guideline recommendations to offer LEN maintenance therapy to all NDMM patients, post-ASCT

McCarthy et al ASH 2018

Maintenance Therapy Post-Transplant with Lenalidomide, Bortezomib and Dexamethasone (RVD) Decreases Early Relapse in High Risk Patients

1. Stringent CR 51%, 96% VGPR
2. Median PFS 32 months
3. Three year OS 93%

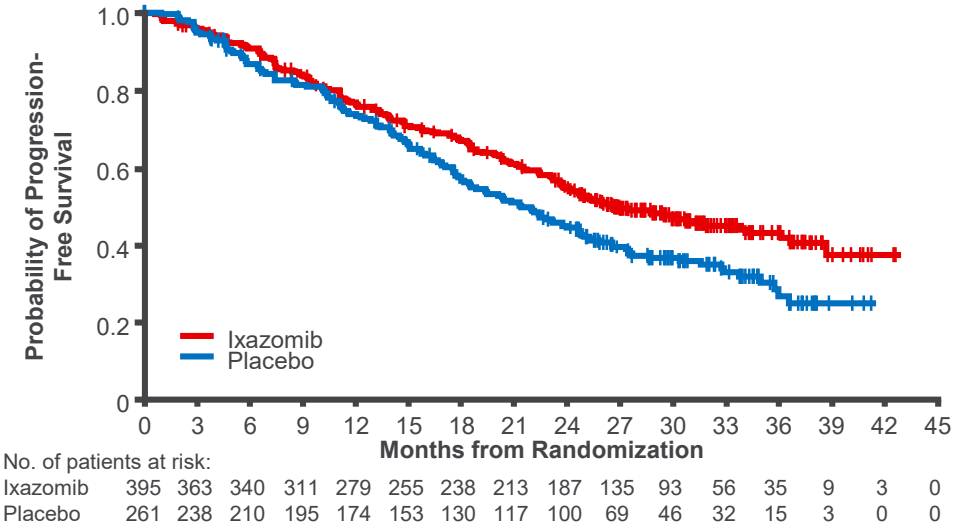
Incorporate both lenalidomide and bortezomib in maintenance therapy of high risk MM.

Nooka et al, Leukemia 2014: 28: 690-3.

Maintenance Oral Proteasome Inhibitor Ixazomib Following ASCT in NDMM: Phase 3 TOURMALINE-MM3 Trial

39% improvement in overall PFS with ixazomib vs. placebo

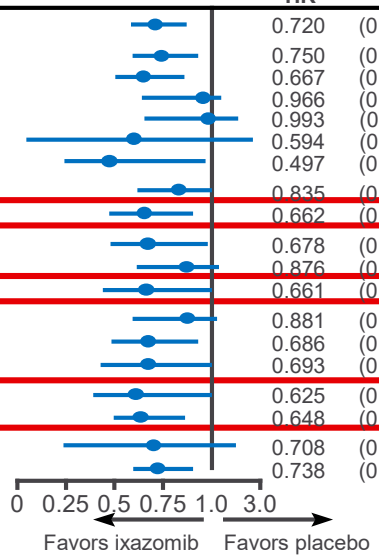
- There was a significant 39% improvement in overall PFS from time of randomization for patients receiving ixazomib vs. placebo maintenance:
  - HR: 0.72; 95% CI: 0.582–0.890
  - p=0.002
  - Median 26.5 months vs. 21.3 months
- With only 14% of deaths reported, at a median follow-up of 31 months, median OS has not been reached in either treatment arm and follow up continues



Dimopoulos et al ASH 2018

PFS benefit observed across patient subgroups

Variable	Subgroup	% of patients Ixazomib	% of patients Placebo	HR	95% CI
All subjects	All (n = 656)	100	100	0.720	(0.582, 0.890)
Induction regimen	PI exposed (n = 585)	89	89	0.750	(0.600, 0.938)
	PI without IMiD (n = 389)	59	59	0.667	(0.510, 0.874)
	PI with IMiD (n = 196)	30	30	0.966	(0.647, 1.442)
	PI + thalidomide* (n = 177)			0.993	(0.643, 1.532)
	PI + lenalidomide* (n = 24)			0.594	(0.132, 2.683)
	No PI; with IMiD (n = 71)	11	11	0.497	(0.254, 0.973)
Age	<60 years (n = 356)	58	49	0.835	(0.620, 1.125)
	≥60 years and <75 years (n = 300)	42	51	0.662	(0.480, 0.914)
Pre-induction ISS stage	I (n = 245)	38	36	0.678	(0.471, 0.975)
	II (n = 221)	33	35	0.876	(0.611, 1.256)
	III (n = 190)	29	29	0.661	(0.438, 0.998)
Response at study entry	CR (n = 225)	33	36	0.881	(0.593, 1.307)
	VGPR (n = 294)	45	44	0.686	(0.498, 0.945)
	PR (n = 137)	21	20	0.693	(0.440, 1.093)
Cytogenetic risk	High-risk (n = 115)	15	21	0.625	(0.383, 1.019)
	Standard-risk (n = 404)	64	58	0.648	(0.490, 0.857)
Renal function based on baseline creatinine clearance	30–<60 ml/min (n = 58)	10	8	0.708	(0.240, 2.090)
	≥60 ml/min (n = 595)	90	92	0.738	(0.592, 0.920)



Dimopoulos et al ASH 2018

Therapy for Newly Diagnosed MM Transplant Ineligible (continuous therapy)

Triplets preferred at attenuated dose/schedule:

