## WELCOME & INTRODUCTIONS

*The Changing Landscape of Myeloma Treatment*


**To register or to view the BCC schedule, visit www.LLS.org/bcc.**

| Northern California Blood Cancer Conference | Texas Blood Cancer Conference |
|---|---|
| San Francisco, CA | San Antonio, TX |
| **January 25, 2020** | **February 8, 2020** |

***Program will begin shortly***

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## THE CHANGING LANDSCAPE OF MYELOMA TREATMENT

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**DISCLOSURES**

*The Changing Landscape of Myeloma Treatment*

| Nature of Relevant Financial Relationship | Commercial Interest |
|---|---|
| Grant or research support | Amgen, Celgene, Janssen, Millennium/Takeda, Novartis Pharmaceuticals, Pharmacyclics |
| Paid consultant | Amgen, Antengene, Celgene, Janssen, Karyopharm, Millennium/Takeda, Novartis Pharmaceuticals, Oncopeptides, Sanofi |

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# Overview: Newly Diagnosed Myeloma

General Considerations Frontline Therapy

Transplant Eligible

Transplant Ineligible

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# Factors in Selecting MM Therapy

**PATIENT**

- Age/Frailty
- Performance Status
- Lifestyle/Pt preferences
- Drug Metabolism
- Compliance/Adherence
- Caregiver support
- Renal Insufficiency
- Comorbidities
  - Neuropathy
  - Cardiac
  - Diabetes
  - Low blood counts

**DISEASE**

Burden
- ISS/LDH
- Marrow burden
- Biochemical vs CRAB symptoms
- Rate of progression
- Extramedullary

Biology
- LDH elevation
- Molecular
  - Del[17p - % cells?
  - t(4;14), t(14;16),
  - ampl 1q

**TREATMENT**

Access/Trial Availability

If Previously Treated
- Depth/duration
- Relapse > 60d vs progression

Toxicity
- Myelosuppresion
- Neuropathy
- VTE
- Secondary cancers

Administration Route

Single or Combination

Cost and Co-pays

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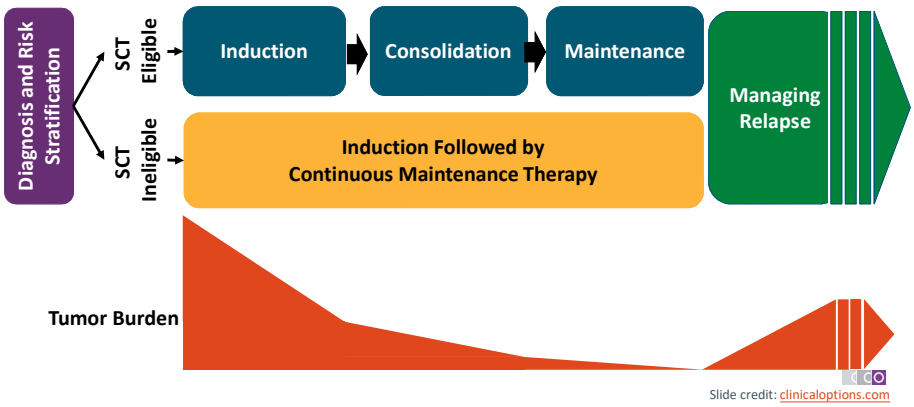
## Current Treatment Paradigm for Active Myeloma




Slide credit: clinicaloptions.com

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# Innumerable Combinations and Sequences of Anti- Myeloma Agents

| Steroids | Conventional Chemo | IMiDs | Proteasome Inhibitors | HDAC inhibitors | Immunologic approaches |
|---|---|---|---|---|---|
| Prednisone | Melphalan | Thalidomide | Bortezomib | Panobinostat | Daratumumab: anti CD38 |
| Dexamethasone | Cyclophosphamide | Lenalidomide | Carfilzomib (low/high dose) | | Elotuzumab : anti CS1/SLAMF7 |
| | Doxil | Pomalidomide | Ixazomib | | |
| | DCEP/D-PACE | | | | |
| | METRO28 | | | | |
| | BCNU | | | | |
| | Bendamustine | | | | |

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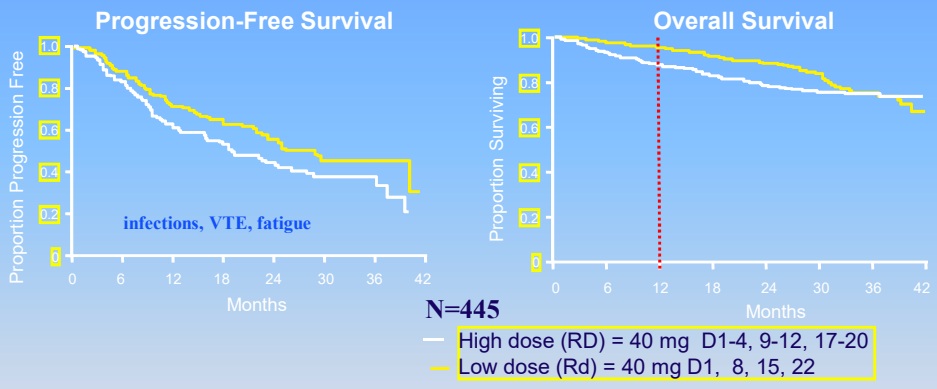
# More Not Always Better: Lenalidomide + High vs. Low Dose Dexamethasone




N=445

High dose (RD) = 40 mg D1-4, 9-12, 17-20
Low dose (Rd) = 40 mg D1, 8, 15, 22

Median follow-up: 35.8 months
ORR: 79% RD vs 68% Rd, *P* = 0.008
Median PFS: 19.1 months RD; 25.3 months Rd; *P* = 0.026
Median OS: Not reached (but DSMC mandated crossover after 12.5 mo analysis with 1 year OS 96% vs. 87% (log rank p 0.0002)

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(11):29-37.

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# Goals of Initial Therapy: Optimize Risk/Benefit

- Increase Benefits:
  - Overall Survival
  - Progression Free Survival
  - Rapid/deep response i.e. reversal of CRAB symptoms
  - Improve Quality of Life
  - Adequate Stem Cell Harvest (if eligible)
  - Overcome High Risk Disease
  - Attain Minimal Residual Disease Negativity
- Decrease Risks:
  - Treatment Related Death
  - Treatment Related Morbidity: eg. VTE, SPM, VZV, neutropenia, CHF
  - Avoid clonal resistance ie. minimize impact on 2nd PFS/TTP
  - Patient Costs
  - Health Care Costs

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Transplant Ineligible

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## Who is Eligible for Transplant?

- Age < 70 - ? Upper limit if fit
- Good performance status
- Adequate organ function
  - EF > 50%
  - FEV1, FVC, DLCO > 50% predicted
- Absence of concomitant multi-organ amyloid
- Adequate stem cell harvest ≥ 4 * 10 ^6 CD34 /kg
- No active infections

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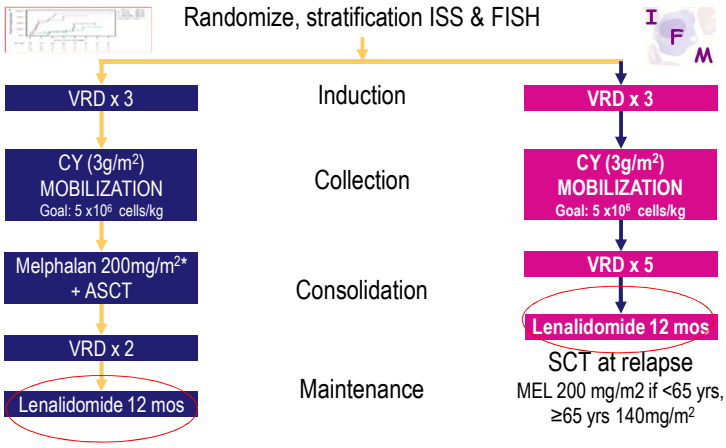
## Determination (IFM/DFCI 2009) Study - Design

Newly Diagnosed, SCT Candidates




http://www.clinicaltrials.gov/ct2/show/NCT01208662?term=nct01208662&rank=1.

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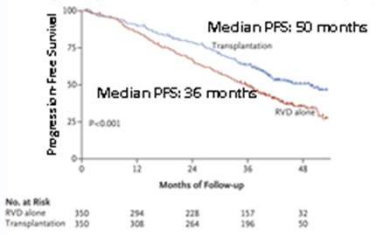
# IFM Outcomes of Determination: RVD with Transplantation Results in Superior Efficacy

| Best Response | Deferred ASCT | Upfront ASCT | P Value |
|---|---|---|---|
| ORR | 97% | 99% | |
| PR | 20% | 11% | |
| VGPR | 29% | 29% | |
| CR | 48% | 59% | 0.03 |
| ≥VGPR | 77% | 88% | 0.001 |
| MRD-[1] | 65% | 79% | <0.001 |

[1]MRD tested by flow cytometry in VGPR/CR pts

Median Follow-Up: 44 months for the deferred ASCT group, 43 months for the upfront ASCT group




**4-Year OS: 82% vs 81% for deferred and upfront ASCT, respectively**

*Attal M et al. NEJM 2017;376:1311-20.*

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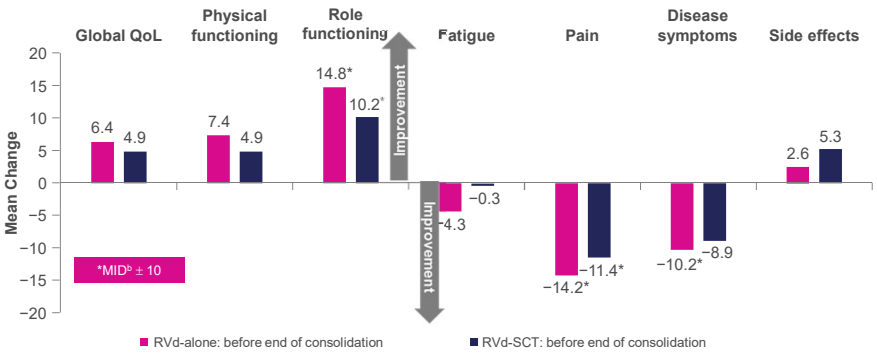
# IFM OUTCOMES of DeTERMINATION: IMPROVEMENT IN HRQoL FROM BASELINE TO AFTER STEM CELL HARVEST




[a] The data presented is at visit 5, which is the last assessment (i.e. approximately 28 days) prior to the expected end date of the consolidation treatment.
[b] Change in score of ≥ 10 points (from baseline) is considered a clinically meaningful difference for both EORTC QLQ-C30 and QLQ-MY20.
* Significance between the groups at $P < 0.05$ based on a two-sample t-test. A positive value indicates improvement from baseline and vice versa.