Lenalidomide (Len)/ Bortezomib (Bort)/ Dexamethasone (Dex) RVD Lite

Cyclophosphamide (Cy)/Bort/Dex CyBorD

Carfilzomib RD if neuropathy KRD

Ixazomib RD all oral regimen IRD

Daratumumab RD DRD

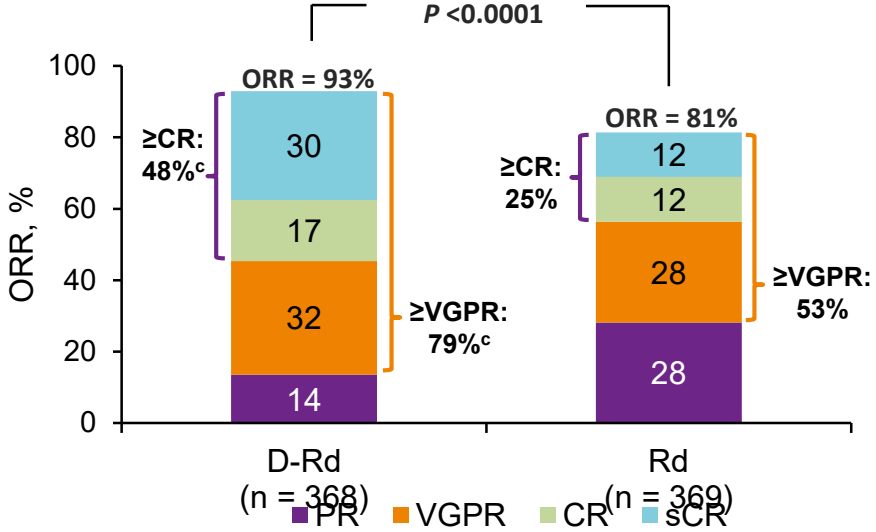
Quadruplet Dara Bort Mel Pred D-VMP (ex US)

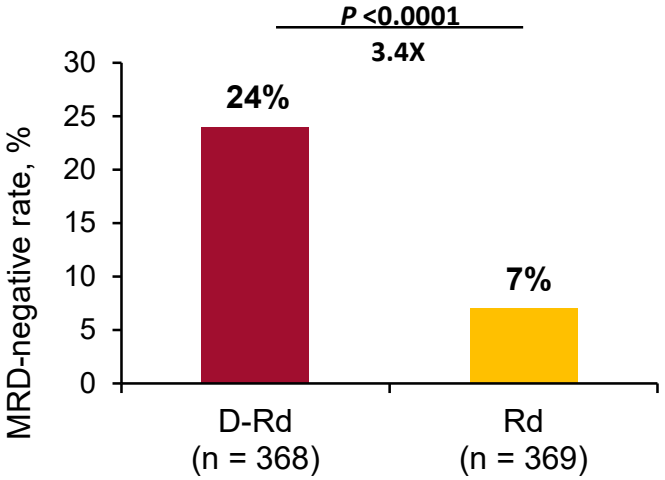
Doublets used in frail patients, ie Bort/Dex or Len/Dex at reduced doses

Maintenance Len in standard risk, Bort or Len Bort in high risk

Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Rd in Newly Diagnosed Multiple Myeloma Ineligible for Transplant (MAIA)

Facon et al, ASH 2018





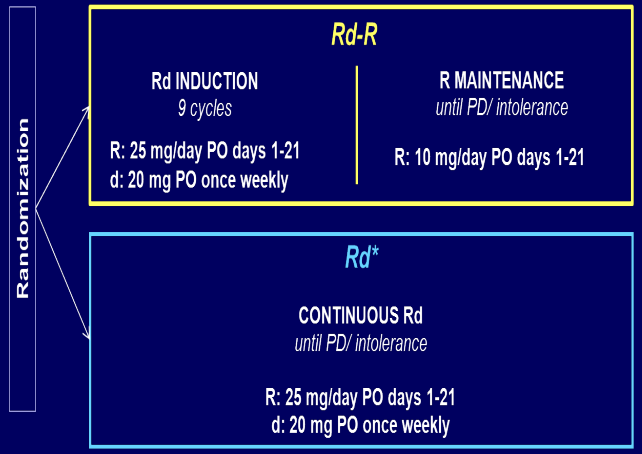
Significantly higher ORR, ≥CR rate, ≥VGPR rate, and >3-fold higher MRD-negative rate with D-Rd

- **Lower risk of progression or death with MRD negativity**

Rd-R vs Rd Continuous in Elderly Intermediate Fit Newly Diagnosed MM

Study design

199 intermediate-fit patients have been enrolled and could be evaluated



*The dose and schedule of continuous Rd was the one adopted in patients >75 years in the FIRST trial (Hulin C et al. JCO 2016)

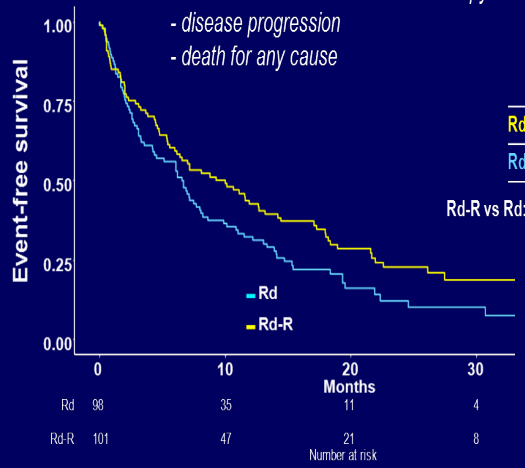
R, lenalidomide; d, dexamethasone; PO, orally; PD, progressive disease

Rd vs Rd-R: Event-free Survival

Median follow-up 25 months

Primary endpoint: Event-free Survival (EFS)

Definition of the event:*
- *hematologic grade 4 AEs*
- *non-hematologic grade 3-4 AEs including SPM*
- *discontinuation of lenalidomide therapy*
- *disease progression*
- *death for any cause*