Roussel et al. ASH 2018

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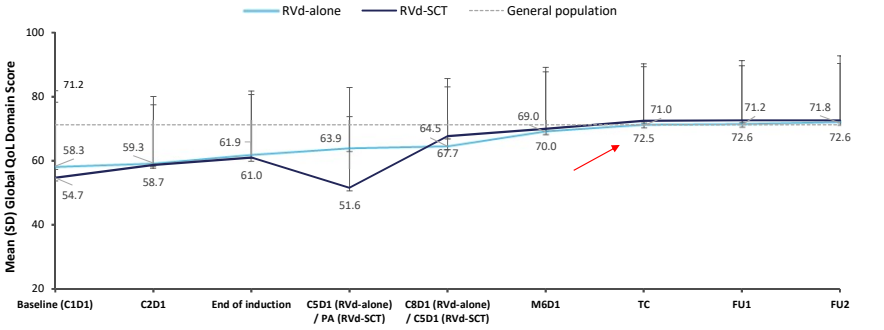
## IFM OUTCOMES of DeTERMINATION: GLOBAL QoI DecREASES DURING SCT BUT RECOVERS RAPIDLY




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| RVd-alone | 306 | 181 | 240 | 243 | 224 | 199 | 156 | 117 | 86 |
| RVd-SCT | 294 | 171 | 224 | 129 | 198 | 183 | 138 | 99 | 89 |

[a] End of induction is end of cycle 3 / prior to pre-mobilization; follow-up visit 1 is 2 years after initial dosing; follow-up visit 2 is 3 years after initial dosing.
[b] General population (N = 7,802). Mean (SD) global QoL value for general population is 71.2 (22.4). Reference values for general population were used as a benchmark to help interpret findings.[1]

1. Scott NW, et al. EORTC QLQ-C30 Reference Values, 2008. Available from: http://www.eortc.org/app/uploads/sites/2/2018/02/reference_values_manual2008.pdf. Accessed 2018 Aug 16.

Roussel et al. ASH 2018

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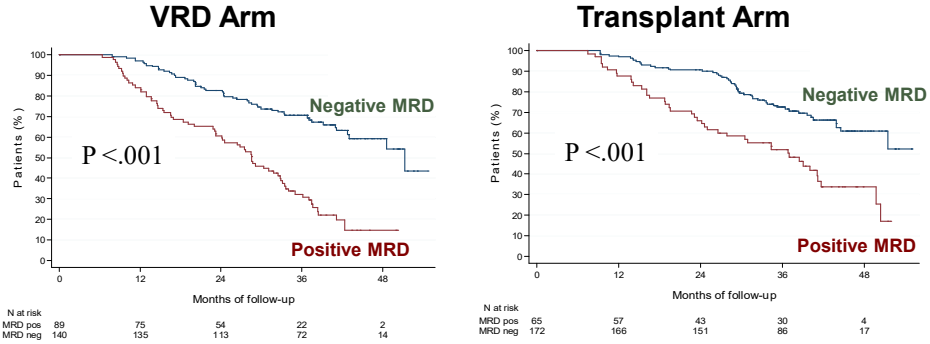
## DETERMINATION Trial: PFS by MRD (FCM) Post Consolidation




Must patients who attain MRD negativity after induction also go to SCT?

Figures adapted from: Attal M, et al. Blood. 2015;126:391.

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# Maintenance Post Stem Cell Transplant

- Magnitude of benefit and quality of evidence:
  - Best: lenalidomide – 50% improvement in PFS, 25% improvement in OS, but monitor for secondary malignancies
  - Single study : ixazomib – 28% improvement in PFS , but ? comparable high risk
- Consider dual agent maintenance for high risk disease

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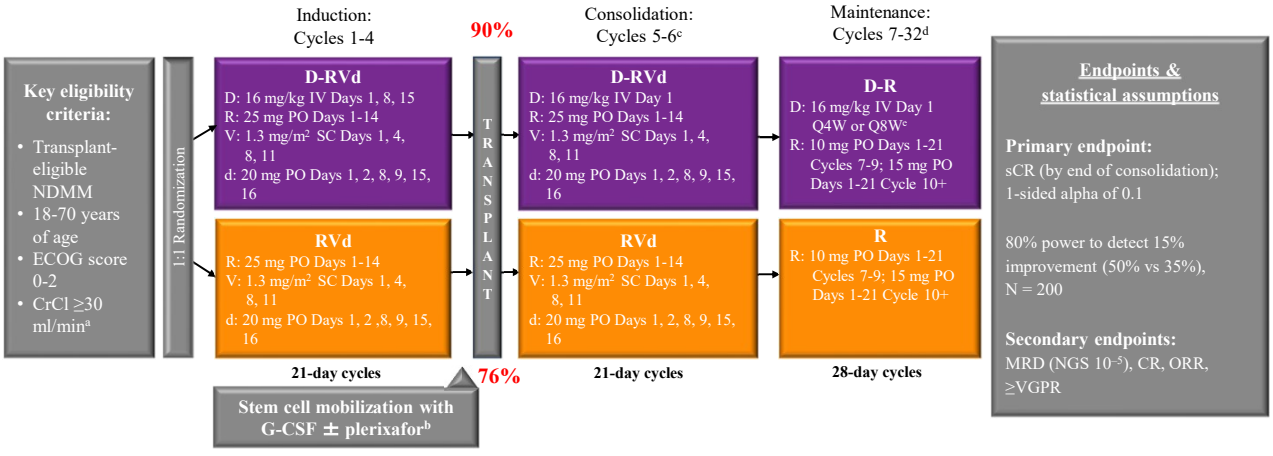
# GRIFFIN Randomized Phase 2 (US): D-RVd vs RVd in Transplant Eligible NDMM




- Median age ~60; ISS3 14%, High risk 15%
- Lower ASCT rate in RVd arm due to early discontinuations

Voorhees et al IMW 2019.

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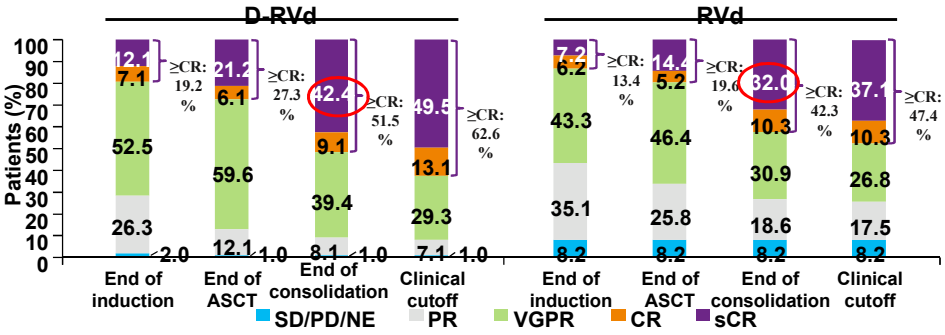
# GRIFFIN : D-RVd vs RVd Efficacy




Post consolidation DRVd vs RVd:

- sCR: 42.4 vs 32% (OR 1.57 95% CI, 0.87-2.82; 1-sided *P* = 0.068 ie primary endpoint met @pre-set 1-sided α 0.1
- ORR: 99% vs 91.8%, 2-sided P = 0.0160
- MRD neg ($10^{-5}$ by NGS): 44.2% vs 14.6%

**Response rates and depths were greater for D-RVd at all time points**

SD, stable disease; PD, progressive disease; NE, not evaluable.

Voorhees et al IMW 2019.

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# GRIFFIN D-RVd vs RVd: Subgroup Analyses by the End of Consolidation

***Stringent Complete Response[a]***

| Subgroup, n/N (%) | RVd | D-RVd | Odds Ratio (95% CI) |
|---|---|---|---|
| Sex | | | |
| Male | 18/55 (32.7) | 21/55 (38.2) | 1.27 (0.58–2.78) |
| Female | 13/42 (31.0) | 21/44 (47.7) | 2.04 (0.84–4.92) |
| Age | | | |
| <65 years | 22/70 (31.4) | 30/72 (41.7) | 1.56 (0.78–3.10) |
| ≥65 years | 9/27 (33.3) | 12/27 (44.4) | 1.60 (0.53–4.82) |
| ISS disease stage | | | |
| I | 11/48 (22.9) | 19/48 (39.6) | 2.20 (0.91–5.35) |
| II | 12/35 (34.3) | 17/37 (45.9) | 1.63 (0.63–4.22) |
| III | 7/13 (53.8) | 6/14 (42.9) | 0.64 (0.14–2.94) |
| Type of MM[c] | | | |
| IgG | 8/51 (15.7) | 15/51 (29.4) | 2.24 (0.85–5.88) |
| Non-IgG | 23/46 (50.0) | 25/45 (55.6) | 1.25 (0.55–2.85) |
| Cytogenetic risk[d] | | | |
| High risk | 4/13 (30.8) | 3/16 (18.8) | 0.52 (0.09–2.90) |
| Standard risk | 26/80 (32.5) | 39/79 (49.4) | 2.03 (1.06–3.85) |
| ECOG performance status | | | |
| 0 | 13/39 (33.3) | 16/38 (42.1) | 1.45 (0.58–3.67) |
| 1 or 2 | 18/58 (31.0) | 25/60 (41.7) | 1.59 (0.74–3.38) |