	N	Median EFS
Rd-R	101	9.3 months
Rd	98	6.6 months

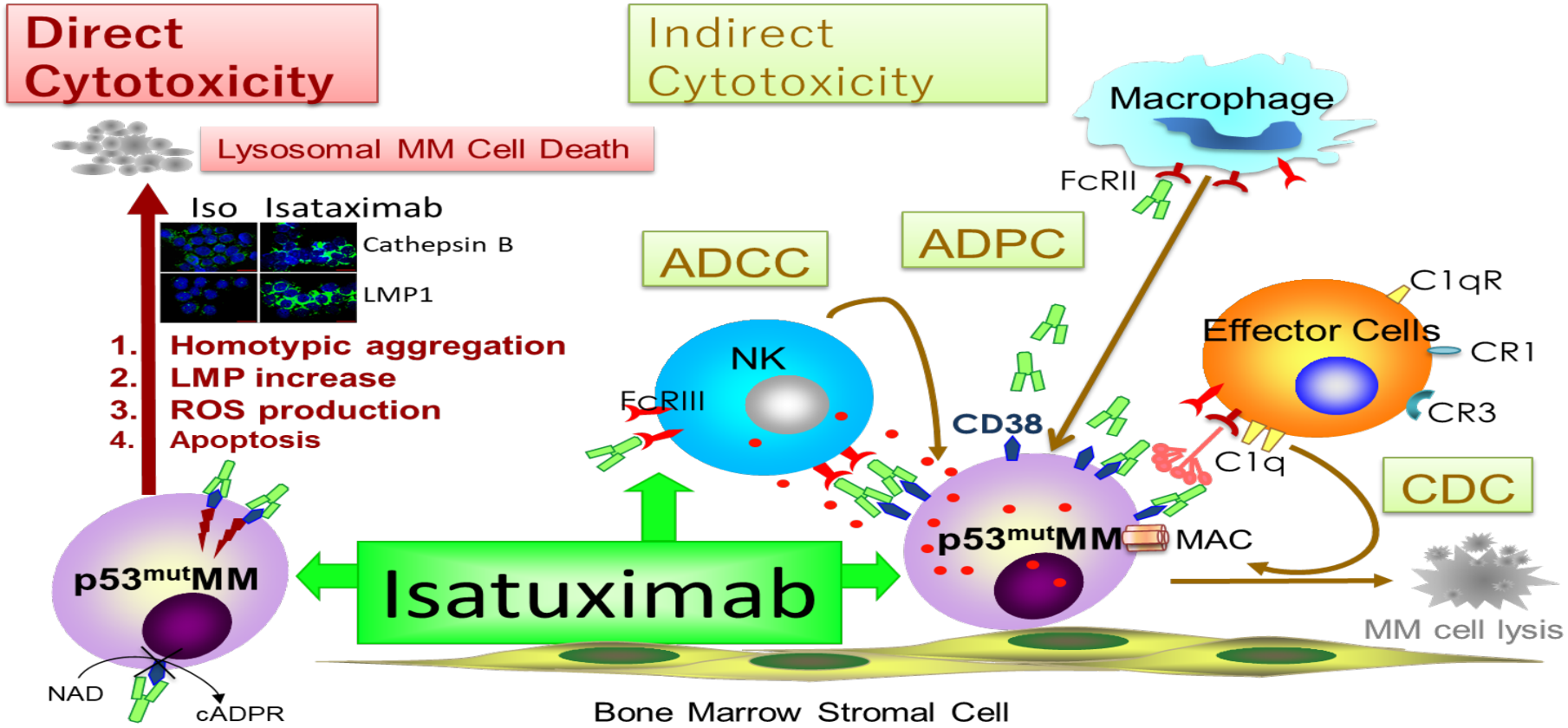
Rd-R vs Rd: HR 0.72; CI 0.52-0.99; p=0.044

R, Lenalidomide; d, dexamethasone; EFS, event-free survival; AEs, adverse events; SPM, second primary malignancy

*related to study drugs

Larocca et al ASH 2018

Isatuximab Anti-CD38 MoAb Triggers ADCC, ADPC, CDC, and Lysosomal MM Cell-Death



Tai et al Leukemia 2016;30:399

Isatuximab CD 38 Ab Bortezomib, Lenalidomide, Dexamethasone in NDMM Non-Eligible for Transplant

- ORR confirmed as 100% in efficacy-evaluable patients: ≥VGPR was achieved in 92%
- Overall, 7/16 MRD-evaluable patients (44%) achieved MRD negativity by NGS and/or NGF at the 10^{-5} sensitivity level
- The isatuximab regimen was well tolerated with a manageable safety profile
- Median infusion duration for isatuximab was 3.7 h for 1st infusion and 2.7 h for subsequent infusions

Ocio et al 2018

Therapy for Relapsed MM Depends on Prior Treatment/Clinical Features:Triplets Preferred With Second Generation IMiDs, Pis, MoAbs

Active In Len and Bort refractory MM

Carfilzomib Pom Dex (no neuropathy)

Dara Pom Dex (deep responses)

Elo Pom Dex (well tolerated)

Active in Bort refractory MM

Elotuzumab/Len/Dex (indolent relapse), Ixazomib Len/Dex (all oral), Carfilzomib Len/Dex (no neuropathy), Dara Len dex (MRD- responses)

Active in Len refractory MM

Pom Bort/Dex, Dara Bort Dex (MRD- responses)

Pom, Carfil, Ixa, Dara, Elo achieve responses in del17p MM

Carfilzomib, Pomalidomide and Dexamethasone (KPd) in MM Refractory to Bortezomib and Lenalidomide (n=60)

Time to response (median)	**2 months**
Response after 8 KPd	
CR/sCR	**31 %**
≥ VGPR	**65 %**
≥ PR	**87 %**
Poor vs Standard-risk FISH	**No difference**
Best overall response	
CR/sCR	**42 %**
≥ VGPR	**76 %**
≥ PR	**92 %**