0.1 1 10 100
RVd Better D-RVd Better

***Minimal Residual Disease Negative[b]***

| Subgroup, n/N (%) | RVd | D-RVd | Odds Ratio (95% CI) |
|---|---|---|---|
| Sex | | | |
| Male | 6/60 (10.0) | 20/58 (34.5) | 4.74 (1.74–12.91) |
| Female | 9/43 (20.9) | 26/46 (56.5) | 4.91 (1.92–12.55) |
| Age | | | |
| <65 years | 10/75 (13.3) | 35/76 (46.1) | 5.55 (2.48–12.40) |
| ≥65 years | 5/28 (17.9) | 11/28 (39.3) | 2.98 (0.87–10.17) |
| ISS disease stage | | | |
| I | 5/50 (10.0) | 21/49 (42.9) | 6.75 (2.28–19.94) |
| II | 7/37 (18.9) | 17/40 (42.5) | 3.17 (1.13–8.91) |
| III | 3/14 (21.4) | 8/14 (57.1) | 4.89 (0.93–25.67) |
| Type of MM[c] | | | |
| IgG | 8/52 (15.4) | 24/55 (43.6) | 4.26 (1.69–10.71) |
| Non-IgG | 7/51 (13.7) | 20/46 (43.5) | 4.84 (1.80–12.99) |
| Cytogenetic risk[d] | | | |
| High risk | 3/14 (21.4) | 5/16 (31.3) | 1.67 (0.32–8.74) |
| Standard risk | 12/83 (14.5) | 39/82 (47.6) | 5.37 (2.54–11.36) |
| ECOG performance status | | | |
| 0 | 3/40 (7.5) | 17/39 (43.6) | 9.53 (2.51–36.25) |
| 1 or 2 | 12/62 (19.4) | 29/62 (46.8) | 3.66 (1.64–8.18) |

1 10 100
RVd Better D-RVd Better

**D-RVd was favored across all subgroups for MRD negativity and across all subgroups for sCR rate, except high-risk cytogenetics and ISS stage III disease (though ns small)**

[a]Response-evaluable population. [b]ITT population. [c]Based on patients who had measurable disease in serum. [d]Based on patients with available cytogenetics results. A high-risk cytogenetic profile was defined by the detection of a del(17p), t(4;14), and/or t(14;16) cytogenetic abnormality on fluorescence in situ hybridization testing.

Voorhees et al IMW 2019.

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# GRIFFIN : D-RVd vs RVd Safety

| | D-RVd (n = 99) | | RVd (n = 102) | |
|---|---|---|---|---|
| | Any grade | Grade 3 or 4 | Any grade | Grade 3 or 4 |
| **Hematologic, n (%)** | | | | |
| Neutropenia | 48 (49) | 32 (32) | 32 (31) | 15 (15) |
| Thrombocytopenia | 43 (43) | 16 (16) | 31 (30) | 8 (8) |
| Leukopenia | 34 (34) | 15 (15) | 27 (27) | 7 (7) |
| Anemia | 32 (32) | 8 (8) | 32 (31) | 6 (6) |
| Lymphopenia | 30 (30) | 23 (23) | 29 (28) | 23 (23) |
| **Non-hematologic, n (%)** | | | | |
| Fatigue | 61 (62) | 5 (5) | 56 (55) | 4 (4) |
| Peripheral neuropathy[b] | 58 (59) | 7 (7) | 74 (73) | 7 (7) |
| Diarrhea | 53 (54) | 6 (6) | 43 (42) | 4 (4) |
| Constipation | 46 (47) | 2 (2) | 41 (40) | 1 (1) |
| Nausea | 46 (47) | 1 (1) | 47 (46) | 1 (1) |
| Upper respiratory tract infection | 46 (47) | 1 (1) | 37 (36) | 1 (1) |
| Pyrexia | 39 (39) | 2 (2) | 25 (25) | 3 (3) |
| Insomnia | 39 (39) | 2 (2) | 30 (29) | 1 (1) |
| Cough | 38 (38) | 0 | 25 (25) | 0 |
| Edema peripheral | 32 (32) | 2 (2) | 35 (34) | 3 (3) |
| Back pain | 32 (32) | 1 (1) | 28 (28) | 4 (4) |
| **Infusion-related reactions** | 41 (41) | 5 (5) | – | – |

- Any-grade infections DRVd vs RVd: 81 (82%) vs 56 (55%); grade 3/4 infections were similar 17 (17%)patients each
- Median CD34$^{+}$ cell yield ($10^{6}$ cells/kg) 8.1vs 9.4; 66 (70%) vs 44(55%) plerixafor use but engraftment times comparable

Voorhees et al IMW 2019.

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# Summary: NDMM with SCT

| Study | IFM 2009 RVd-SCT vs RVd | | FORTE KRd-SCT vs KRd | | Cassiopeia SCT Dara VTd vs VTd | | Griffin SCT DaraVRd vs VRd | |
|---|---|---|---|---|---|---|---|---|
| # (28 day cycles) chemo induction to post consolidation | 3.75 | 6 | 8 | 12 | 6 | | 4.5 | |
| SCH mobilization | Cyclophosphamide | | Cyclophosphamide | | Cyclophosphamide | | GCSF+ Plerixafor | |
| post-consolidation ORR | N/A | N/A | N/A | N/A | 93% | 81% | 99% | 91.8% |
| post-consolidation ≥ VGPR | 78% | 69% | 89% | 87% | 83.4% | 78% | 90.9% | 73.2% |
| post-consolidation sCR | N/A | N/A | 44% | 43% | 28.9% | 20.3% | 42.4% | 32% |
| PFS improvement over control arm | 35% | | Unknown | | 53% | | NR | |

Attal et al. NEJM . 2017; 376:1311-1320
Gay et al ASCO 2019.
Moreau et al. Lancet 2019; 394: 29-39
Voorhees et al IMW 2019.

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# Overview: Newly Diagnosed Myeloma

General Considerations Frontline Therapy

Transplant Eligible

Transplant Ineligible

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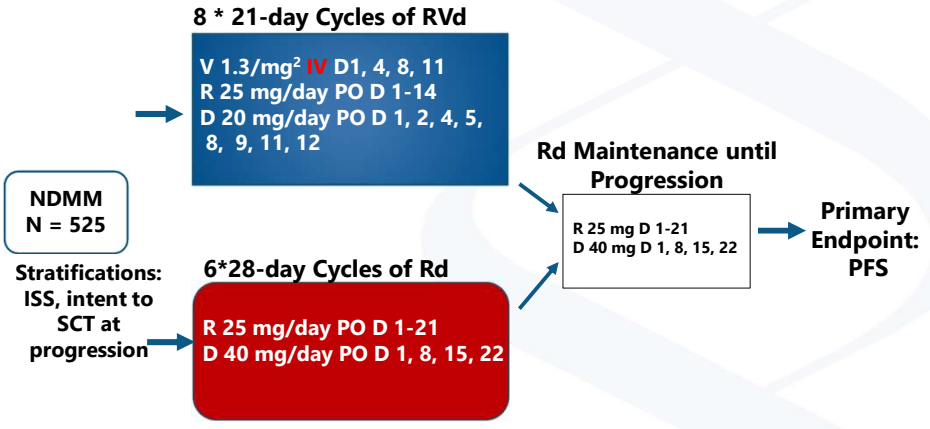
## Doublet vs Triplet Inducton: SWOG S0777 Phase 3
## RVd vs Rd Without Intent for Initial ASCT




- Median overall follow-up was 55 months
- Median age 63; 43% patients age ≥65 years

Durie et al, ASH 2015

Leading cancer research. **Together.**

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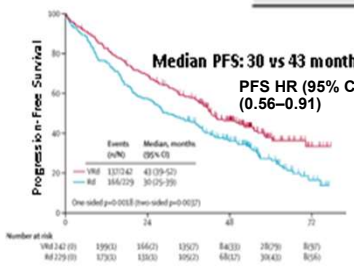
# RVd Superior Efficacy Compared to Rd

| Response | RVD | RD |
|---|---|---|
| ORR | 81.5% | 71.5% |
| PR | 38% | 39.7% |
| VGPR | 27.8% | 23.4% |
| CR | 15.7% | 8.4% |
| ≥VGPR | 43.5% | 31.8% |





Durie B et al. Lancet 2017;389:519-27.

Leading cancer research. **Together.**



SWOG

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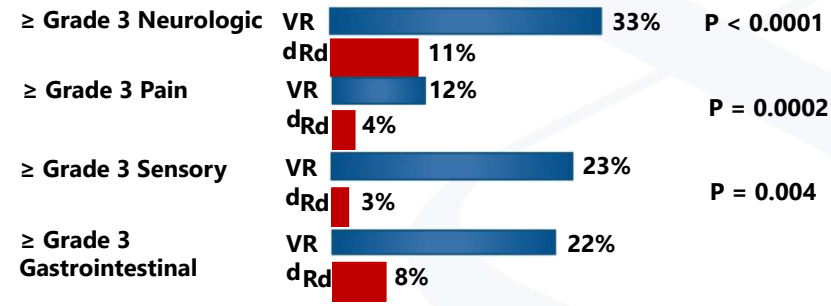
# RVD vs VD Adverse Events




*Includes only those toxicities at least possibly attributable to protocol treatment

**Note: Bortezomib administered I.V. twice/week**

**Eagerly Awaited: RVD vs KRD**

**ECOG E1A11.** Bortezomib or Carfilzomib with Lenalidomide and Dexamethasone in Treating Patients with Newly Diagnosed Multiple Myeloma

Leading cancer research. **Together.**

Durie et al, ASH 2015

NCI National Clinical Trials Network



SWOG

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# Summary: NDMM without SCT

| Study | SWOG 777 VRd vs Rd | | RVd-lite |
|---|---|---|---|
| N | 242 | 229 | 50 |
| Median age | 63 | | 73 |
| ORR | 82% | 72% | 86% |
| CR | 16% | 8.4% | 44% |
| Median PFS, mos | 43 | 30 | 35.1 |
| PFS improvement over control arm | 29% | | N/A |
| OS improvement over control arm | 29% | | N/A |

*V for 6 mos (twice weekly every 21 d * 8 cycles)

*V for 17 mos (weekly every 35d *9 cycles, then every 2wk:28d *6)

Duriet et al. Lancet 2017; 389: 519-527
O'Donnell. Br J Haematol. 2018;182:222.
Mateos MV, et al. NEJM. 2018;378:518-528.
Dimopolous et al. ASH 2018
Facon et al. NEJM 2019; 380:2104-15.