HOVON EMN

ASH 2018

Isatuximab Anti-CD 38 Ab + Pom/Dex in RRMM

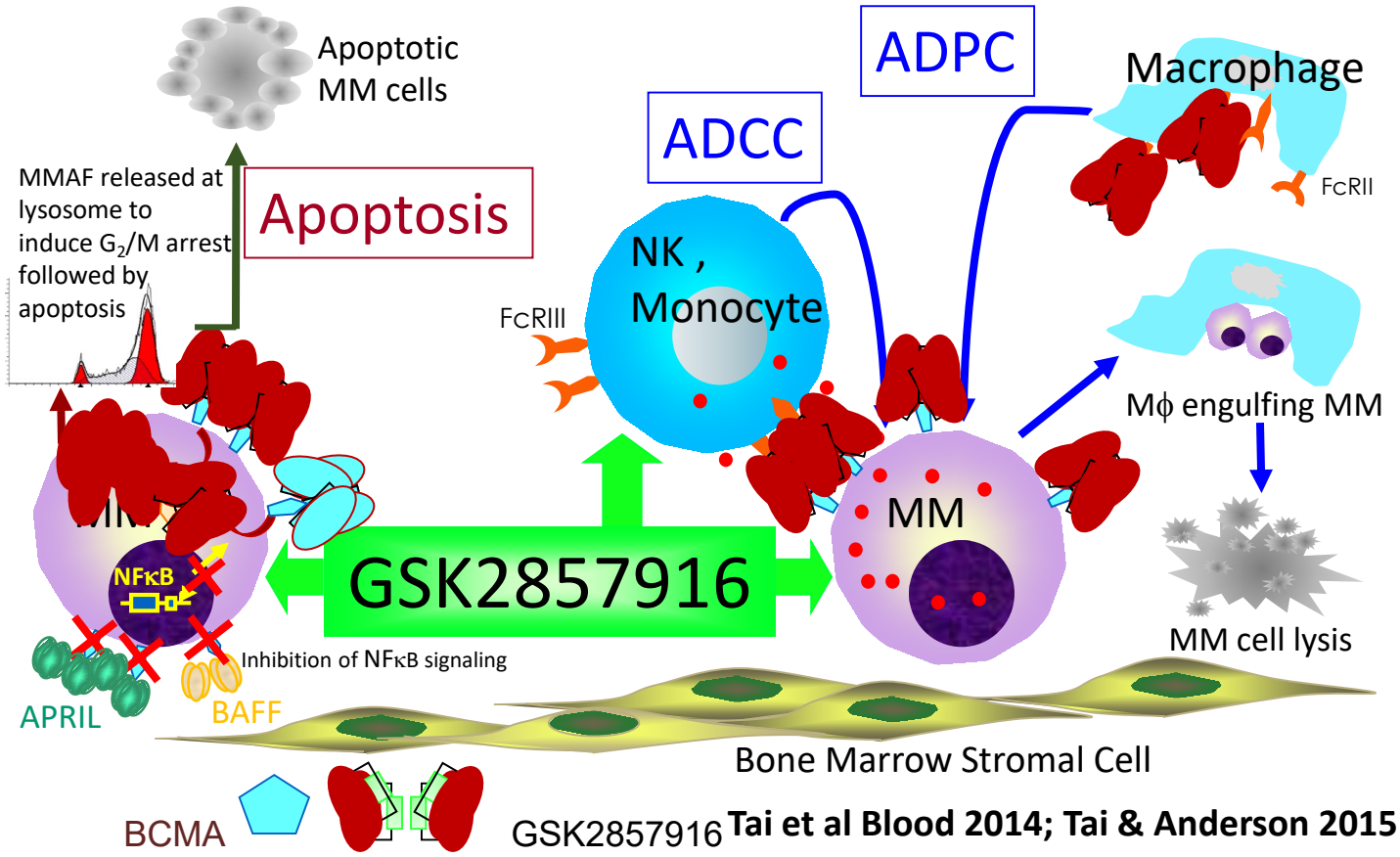
- The combination of isatuximab with Pom or with Len augments T and NK cell mediated lysis of MM cells and decreases Tregs

- The combination of isatuximab with Pom/dex has an acceptable and manageable safety profile in patients with RRMM.

- ORR 60%, including 61.3% ORR treated at isatuximab 10 mg/kg and 54.1% in IMiD-refractory patients
-
- Global Phase III study of isatuximab +/- Pom/dex in RRMM patients (NCT02990338) fully accrued

Tai et al Clin Cancer Res 2017;23:4290
Richardson PG., et al, ASH 2017

A BCMA Auristatin Immunotoxin Induces Strong Anti-MM Effects



Tai et al Blood 2014; Tai & Anderson 2015

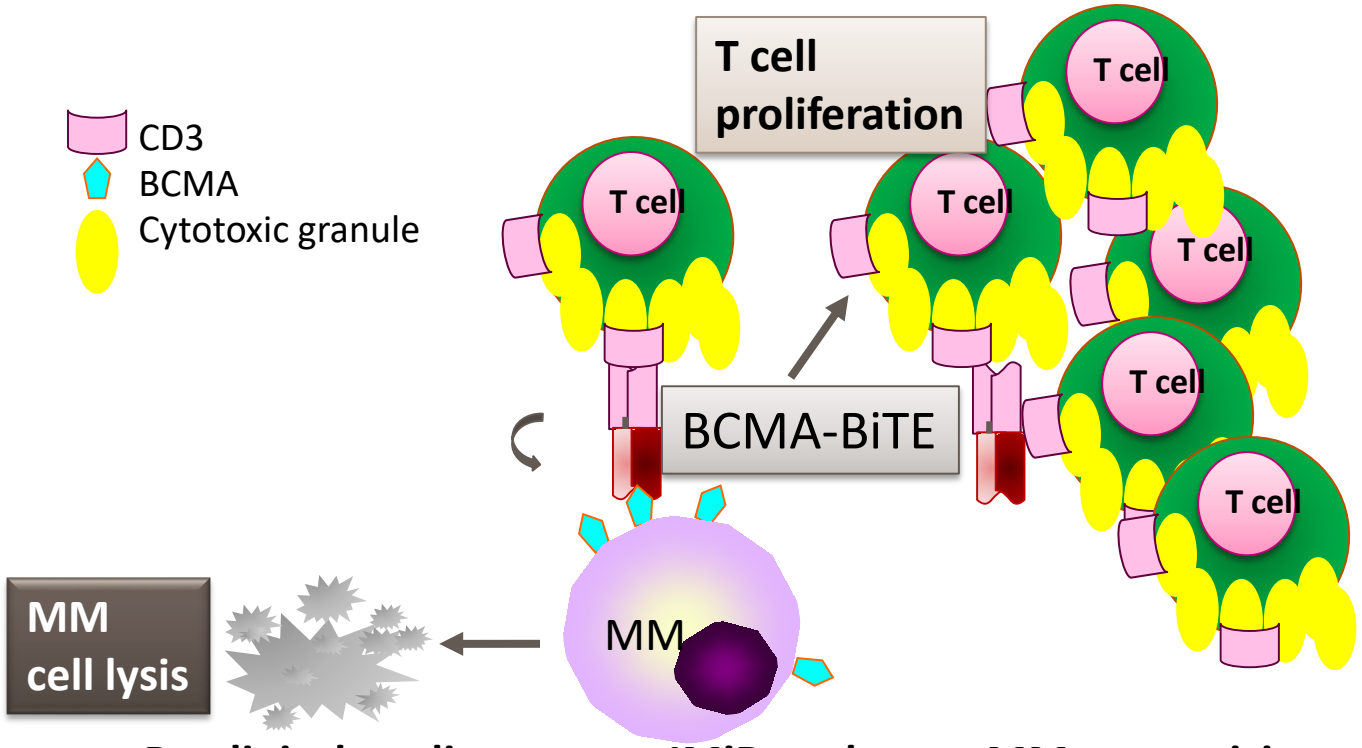
GSK2857916 Aurostatin Immunotoxin Targeting BCMA in Relapsed/Refractory Multiple Myeloma