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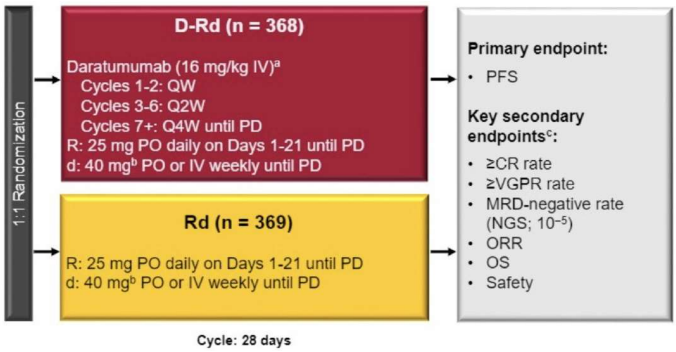
# Phase III MAIA Study: ASCT-Ineligible Newly-Diagnosed Myeloma

- NDMM ASCT ineligible
- Median age 73 (45-90)
- ECOG 0-2
- CrCl ≥30 mL/min
- Transaminases<2.5xULN
- 14% were high risk t(4;14), t(14;16), or del17p




- Treatment discontinuation rate favored daratumumab arm vs. control:
  - Disease progression: 14.6% vs. 23.8%
  - Adverse events: 7.4% vs. 16.2%
  - Death: 6.9% vs 6.3%

Facon NEJM 2019; 380:2104-15.

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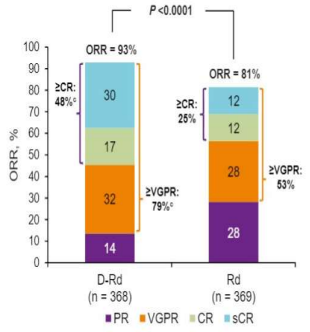
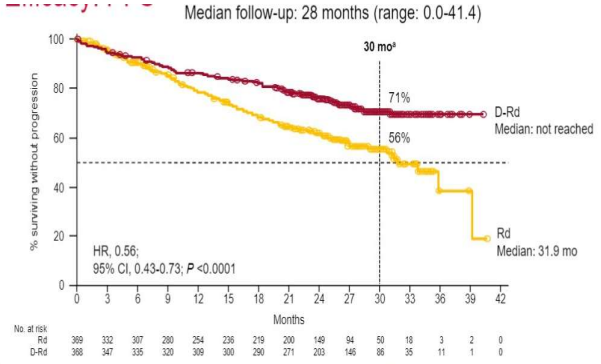
# Phase III MAIA: Improved Efficacy with DaraRd vs Rd




Significantly higher efficacy including MRD neg (NGS; $10^{-5}$ ) 24% vs 7%




44% reduction in the risk of progression or death in patients receiving D-Rd

- Median OS NR In both arms with DRd vs Rd events 62 (17%) vs 76 (21%), HR 0.78 (0.56-1.1)

Facon NEJM 2019; 380:2104-15.

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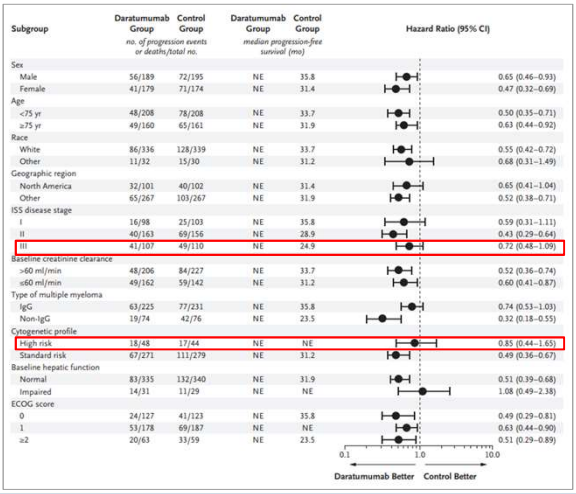
# Efficacy Dara Rd vs Rd: PFS in Prespecified Subgroups




**Daratumumab treatment favored in most subgroups analyzed**

Facon NEJM 2019; 380:2104-15.

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## Safety: Dara Rd vs Rd

Table 3. Most Common Adverse Events and Second Primary Cancers Reported during Treatment in the Safety Population.*

| Event | Daratumumab Group (N=364) | | Control Group (N=365) | |
|---|---|---|---|---|
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| | *number of patients (percent)* | | | |
| Hematologic adverse events | | | | |
| Neutropenia | 207 (56.9) | 182 (50.0) | 154 (42.2) | 129 (35.3) |
| Anemia | 126 (34.6) | 43 (11.8) | 138 (37.8) | 72 (19.7) |
| Leukopenia | 68 (18.7) | 40 (11.0) | 34 (9.3) | 18 (4.9) |
| Lymphopenia | 66 (18.1) | 55 (15.1) | 45 (12.3) | 39 (10.7) |
| Nonhematologic adverse events | | | | |
| Infections | 314 (86.3) | 117 (32.1) | 268 (73.4) | 85 (23.3) |
| Pneumonia | 82 (22.5) | 50 (13.7) | 46 (12.6) | 29 (7.9) |
| Diarrhea | 207 (56.9) | 24 (6.6) | 168 (46.0) | 15 (4.1) |
| Constipation | 149 (40.9) | 6 (1.6) | 130 (35.6) | 1 (0.3) |
| Fatigue | 147 (40.4) | 29 (8.0) | 104 (28.5) | 14 (3.8) |
| Peripheral edema | 140 (38.5) | 7 (1.9) | 107 (29.3) | 2 (0.5) |
| Back pain | 123 (33.8) | 11 (3.0) | 96 (26.3) | 11 (3.0) |
| Asthenia | 117 (32.1) | 16 (4.4) | 90 (24.7) | 13 (3.6) |
| Nausea | 115 (31.6) | 5 (1.4) | 84 (23.0) | 2 (0.5) |
| Second primary cancer† | 32 (8.8) | NA | 26 (7.1) | NA |
| Invasive second primary cancer | 12 (3.3) | NA | 13 (3.6) | NA |
| Any infusion-related reaction | 149 (40.9) | 10 (2.7) | NA | NA |

Lenalidomide dose intensity % (range)
DaraRd vs. Rd
76.2% (7.9-240.9) vs. 91.4% (4.8-234.2)

Facon NEJM 2019; 380:2104-15.

31

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## Summary: NDMM without SCT

| Study | SWOG 777 VRd vs Rd | | RVd-lite | MAIA DaraRd vs Rd | |
|---|---|---|---|---|---|
| N | 242 | 229 | 50 | 368 | 368 |
| Median age | 63 | | 73 | 73 | |
| ORR | 82% | 72% | 86% | 93% | 81% |
| CR | 16% | 8.4% | 44% | 49% | 25% |
| Median PFS, mos | 43 | 30 | 35.1 | NR | 31.9 |
| PFS improvement over control arm | 29% | | N/A | 44% | |
| OS improvement over control arm | 29% | | N/A | N/A | |

Duriet et al. Lancet 2017; 389: 519-527
O'Donnell. Br J Haematol. 2018;182:222.

Mateos MV, et al. NEJM. 2018;378:518-528.
Dimopolous et al. ASH 2018
Facon et al. NEJM 2019; 380:2104-15.

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## Overview: Relapsed Myeloma

- First relapse: randomized studies
  - Lenalidomide-dexamethasone control arms
  - Bortezomib-dexamethasone control arms
  - High-risk disease
- Second and third relapse
- Fourth relapse and beyond

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## Randomized Studies in Early Relapse 1–3 lines of Prior Therapy, General Considerations

- Choice of PI- or IMiD-based partner depends on prior treatment
- Historically, +/- steroids
  - thalidomide/bortezomib/lenalidomide: ORR 30-60%, PFS 6-11 mos
  - carfilzomib/pomalidomide/daratumumab: ORR 25-30%, PFS 3.5-4 mos
- Triplets consistently perform better than doublets
- Cross trial comparisons should not be done as
  - Patient populations are different
  - Disease burden and high-risk genetics are different
  - Prior therapy exposures are different
  - As a result, outcomes of identical control arms vary significantly between trials

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# Randomized Studies With Lenalidomide-Dexamethasone Control Arms

| | Carfilzomib* | | Elotuzumab | | Daratumumab | | Ixazomib | |
|---|---|---|---|---|---|---|---|---|
| **N** | **KRd vs Rd** | | **ERd vs Rd** | | **DRd vs Rd** | | **IRd vs Rd** | |
| **Efficacy** | **Tx** | **Control** | **Tx** | **Control** | **Tx** | **Control** | **Tx** | **Control** |
| ORR | 87.1% | 66.7% | 79% | 66% | 93% | 76% | 78.3% | 71.5% |
| CR | 32% | 9.3% | 5% | 9% | 55% | 23% | 12% | 7% |
| Median PFS, mos | 26 | 16.6 | 19 | 14.9 | NR | 17.5 | 21 | 14.7 |
| **PFS improvement over control arm** | 31% | | 29% | | 56% | | 26% | |

Dimopoulos MA et al. *N Engl J Med*. 2016;375:1319; Dimopoulos MA et al. *Br J Haematol*. 2017;178:896; Stewart AK et al. *N Engl J Med*. 2015;372:142; Stewart AK et al. *Blood*. 2017;130: Abstract 743.; Dimopoulos M et al. *J Hematol Oncol*. 2018;11:49; Moreau P et al. *N Engl J Med*. 2016;374:1621.

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# Randomized Studies With Bortezomib-Dexamethasone Control Arms

| | Daratumumab* | | Carfilzomib | | Panobinostat | | Pomalidomide | | Venetoclax | |
|---|---|---|---|---|---|---|---|---|---|---|
| **N** | **DVd vs Vd** | | **Kd vs Vd** | | **FVd vs Vd** | | **PVd vs Vd** | | **VenVd vs Vd** | |
| **Efficacy** | **Tx** | **Control** | **Tx** | **Control** | **Tx** | **Control** | **Tx** | **Control** | **Tx** | **Control** |
| ORR | 85% | 63% | 76% | 63% | 55% | 61% | 82% | 50% | 82% | 68% |
| CR | 30% | 10% | 13% | 6% | 11% | 6% | 16% | 4% | 13% | 1% |
| Median PFS, mos | 16.7 | 7.1 | 18.7 | 9.4 | 12 | 8.08 | 11 | 7 | 22.4 | 11.5 |
| **PFS improvement over control arm** | 68% | | 47% | | 37% | | 39% | | 37% | |

Risk of death doubled with venetoclax

Richardson PG et al. *J Clin Oncol*. 2018;36: Abstract 8001 Palumbo A et al. *N Engl J Med*. 2016;375:754; Spencer A et al. *Haematologica*. 2018; Sep 20 [epub ahead of print]; Dimopoulos MA et al. *Lancet Oncol*. 2016;17:27; San Miguel JF et al. *Lancet Oncol*. 2014;15:1195; Kumar, S EHA 2019.