- BCMA Selectively expressed on MM/plasma cells
- BCMA MoAb linked to aurostatin immunotoxin
- Median follow-up 6.6 months
- ORR of 60% in heavily pre-treated MM
- Median PFS 7.9 months
- Well tolerated and side effects manageable
  - Thrombocytopenia and corneal events most frequent AEs
  - IRRs occurred in only 23% of patients without pre-medication; no IRRs occurred on subsequent infusions
- Additional monotherapy and combination studies are planned

Trudel et al ASH 2017
Lancet Oncol 2018; 19: 1641

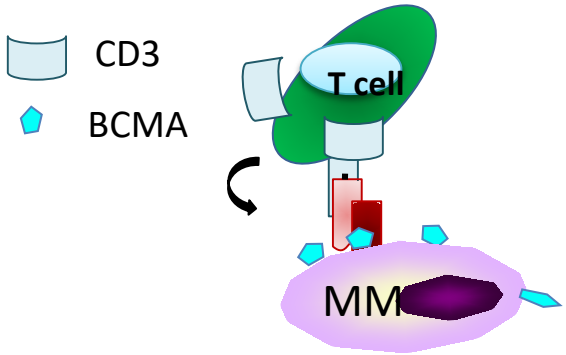
DOR, duration of response; IRR, infusion-related reaction; MM, multiple myeloma; ORR, overall response rate; PFS, progression-free survival; VGPR, very good partial response

BCMA-BiTE-Based Immunotherapy



Preclinical studies suggest IMiDs enhance MM cytotoxicity

Hipp, Tai et al Leukemia 2017; 31:1743-51.



AMG 420 an Anti-BCMA BiTE® in RRMM

Safety	N=42
Discontinue due to PD, n (%)	21 (50)
Discontinue due to AE, n	7 (17)
SAEs, n (%)	20 (48)
Infection, n (%)	12 (29)
CRS, n Gr1/2/3	13/2/1
Gr3 peripheral neuropathy, n (%)	2 (5)
Gr3 edema	1 (2)
Required hospitalization, n (%)	17 (40)
Prolonged hospitalization, n (%)	4 (10)

Response	N=42
Mean cycles given (SD), n	2.4 (2.4)
Median cycles given (range), n	1 (1-10)
Responders (n=13)	
Mean cycles given (SD), n	5.4 (3.1)
Median cycles given (range), n	6 (1-10)
Median time to first/best response, mo	1.4/2.8
CR rate, n (%)	**7 (17)**
VGPR rate, n (%)	**1 (2)**
PR rate, n(%)	**3 (7)**

- **2/3 patients experienced DLT at DL 800 µg/d:**
  - **Gr3 CRS, and Gr3 peripheral polyneuropathy**

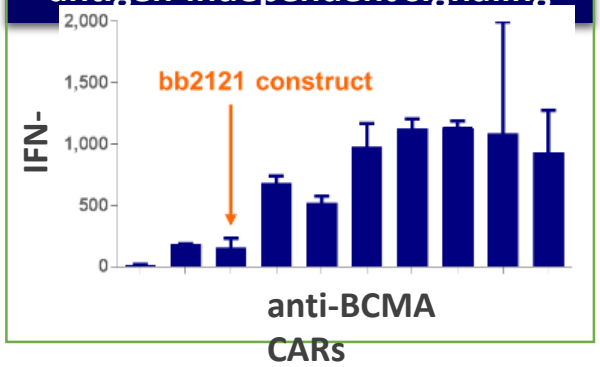
AMG 420, a short half- life BiTE targeting BCMA, showed activity in RRMM. No major toxicities were observed up to 400 µg/d,

Topp et al ASH 2018

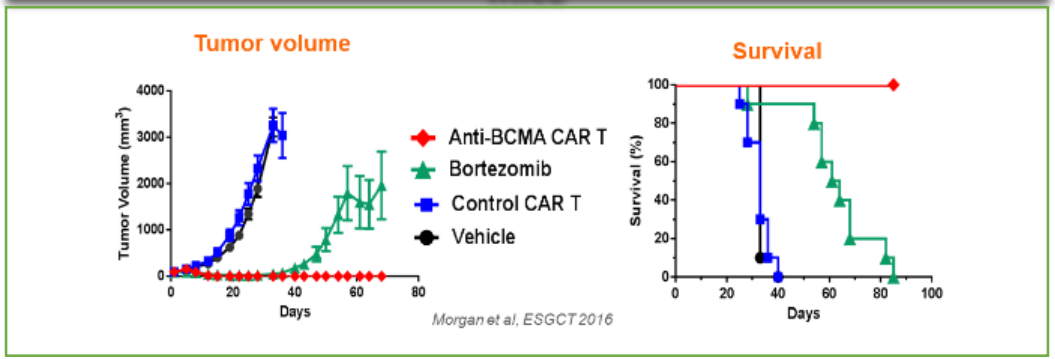
bb2121: An Anti-BCMA Chimeric Antigen Receptor T Cell Product Candidate

- bb2121 is a second-generation CAR construct targeting BCMA,
- Autologous T cells transduced with a lentiviral vector encoding an anti-BCMA scFv, a 4-1BB costimulatory motif to promote proliferation and persistence, and a CD3ζ T cell activation domain
- Construct demonstrated potent preclinical in vivo activity with low tonic signaling