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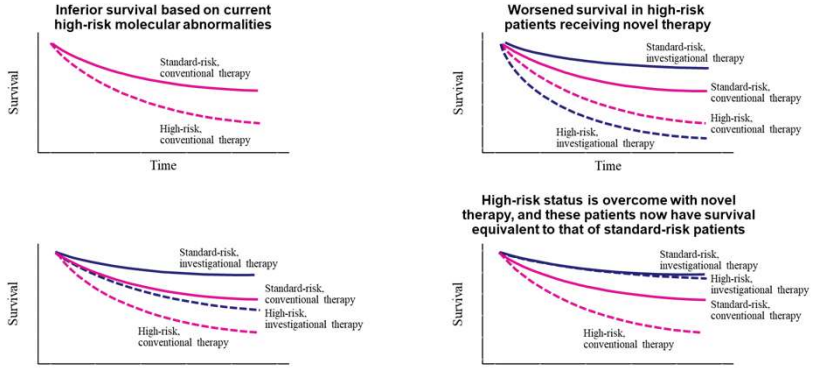
# Summary of High Risk Outcomes in Randomized Studies

*Possible Outcomes of a Hypothetical Phase III Study Comparing a Novel Agent X to Conventional Therapy*




- Variability in definition of high risk, method of testing for high risk, and availability of high risk data
- All novel agents improve PFS for high-risk patients, but still inferior to standard risk patients treated with novel therapies (ie high risk not overcome)
  - Some data that PIs especially improve outcomes in t(4;14)

Lancman G et al. *Clin Adv Hematol Oncol.* 2017;15:870.

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# Overview: Relapsed Myeloma

- First relapse
- Second and third relapse
  - Lenalidomide-refractory disease
  - Carfilzomib-based backbones
  - Pomalidomide-based backbones
- Fourth relapse and beyond

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# Outcomes of Lenalidomide Refractory Patients in Randomized Studies With Bortezomib-Dexamethasone Control Arms

- Many recent phase 3 RRMM studies were len-based and excluded len-refractory patients
- The increasing adoption of len maintenance highlights a need for large studies in len-refractory RRMM

| | Daratumumab* | | Carfilzomib | | Pomalidomide | |
|---|---|---|---|---|---|---|
| N | DVd vs Vd | | Kd vs Vd | | PVd vs Vd | |
| N | 251 | 247 | 464 | 465 | 281 | 278 |
| Median PFS, months | 16.7 | 7.1 | 18.7 | 9.4 | 11 | 7 |
| N = Len refractory | 45 | 60 | 113 | 122 | 200 | 191 |
| PFS | 9.3 | 4.4 | 8.6 | 6.6 | 9.5 | 5.6 |

PFS of len refractory patients inferior to those of total study population.

Lentzsch S et al. Presented at Japanese Society of Hematology 79th Annual Meeting; October 2017. Abstract OS3-12D-2; Moreau P et al. *Leukemia*. 2017;31:115; Dimopoulos MA et al. *Lancet Oncol*. 2016;17:27; Richardson PG et al. *J Clin Oncol*. 2018;36: Abstract 8001.

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# Carfilzomib Combines Well With IMiDs and Antibodies

| Drugs/Design | N | RRMM Med Lines | ORR | Median PFS mos (HR) | Median OS mos |
|---|---|---|---|---|---|
| K 20/27 + dex 8 | **266** | 5 | 24% | 3.7 | 15.6 |
| K 70 wk D40 vs K 20/27 biw D40 | **240 vs 238** | 2–3 | 62 vs 41% | 11.2 vs 7.6 (0.69) | NR |
| K 20/36 biw Cy 500mg qwk Dex vs VCD | **201 vs 99** | 1 | 84% vs 68% | 18 | NR |
| K 20/36 biw + pomalidomide + dex | 60 | 1 | 87% | 18 | NR |
| Daratumumab K 20/70 qwk dex | 85 | 2 | 84% | NR | NR |
| Daratumumab K 20/56 biw dex | 466 | N/A | N/A | NR vs 15.8 (0.63) | NR |

- Attention to K dose and schedule (based on partner drugs, avoid 70 mg/m2 qwk with IMIDs given increase cardiac signal)
- Attention to infusion time (30 min for all doses $\geq$ 36 mg/mg2)
- Efficacy of carfilzomib improves as moves into earlier lines of therapy
- Encouraging activity in lenalidomide refractory disease
- In randomized phase 3 studies, low rates of cardiac events as well as low rates of K reduction/discontinuations/deaths, supported by overall survival benefits

Siegel DS et al. *Blood*. 2012;120:2817; Moreau P et al. *Lancet Oncol*. 2018;19:953; Yong K et al. *Blood*. 2017;130: Abstract 835; EHA 2018; Shah JJ et al. *Blood*. 2015; 126:2284; Sonneveld P et al. *Blood*. 2018;132: Abstract 801. (Presentation Monday, December 3 at 3:15 PM.); Chari A et al. *J Clin Oncol*. 2018;36: Abstract 8002; Chari A et al. *J Clin Oncol*. 2018;36: Abstract 8014; Amgen Press Release 2019; Chari A et al. *Blood Adv*. 2018;2:1633.

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# Pomalidomide Approved for Lenalidomide-Resistant Myeloma

| Drugs/Design | N | RRMM Med Lines | ORR | Median PFS mos (HR) | Median OS mos |
|---|---|---|---|---|---|
| Pom 4 Dex vs **High-dose dex** | **302 vs 153** | 5 | 31 vs 10% | 4.0 vs 1.9 (0.48) | 12.7 vs 8.1 |
| Pom 4 Dex | 51 | 2 | 29% | 13.8 | N/A |
| Pom4 /cy 400 qwk /dex vs Pom dex | **34 vs 36** | 4 | 65 vs 39% | 9.5 vs 4.4 (0.54) | NR vs 16.8 |
| Pom 4 + cy 50 bid + dex | 28 | 3 | 67% | 14.5 | NR |
| Pom + bortezomib + dex vs Pom dex | **200 vs 191** | 2 | 82% vs 50% | 11 vs 7 (0.61) | NR |
| Pom 4 + daratumumab + dex | 103 | 4 | 66% | 9.9 | 17.5 |
| Pom + elotuzumab +dex vs Pom dex | **60 vs 57** | 3 | 53 vs 26% | 10.3 vs 4.7 (0.54) | NR |

- Efficacy of pomalidomide improves as moves into earlier lines of therapy
  - Highlights need for randomized studies
- Monitor neutropenia especially with cyclophosphamide, CD38 mAbs – though typically without apparent increase in rates of infection

San Miguel J et al. *Lancet Oncol*. 2013;14:1055; Siegel D et al. *J Clin Oncol*. 2017;35: Abstract 8027; Baz RC et al. *Blood*. 2016;127:2561; Chari A et al. *Blood*. 2016;128: Abstract 4520; Richardson PG et al. *J Clin Oncol*. 2018;36: Abstract 8001; Chari A et al. *Blood*. 2017;130:974; Richardson et al ASCO 2018 ; Dimopoulos MA et al. *N Engl J Med*. 2018;379:1811.

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# Overview: Relapsed Myeloma

- First relapse
- Second and third relapse
- Fourth relapse and beyond
  - VDCEP/VDTPACE
  - Salvage stem cell transplant
  - Selinexor

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# VDCEP/VDTPACE 96-Hour Infusional Chemotherapy

**V (1·0 mg/m² SQ) day 1,4,8,11**
**T (200 mg/d p.o.) day 1–4**
**D (40 mg/d p.o.) day 1–4**
**P (7·5 mg/m²/d) day 4–7**
**A (7·5 mg/m²/d) day 4–7**
**C (300 mg/m²/d) day 4–7**
**E (30 mg/m²/d) day 4–7**

- VDCEP = Velcade + dex + Cytoxan + Etoposide + platinum (can be given via peripheral IV if inpatient)
- VDTPACE = VDCEP + thalidomide + doxorubicin (requires central line)
- N =141, median 4 lines of prior therapy, ORR 54.4%, median PFS 3.1 and OS 8.1 mos
- Use lower doses for cytopenic patients, concurrent XRT, poor KPS, renal insufficiency
- TLS prophylaxis and monitoring, GCSF support, gram negative antibiotic prophylaxis, transfusion support

Lakshman A et al. *Am J Hematol*. 2018;93:179.

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# Salvage Stem-Cell Transplant

- 72% of thrombocytopenic (N=36) patients recovered to >75,000/µL
- 64% of neutropenic patients (N=14) recovered to ANC >1,500

| Ref | N | Dates of SCT2 | Lines of Prior Therapy | ORR | PFS (mo) | OS (mo) |
|---|---|---|---|---|---|---|
| 2 | 83 | Before 2006 | NR | NR | 15.6 | 34.8 |
| 4 | 106 | 1990–2002 | NR | 63% | NR | 37 |
| 8 | 81 | 1992–2009 | 1 | 97.4% | 16.4 | 53 |
| 9 | 200 | 1992–2010 | 2 | 80.4% | 15.2 | 42.3 |
| 10 | 83 | 1994–2011 | NR | NR | 15.5 | 31.5 |
| 11 | 187 | 1995–2008 | NR | NR | 11.2 | 30 |
| 12 | 98 | 1994–2009 | 3 | 85% | 10.3 | 33 |
| 14 | 75 | 1995–2012 | 1 | 82% | 10.1 | 22.7 |
| 15 | 111 | 2000–2013 | NR | 92% | 18 | 48 |
| Current study | 74 | 1998–2016 | 4 | 68% | 6.1 | 19.3 |

ANC = absolute neutrophil count; µL = microliter ; BCNU = carmustine.
Tremblay D, et al. *Bone Marrow Transplant*. 2017;52:1468.

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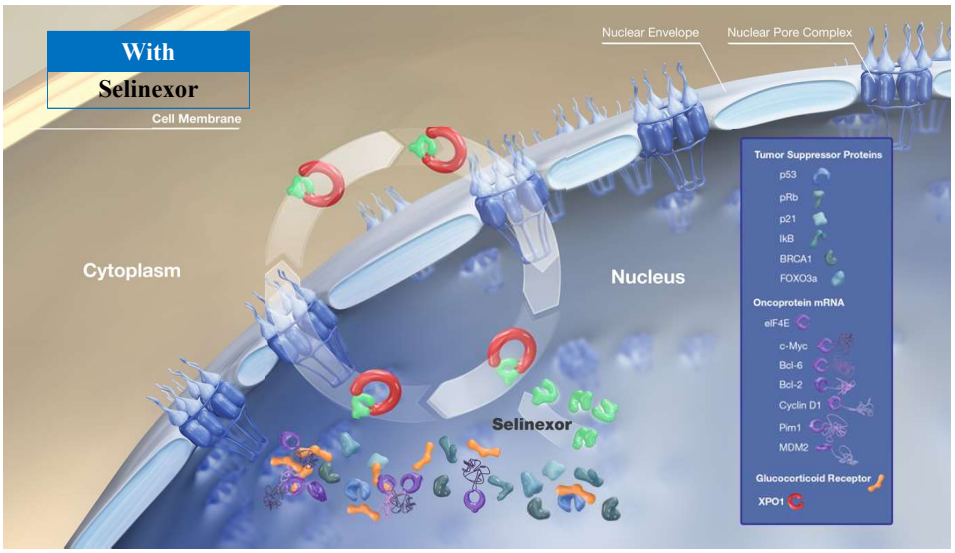
# Selinexor Inhibits XPO1 and Induces Cancer Cell Death




XPO1 in MM

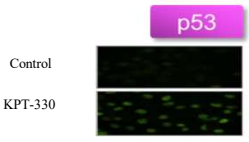
- Transports >200 proteins from the nucleus to cytoplasm
- Expression increased in MM vs normal PC/MGUS/SMM
- Correlates with shorter survival and increased bone disease

Selinexor

- Inhibits XPO1 through reversible covalent modification

Selinexor Mechanisms of Action

1. Nuclear retention/activation of tumor suppressor **proteins** and **glucocorticoid receptor**
2. Reduction of oncoproteins through nuclear retention of their **mRNAs**

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# Selinexor: First in Class Oral XPO inhibitor

- Penta exposed, triple class refractory
- Cr Cl > 20, ANC > 1,000, plts > 75k (50k if marrow > 50% PC)
- {Selinexor 80 mg + Dex 20 mg} both po D1, 3 q week

| | N=122* |
|---|---|
| **Age**, years median (range) | 65 (40–86) |
| **Time from diagnosis**, years median (range) | 6.6 (1.1–23.4) |
| **High risk**: (del17p, t(4;14), t(14;16), 1q21) | 65 (53%) |
| **Median prior regimens (range)** | **7 (3–18)** |
| **Refractory to PI/IMiD/Dara/GC**<br>• Refractory to K/P/D<br>• Stem cell transplant<br>– ≥2 Transplants<br>• Intensive combination chemo (eg, DT-PACE)<br>• CAR T-cell therapy | 122 (100%)<br>**117 (96%)**<br>102 (84%)<br>29 (28%)<br>32 (26%)<br>2 (2%) |

- ORR 26.2%, including 2 sCRs
  - PRs in both CAR T patients
  - ≥MR 39.3%
  - ≥SD 79%
- Median time to response 1 month
- Median PFS 3.7 months
- Median OS 8.0 months

| | Grade 3/4 | All Grades |
|---|---|---|
| Nausea | 10% | 67% |
| Anorexia | 2% | 50% |
| Vomiting | 3.3% | 35% |
| Fatigue/asthenia | 21% | 68% |
| Hyponatremia | 16% | 31% |
| Thrombocytopenia | 53% | 67% |
| Neutropenia | 18% | 36% |

Jagannath S et al. Presented at Society of Oncologic Hematology 6th Annual Meeting; September 2018.
Chari A et al. *Blood*. 2018;132: Abstract 598. Presentation Monday, December 3 at 7:45 AM.

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# Selinexor and Backbone Treatments of Myeloma Patients (STOMP): Phase 1 Preliminary Results

- The RP2D for selinexor in combination studies is likely weekly 100 mg (with PIs) and 60 mg (with IMIDs)
- Efficacy encouraging in combination setting, including in backbone refractory patients

| Stomp Patient Characteristics | SRd | SPd | SDara d | SVd | SKd |
|---|---|---|---|---|---|
| | 60 mg | 60 mg | 100 mg | 100 mg | 100 mg |
| Patients enrolled | 19 | 34 | 21 | 42 | 21 |
| Median time dx to rx, years | 4 | 6 | 5 | 5 | 4.5 |
| Median prior regimens | 1 | 4 | 3 | 3 | 4 |
| **Overall response rate** | **NR** | **50%*** | **74%** | **84%** | **63%** |
| **Progression-free survival** | **NR** | **10.3 mos** | **NR** | **9.2 mos** | **3.7 mos** |

*N=30 evaluable

Lonial S et al. Presented at National Comprehensive Cancer Network 23rd Annual Conference; March 2018, Poster 100; White DJ et al. *Blood*. 2017;130: Abstract 1861.; Bahils NJ et al. *Blood*. 2018; Oct 23 [Epub ahead of print]; Chen C et al. *Blood*. 2018;132: Abstract 1993. Gasparetto CJ et al. *Blood*. 2018;132: Abstract 599. Presentation Monday, December 3 at 8:00 AM; Jakubowiak A et al. *Blood*. 2016;128: Abstract 973.

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# Promising Anti-B-Cell Membrane (BCMA): Novel Treatment Approaches

- Belantamab Mafodotin: Antibody Drug Conjugate
- T-cell engagers/Bispecifics
- Chimeric Antigen T-cell Receptors (CAR T)

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# Deep and Durable Responses in Patients with Relapsed/Refractory Multiple Myeloma Treated with Monotherapy GSK2857916, an Antibody Drug Conjugate Against B-cell Maturation Antigen: Preliminary Results from Part 2 of Study BMA117159 (DREAMM-1)

Suzanne Trudel1, NikolettaLendvai2, Rakesh Popat3, Peter M. Voorhees4, Brandi Reeves5, Edward N. Libby6, Paul G.Richardson7, Larry D. Anderson Jr8, Heather J. Sutherland9, KweeYong3, Axel Hoos10, Michele M. Gorczyca10, Soumi Lahiri10, ZangdongHe10, Daren Austin10, Joanna Opalinska10, Adam D. Cohen



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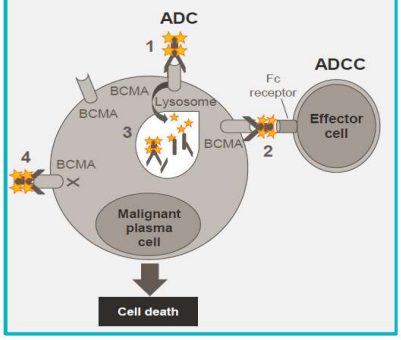
## Background

- BCMA: expressed on differentiated B cells; requisite for long-lived plasma cells' survival
- **BCMA is broadly expressed on malignant plasma cells**
- **GSK2857916:** humanized, afucosylated IgG1 **anti-BCMA antibody;** neutralization of soluble BCMA
  - Preclinical studies demonstrate its selective and potent activity[1]

| GSK2857916 | |
|---|---|
| Cytotoxic agent | – MMAF (non-cell permeable, highly potent auristatin |
| Afucosylation | – Enhanced ADCC |
| Linker | – Stable in circulation |

**Four mechanisms of action:**
1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death
4. BCMA receptor signaling inhibition




[1]Tai YT, et al. Blood 2014;123(20):3128-38.

ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B-cell maturation antigen; IgG, immunoglobulin G; MMAF, monomethyl auristatin-F



**Trudel et al, ASH 2017**

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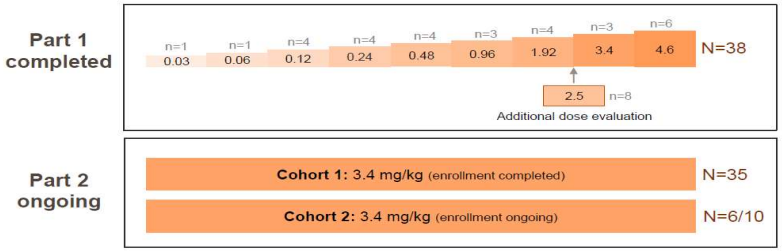
## DREAMM-1: FTIH Study Design

- Overall, 38 patients were evaluated in **Part 1 – no DLTs were observed**
- **Part 2: Expansion**
  - **Cohort 1:** relapsed/refractory MM (N=35; enrollment complete)
  - **Cohort 2:** BCMA-positive relapsed DLBCL or follicular lymphoma (N≈10; ongoing)
- **Expansion dose:** 3.4 mg/kg
- **Schedule:** 1h IV, once every 3 weeks
- **Treatment duration:** up to 16 cycles (up to 1 year)




BCMA, B-cell maturation antigen; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; FTIH, first-time-in-human; IV, intravenous; MM, multiple myeloma. Previously presented at ASH 2016, abstract number 1148.