bb2121 demonstrates low antigen-independent signaling

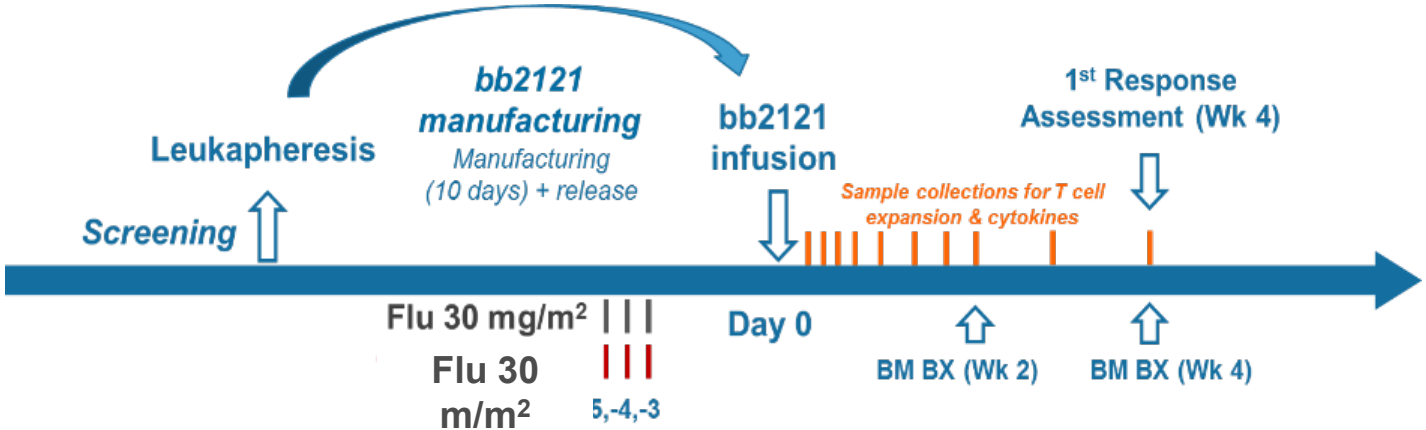


bb2121 improves survival and drives tumor clearance in MM mice



Raje N, et al. EHA 2018, abstract S138; Berdeja JG, et al ASH

CRB-401 BCMA CAR T: Phase 1 Study in RRMM



Dose Escalation
Prior IMiD + PI

50 × 10^6 → 150 × 10^6 → 450 × 10^6 → 800 × 10^6

Dose Expansion (N=22)
Prior IMiD + PI + Dara

≥50% BCMA expression (n=12)

Dose range: 150–450 × 10^6 CAR+ cells

Raje N, et al. EHA 2018, abstract S138.

bb2121 BCMA CAR T cells

bb2121 at active doses (≥150 × 10^6 CAR+ T cells) induces deep and durable responses in a heavily pretreated population with R/R MM

- **Median PFS of 11.8 months for patients in the dose escalation cohort**
- **MRD-negative results in 100% of 16 evaluable responding patients; median PFS of 17.7 months**
- **Mostly grade 1/2 CRS observed with infrequent tocilizumab and corticosteroid use**
- **Ongoing trial for FDA approval.**

Raje N, et al. EHA 2018, abstract S138.

Phase I Clinical Study of bb21217, a Next-Generation Anti-BCMA CAR T Cell Therapy

- **bb21217 cultured with PI3 kinase inhibitor bb007 to enrich for memory T cells**
- **bb21217 demonstrated promising early clinical activity in heavily pretreated patients with relapsed/refractory multiple myeloma at first dose level tested**
  - **83% ORR with 90% of responses ongoing**
  - **Elimination of MRD in the bone marrow of all 4 evaluable responders**
- **Safety profile appears consistent with known toxicities of CAR T cell therapies**
- **Early clinical evidence of enrichment for memory-like T cells among circulating CAR+ T cells and sustained functional CAR+ T cell persistence**
- **Dose escalation is ongoing**
- **Longer follow-up in a larger patient population will clarify the depth and durability of bb21217 tumor responses and dose response**

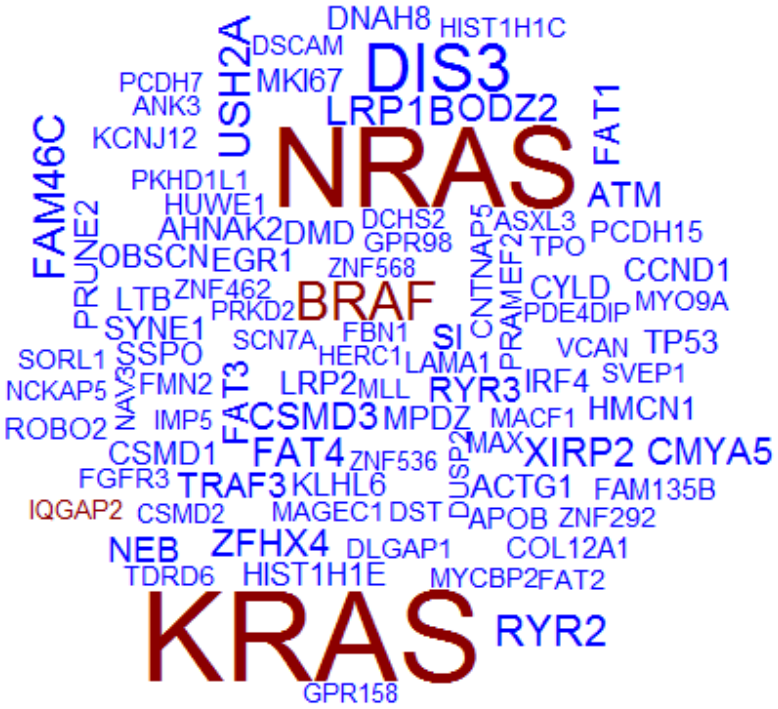
Shah et al ASH 2018

JCARH125, Anti-BCMA CAR T-cell Therapy for Relapsed/Refractory MM: Phase 1/2 Multicenter Study (EVOLVE)

- JCARH125 is a BCMA CAR T cell product with a fully human binder that **enriches for central memory T cell phenotype (both CD4 and CD8)**
- JCARH125 was **highly active (ORR 82%)** in heavily pretreated RRMM patient population
- CR/sCR was achieved by 27% patients with trend of **deepening responses over time**
  - **CR/sCR (43%) observed at the lowest dose level of 50 × 10^6 CAR T cells**
- JCARH125 **toxicity was generally manageable**
  - CRS grade 1 or 2 occurred in 71% of patients, CRS grade ≥3 in 9% of patients
  - Neurological events grade 1 or 2 occurred in 18% of patients, grade ≥3 in 7% of patients
- JCARH125 was active in patients with **high baseline levels of sBCMA**
- Study continues to enroll patients to further define the phase 2 dose