**Trudel et al, ASH 2017**

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## DREAMM-1 Part 2: Demographics and Baseline Characteristics

| Characteristic | Part 2 (N=35) |
|---|---|
| Age (years), median (min, max) | 60 (46–75) |
| Females/males, % | 51/49 |
| ≥5 prior lines, n (%) | 18 (51) |
| ASCT | 31 (89) |
| **IMiDs, n (%)** | **35 (100)** |
| Lenalidomide | 33 (94) |
| Pomalidomide | 22 (63) |
| Thalidomide | |
| **Refractory to IMiD** | **33 (94)** |
| **PI, n (%)** | **35 (100)** |
| Bortezomib | 34 (97) |
| Carfilzomib | 29 (83) |
| **Refractory to PI, n (%)** | **34 (97)** |
| **Daratumumab, n (%)** | **14 (40)** |
| **Refractory to daratumumab, n (%)** | **14 (40)** |
| **Refractory to IMiD/PI, n (%)** | **31 (89)** |
| **Refractory to IMiD/PI and prior daratumumab, n (%)** | **13 (37)** |
| Cytogenetics risk, n (%)* | |
| High risk | 10 (29) |
| Other (non-high risk, not done, or missing) | 25 (71) |

*Patients with any of the following genetic abnormalities were considered high risk: t(4:14), del17, t(14:16), t(14:20), nonhiperdiploidy, or gain 1q

ASCT, autologous stem cell transplant; IMiD, immunomodulator; PI, proteasome inhibitor

Trudel, et al. *Blood Cancer Journal*; 9 37 (2019)

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## DREAMM-1 Part 2: Adverse Events Regardless of Relationship

| n (%) | N=35 | |
|---|---|---|
| | Any grade | ≥Grade 3* |
| Any event | 35 (100) | 29 (83) |
| Thrombocytopenia | 22 (63) | 12 (34) |
| Vision blurred | 18 (51) | 1 (3) |
| Dry eye | 13 (37) | 1 (3) |
| Anemia | 10 (29) | 6 (17) |
| AST increased | 13 (37) | 2 (6) |
| Cough | 14 (40) | 0 |
| IRR | 3 (9) | 1 (3) |
| Nausea | 11 (31) | 0 |
| Photophobia | 10 (29) | 0 |
| Pyrexia | 10 (29) | 0 |
| Chills | 9 (26) | 0 |
| Fatigue | 8 (23) | 0 |

- Most frequent ≥Grade 3 AEs were thrombocytopenia (34%) and anemia (17%)
- No Grade 5 events were reported
- SAEs occurring in ≥2 patients included IRR (n=2) and lung infection (n=2)
- AEs leading to study treatment discontinuation:
  - Two patients discontinued: one due to Grade 3 thrombocytopenia, one due to Grade 3 thrombocytopenia and Grade 2 CPK increase

AE, adverse event; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; IRR, infusion-related reaction; SAE, serious AE
AEs for ≥20% of patients
*Grouped term includes thrombocytopenia and platelet count decreased

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Trudel, et al. *Blood Cancer Journal;* 9 37 (2019)

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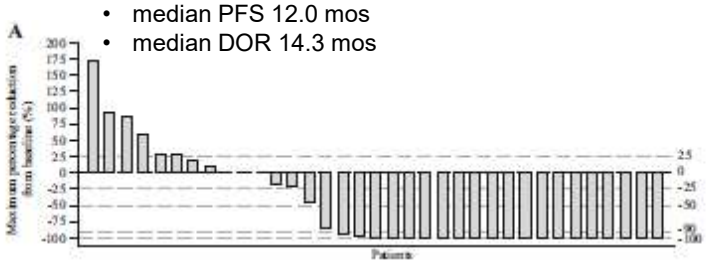
## DREAMM-1 Efficacy Results

21 (60%) ORR = 2 (6%) sCR + 3 (9%) CR + 14 (40%) VGPR + 2 (6%) PR

- median time to first response was 1.2 mos
- median PFS 12.0 mos
- median DOR 14.3 mos




- In dara + PI + IMID refractory (n=13): ORR 38.5%, PFS 6.2 mos

Trudel, et al. *Blood Cancer Journal;* 9, Article number: 37 (2019)

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## Promising Anti-B-Cell Membrane (BCMA): Novel Treatment Approaches

- Belantamab Mafodotin: Antibody Drug Conjugate
- T-cell engagers/Bispecifics
- Chimeric Antigen T-cell Receptors (CAR T)

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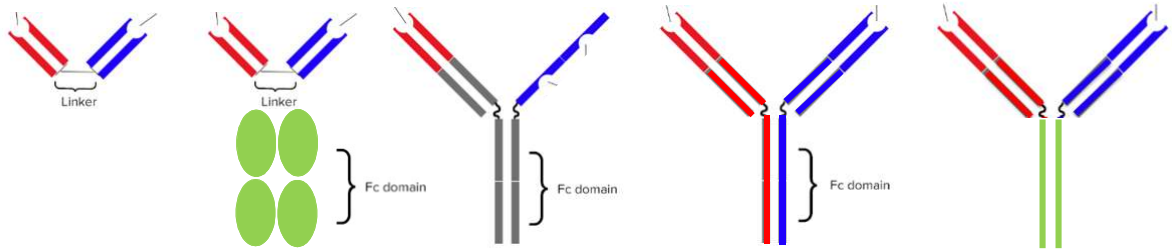
## Targeting BCMA: T-Cell Engagers Heavy Chains Confer Longer Half-life

CD3 binding site
BCMA binding site




**AMG420**
Light chains: 2

**AMG701**
Light chains: 2
Heavy: Half Life Extender

**TNB-383 B**
Light chains: 1
Heavy chains: 2

**JNJ-7957 (DuoBody)**
Light chains: 2
Heavy chains: 2

**Xmab**
Light chains: 2
Heavy chains: 2 (stable heterodimer)

activated T cells form a cytolytic synapse -> release cytokines/performing/granzymes -> apopotosis

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# T-Cell Engaging Drugs Under Investigation in Multiple Myeloma

| Name | Target | Structure | Company | Trial ID |
|---|---|---|---|---|
| AMG-420 | BCMA | BITE | Amgen | NCT02514239 |
| AMG-701 | BCMA | BITE-HLE | Amgen | NCT03287908 |
| CC-93269 | BCMA | BITE | Celgene | NCT03486067 |
| PF-06863135 | BCMA | BITE | Pfizer | NCT03269136 |
| REGN-5458 | BCMA | BITE | Regeneron | NCT03761108 |
| TNB-383B | BCMA | UniAbs | Teneobio | NCT03933735 |
| JNJ-64007957 | BCMA | DuoBody | Johnson & Johnson/Genmab | NCT03145181 |
| JNJ-64007564 | GPRC5d | DuoBody | Johnson & Johnson/Genmab | NCT03399799 |
| GBR-1342 | CD38 | XmAb | Glenmark | NCT03309111 |
| AMG-424 | CD38 | BITE | Amgen | NCT03445663 |
| BFCR4350A | FCRH5 | BITE | Genetech | NCT03275103 |

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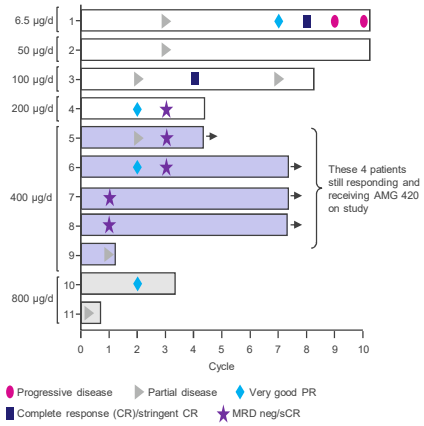
# Treatment With AMG 420, an Anti-BCMA BiTE




Topp MS et al. *Blood*. 2018;132: Abstract 1010.

**Patients**

- Median 4 prior lines of therapy
- Median refractory to 1 prior therapy
  - 31% refractory to PI + IMID
  - 21% refractory to Darzalex

**Efficacy**

- 7/10 (70%) patients dosed at 400 µg/d had responses
  - 4 had MRD negative CR at 10-4

**Safety**

- CRS: mostly low severity (no CNS)
- Infections: 2 deaths (1 fungus/flu; 1 liver failure/viral infection)
  - Catheter infections seen also
- Peripheral neuropathy

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# Promising Anti-B-Cell Membrane (BCMA): Novel Treatment Approaches

- Belantamab Mafodotin: Antibody Drug Conjugate
- T-cell engagers/Bispecifics
- Chimeric Antigen T-cell Receptors (CAR T)

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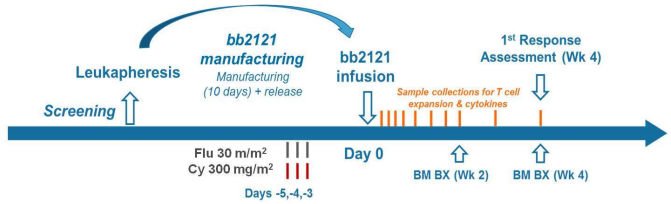
## bb2121 Anti-BCMA CAR T-Cell Therapy in Patients With Relapsed/Refractory Multiple Myeloma: Updated Results From a Multicenter Phase I Study

### CRB-401 PHASE 1 STUDY DESIGN




**Dose Escalation (N=21)**

≥50% BCMA expression

50 × 10⁶ → 150 × 10⁶ → 450 × 10⁶ → 800 × 10⁶

**Dose Expansion (N=22)**

<50% BCMA expression (n=10)

≥50% BCMA expression (n=12)

Dose range: 150–450 × 10⁶ CAR+ cells

*Manufacturing success rate of 100%*

Presented By Noopur Raje at 2018 ASCO Annual Meeting

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**bb2121 Anti-BCMA CAR T-Cell Therapy**

## BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

| Parameter | Escalation (N=21) | Expansion (N=12) |
|---|---|---|
| Median (min, max) follow-up, d | 345 (46, 638) | 87 (29, 184) |
| Median (min, max) age, y | 57 (37, 74) | 64 (46, 75) |
| Men, n (%) | 13 (62) | 8 (67) |
| Median (min, max) time since diagnosis, y | 4 (1, 16) | 6 (1, 36) |
| ECOG PS,[a] n (%) | | |
| 0 | 8 (38) | 2 (17) |
| 1 | 11 (52) | 10 (83) |
| High-risk cytogenetics, n (%) | | |
| del(17p), t(4;14), t(14;16) | 8 (38) | 7 (58) |
| Median (min, max) prior regimens | 7 (3, 14) | 8 (3, 23) |
| Prior autologous SCT, n (%) | 21 (100) | 11 (92) |

| | Exposed | Refractory | Exposed | Refractory |
|---|---|---|---|---|
| Bort/Len | 21 (100) | 14 (67) | 22 (100) | 14 (64) |
| Bort/Len/Car/Pom/Dara | 15 (71) | 6 (29) | 21 (96) | 7 (32) |

Raje, et al. *N Engl J Med* 2019; 380:1726-1737.