Malinkody et al ASH 2018

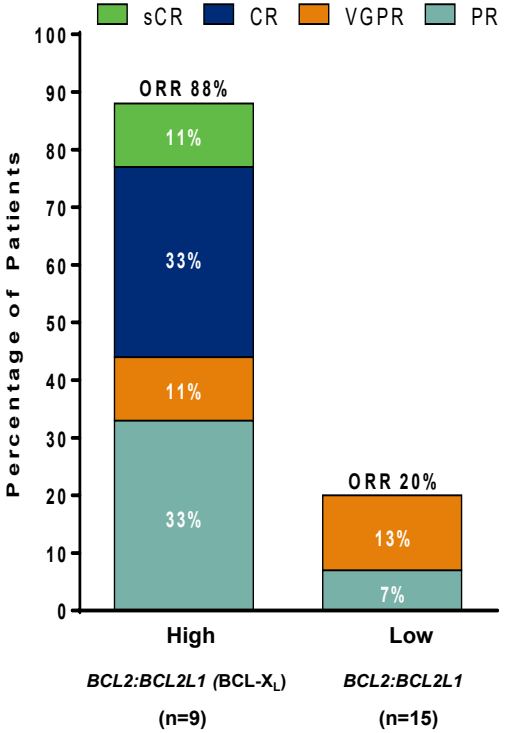
Targeting Mutations in Multiple Myeloma

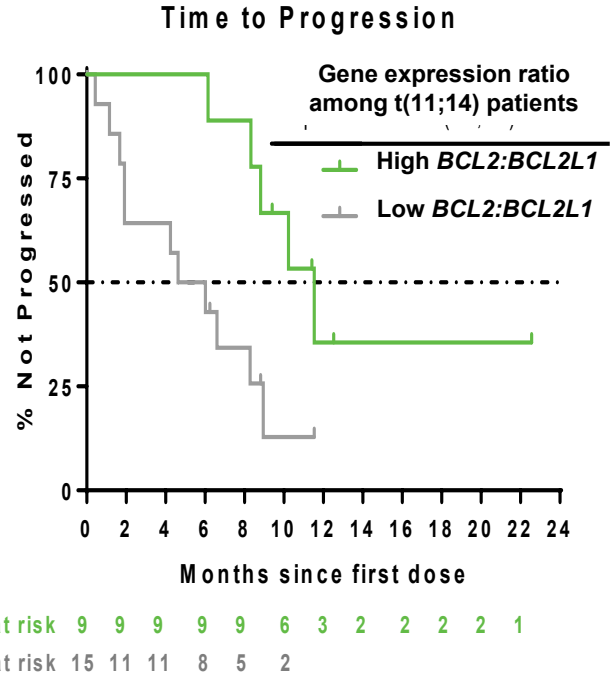


Therapies Targeting Ras Raf MAPK Pathway Achieve Only Transient Responses, Combination Clinical Trials Ongoing

Morgan GJ, Walker BA and Davies FE. Nature Reviews Cancer. 2012 Chapman *et al* Nature Genetics 2011, Walker et al 2012 Blood, Lohr et al Cancer Cell 2014, Bolli et al Nat Comm 2014, Walker BA et al Nat Comms 2015

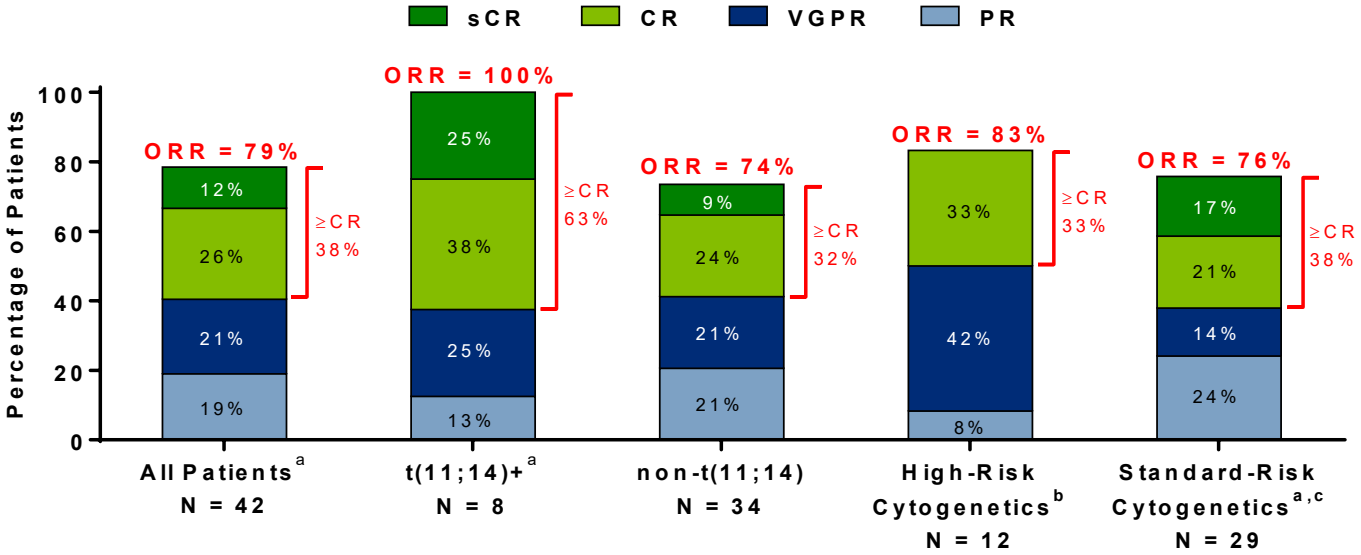
Personalized Medicine: Responses to Venetoclax (Target BCL-2) and Bortezomib (Target Bcl-1) by*BCL2:BCL2L1* Ratio Among t(11;14)-Positive Patients with RRMM





Kumar et al,, Moreau et al ASH 2016

Phase 2 Study of Venetoclax Plus Carfilzomib and Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma