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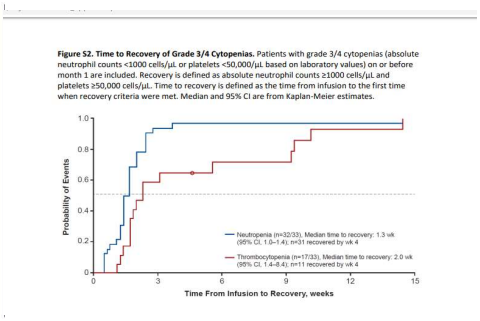
# Adverse Events of Special Interest

**CAR T Treatment-Emergent Adverse Events**
**All Infused Patients (N=33)**

| TEAE, n (%) | Overall | Grade ≥3 |
|---|---|---|
| Cytokine release syndrome[a] | 25 (76) | 2 (6) |
| Neurotoxicity[b] | 14 (42) | 1 (3) |
| Neutropenia | 28 (85) | 28 (85) |
| Thrombocytopenia | 19 (58) | 15 (45) |
| Anemia | 19 (58) | 15 (45) |
| Infection[c] | | |
| Overall | 26 (61) | 9 (21) |
| First Month | 10 (23) | 2 (5) |

- No grade 4 CRS events
- No fatal CRS or neurotoxicity events




Raje, et al. *N Engl J Med* 2019; 380:1726-1737.

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# Tumor Response According to Dose of CAR+ T cells

**Table 3. Tumor Response According to Dose of Chimeric Antigen Receptor–Positive (CAR+) T Cells.***

| Variable | $50\times10^6$ CAR+ T Cells (N=3) | $150\times10^6$ CAR+ Tells (N=8) | $450\times10^6$ CAR+ T Cells | | $800\times10^6$ CAR+ T Cells (N=3) | $150\times10^6$–$800\times10^6$ CAR+ T Cells (N=30) | $50\times10^6$–$800\times10^6$ CAR+ T Cells (N=33) |
|---|---|---|---|---|---|---|---|
| | | | <50% BCMA (N=8)† | ≥50% BCMA (N=11)† | | | |
| Objective response‡ | | | | | | | |
| No. of patients with a response | 1 | 6 | 8 | 10 | 3 | 27 | 28 |
| Rate — % (95% CI) | 33 (1–91) | 75 (35–97) | 100 (63–100) | 91 (59–100) | 100 (29–100) | 90 (74–98) | 85 (68–95) |
| Best overall response — no. (%) | | | | | | | |
| Stringent complete response | 0 | 5 (63) | 3 (38) | 4 (36) | 0 | 12 (40) | 12 (36) |
| Complete response | 0 | 0 | 0 | 1 (9) | 2 (67) | 3 (10) | 3 (9) |
| Very good partial response | 0 | 0 | 4 (50) | 4 (36) | 1 (33) | 9 (30) | 9 (27) |
| Partial response | 1 (33) | 1 (12) | 1 (12) | 1 (9) | 0 | 3 (10) | 4 (12) |
| Stable disease | 2 (67) | 1 (12) | 0 | 1 (9) | 0 | 2 (7) | 4 (12) |
| Progressive disease | 0 | 1 (12) | 0 | 0 | 0 | 1 (3) | 1 (3) |
| Median duration of response (95% CI) — mo | 1.9 (NE–NE) | NE | 7.7 (5.3–14.8) | | 12.9 (10.9–12.9) | 10.9 (7.2–NE) | 10.9 (7.2–NE) |
| Negativity for MRD§ | | | | | | | |
| No. of patients with a response who could be evaluated for MRD | 0 | 4 | 11 | | 1 | 16 | 16 |
| Rate — % | 0 | 100 | 100 | | 100 | 100 | 100 |

Raje, et al. *N Engl J Med* 2019; 380:1726-1737.

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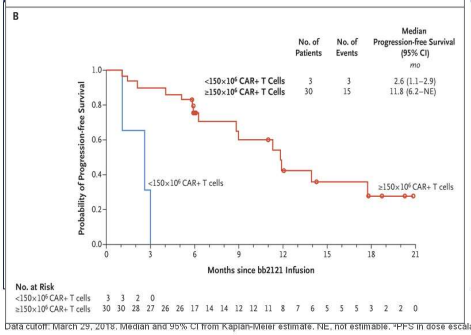
## PROGRESSION-FREE SURVIVAL

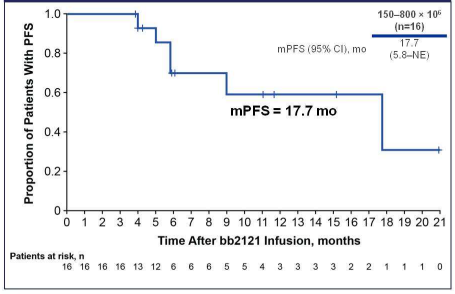
- mPFS of 11.8 months at active doses (≥150 × $10^6$ CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative

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




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

**PFS in MRD-Negative Patients**




Raje, et al. *N Engl J Med* 2019; 380:1726-1737.

Presented By Noopur Raje at 2018 ASCO Annual Meeting

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# BCMA-Directed CAR T Cells in Multiple Myeloma

| | NCI1 | PENN2 | BB2121 BLUEBIRD3 | LCAR-B38M LEGEND4 | MCARH171 MSK/JUNO5 |
|---|---|---|---|---|---|
| Population | 26 (16*) | 24 (19*) | 21 (18*) | 35 (30*) | 6 |
| # Prior Tx | 10 | 7 | 7 | 3–4 | 7.5 |
| Efficacy | | | | | |
| ORR | 81%* | 53%* | 94%* | 100% | NR |
| CR | 18% | | 56% | 63% (sCR) | NR |
| Toxicity | | | | | |
| CRS | 81% | 83% | 71% | 83% | 50% |
| CRS (Gr 3/4) | 37% | 33% | 10% | 5.7% | None |
| Neurotoxicity (all grades) | 19% | 25% | 24% | None | None |

*Responses at therapeutic CAR T dose levels

1. Ali SA et al. *Blood*. 2016;128:1688. 2. Cohen AD et al. *Blood*. 2017;130: Abstract 505. 3. Berdeja JG et al. 2017;130: Abstract 740.
4. Zhang W et al. *Haematologica*. 2017;102: Abstract S103. 5. Smith EL et al. *Blood*. 2017;130: Abstract 742.

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# Pros/Cons of Anti BCMA Therapies

| | CAR T | BITE | ADC |
|---|---|---|---|
| **Pros** | • Unprecedented response rates including MRD negativity in heavily pre-treated patients<br>• One-time intervention ie long chemo holiday resulting in median PFS ~1 year | • Off the shelf<br>• Deep responses<br>• Limited severe CRS - ? elderly<br>• Can be given in community settings | • Off the shelf<br>• Encouraging response rates<br>• 1-hour infusion every 3 weeks<br>• No CRS -<br>• Can be given in community settings |
| **Cons** | • Manufacturing time makes impractical for patients with aggressive disease/patient selection<br>• Requires complex infrastructure – stem cell lab, nursing, ICU/ER training – thus restricted to FACT accredited centers<br>• CRS - ? role in elderly/frail<br>• Impact of bridging chemo on remission duration<br>• Cost given relapses are occurring even in MRD neg<br>• Low white cells and platelets post CAR T requiring ongoing/frequent monitoring and treatment<br>• Management of CAR T relapses challenging especially if soon after fludarabine given impact on T cells | • ? admissions with initial doses until CRS risk low<br>• No data in Limited data in triple class/penta refractory<br>• Dosing/schedule to be determined<br>• Treatment until progression<br>• Toxicities require further study – neuropathy | • Ocular toxicity – will require close collaboration with ophthalmology and ? impact on quality of life<br>• Thrombocytopenia<br>• Treatment until progression<br>• Limited data in triple class/penta refractory |

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## Conclusions: Treatment of Newly Diagnosed Multiple Myeloma

| ASCT Eligible | ASCT Ineligible |
|---|---|
| ▪ Induction<br>– VRd > Rd?<br>– KRd > KCd for high-risk patients or baseline neuropathy<br>– Promising new data dara based quads eg Dara VCTd, ? Dara VRd<br>– VCd/KCd in some situations eg renal dysfunction (?T), IMID intolerance, pre harvest<br>– Extramedullary disease/PCL consider VTD-PACE and ASCT<br>▪ ASCT (RVD ->SCT-> R maintenance) consult recommended for all patients<br>– ? Defer SCT if MRD neg after induction | ▪ continuous therapy until progression<br>▪ dose reductions to improve tolerability<br>▪ Induction regimens<br>– VRd or VRd-lite<br>– Dara-Rd<br>– Others: Rd +/- cyclophosphamide<br>Vd +/- cyclophosphamide |

- = based on randomized phase 3 data

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## Conclusions: Relapsed Disease

**First Relapse:**

- Response rate and PFS progressively diminish with each relapse
- 3-drug therapy results in superior efficacy
- Select evidence-based regimen based on refractoriness to backbone control arms (lenalidomide vs bortezomib vs in near future daratumumab!)
- At attainment of persistent deep response ? de-escalate to 2 or 1 drugs
- High-risk disease remains unmet medical need with novel therapies typically only improving (or worsening –venetoclax) outcomes but not overcoming high risk

**Nth Relapse: as above but combination therapy even more important**

- If significant/fast progression, then consider 96-hr based chemo regimen
- If cytopenic due to disease, consider 96-hr based chemo regimen vs salvage SCT
- Selinexor (combination studies promising)
- Anti BCMA therapies- Antibody drug conjugate, T-cell engagers, CAR T

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## Q&A SESSION

*The Changing Landscape of Myeloma Treatment*

- **Ask a question by phone:**
  - Press star (*) then the number 1 on your keypad.
- **Ask a question by web:**
  - Click “Ask a question”
  - Type your question
  - Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

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LEUKEMIA & LYMPHOMA SOCIETY

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## LLS EDUCATION & SUPPORT RESOURCES

- **Information Specialists**

  Master’s level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  - **EMAIL:** infocenter@LLS.org
  - **TOLL-FREE PHONE:** 1-800-955-4572
- **Caregiver Support:** www.LLS.org/caregiver
- **Free Education Booklets:** www.LLS.org/booklets
- **Free Telephone/Web Programs:** www.LLS.org/programs
- **Live, weekly Online Chats:** www.LLS.org/chat
- **LLS Community:** www.LLS.org/community

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## LLS EDUCATION & SUPPORT RESOURCES


- **LLS Podcast, *The Bloodline with LLS***

  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.thebloodline.org

- **Education Videos**

  Free education videos about survivorship, treatment, disease updates and other topics: www.LLS.org/educationvideos

- **Patti Robinson Kaufmann First Connection Program**

  Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection

- **Free Nutrition Consults**

  Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition

- **What to Ask**

  Questions to ask the treatment team: www.LLS.org/whattoask

- **Other Support Resources**

  LLS Community, discussion boards, blogs, support groups, financial assistance and more: www.LLS.org/support

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