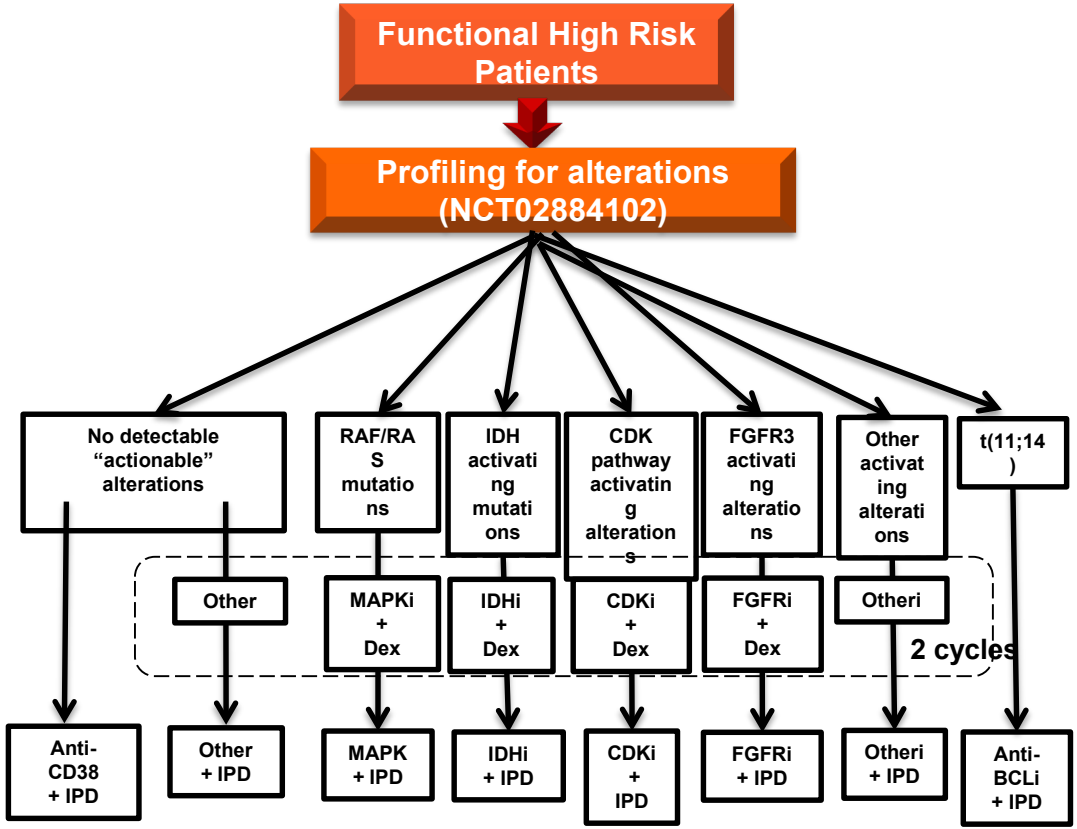


a. One patient died within the first 2 weeks of dosing; no data available.
b. t(4;14) or t(14;16) or del(17p)
c. No high-risk cytogenetics
Data cut-off: 17Sep2018

The 70 mg/m^2 K dose weekly was selected for expansion

Costa et al, ASH 2018

MY DRUG (MMRF TRIAL)

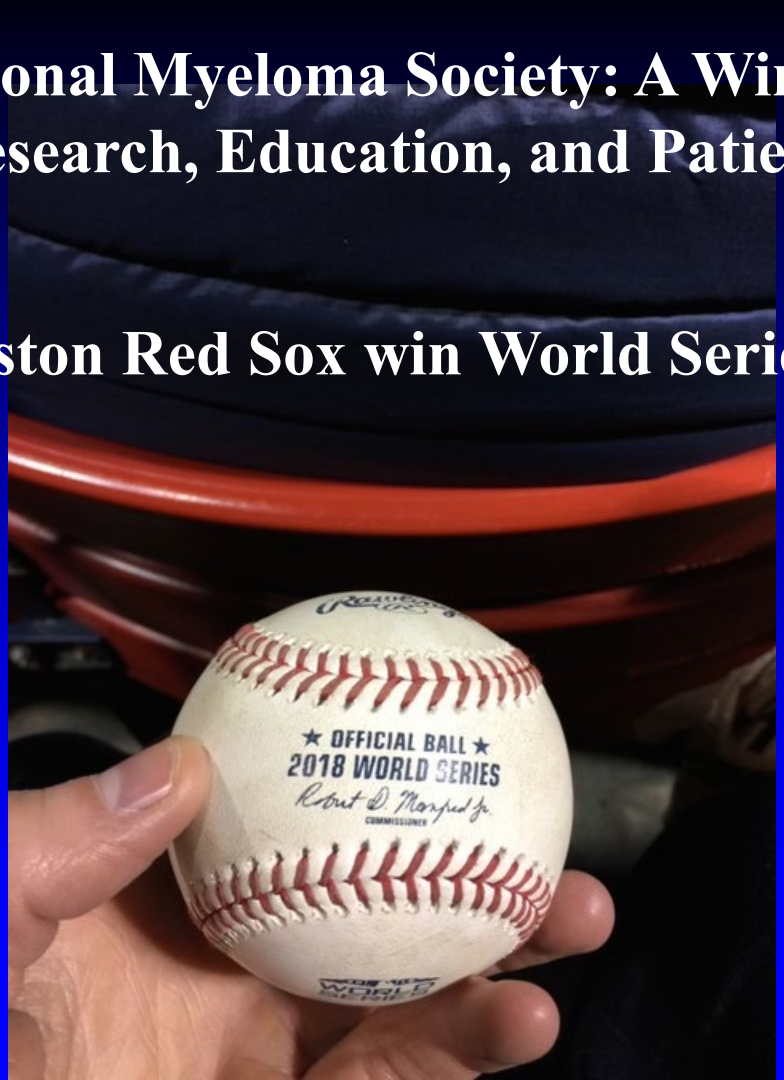


Summary and Conclusions

- Novel agent trials to delay or progression of SMM.
- Triplets standard, doublets in frail, four drug promising in both transplant and non transplant NDMM
- ASCT with novel agents achieves MRD-, increased PFS
- Maintenance lenalidomide in standard risk, with proteasome inhibitors in high risk MM
- Triplets achieve increased extent and frequency of response, PFS, and OS in relapsed MM
- Novel immune therapies: BCMA immunotoxin, Bites, and CAR T cells
- GenomicTargets: Venetoclax, MyDrug

International Myeloma Society: A Winning Team In Research, Education, and Patient Care

Boston Red Sox win World Series!



International Myeloma Society: A WinningTeam

In Research, Education, and Patient Care

New England Patriots win Sixth Superbowl!