New Directions in Treating Multiple Myeloma (MM) in the Era of Novel Agents: A Clinical Perspective from Newly Diagnosed to Relapsed and Refractory MM; ASH 2017

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Harvard Medical School
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Disclosures

Research Funding
• Takeda
• Celgene

Disclosures
• Janssen
• Celgene
• Takeda
MULTIPLE MYELOMA
...not just one disease!

- Risk stratification, recognition of clonal heterogeneity
- Individualization of treatment, advent of novel therapies

Drach J, ASH 2012
Multimodality targeting of MM in the context of the BM microenvironment

Multiple Myeloma survival improving with new drugs: but all patients still relapse after IMiD and PI failure.
MM is a Marathon, not a Sprint

Asymptomatic
Symptomatic
Relapsing
Refractory

M-protein level (g/L)

First line
Second line
Third line

100
50
20

Smouldering myeloma or MGUS
Plateau remission

1st RELAPSE
2nd RELAPSE

Adapted from Borrello I. Leuk Res. 2012;36 Suppl. 1:S3–12.
Multiple Options are now available to treat in NDMM and RR MM…

How do we sequence therapies to ensure the best outcomes for patients?

Adapted from Laubach JP et al, *Leukemia* 2016
Multiple genetically distinct subclones are present at diagnosis\textsuperscript{1-4}

- These evolve over time due to selective pressures from treatment and factors in the microenvironment\textsuperscript{1,4}
- This clonal evolution can result in disease progression and treatment resistance\textsuperscript{5}

Co-occurrence of genomic events and clonal evolution during progression in MM

Key Targets in MM 2017

Genomic abnormalities:
• Target and overcome mutations
• Critical Role of Combination and Continuous Therapy
• Evolving Position and Timing of ASCT

Excess Protein Production:
• Target Protein degradation

Immune Suppression:
• Restore anti-MM immunity
Rational combination strategies in MM

Adapted from Lonial S, Mitsiades CS, Richardson PG. Clin Cancer Res 2011;17:1264-77.
Rational combination strategies in MM

3rd generation IMiDs (POM)

2nd, 3rd generation PI’s (CFLZ, IXA)

+ MoAbs

Adapted from Lonial S, Mitsiades CS, Richardson PG. Clin Cancer Res 2011;17:1264-77.
Current Paradigm of Initial Treatment

- Transplant Candidates
  - Autotransplant
  - Consolidation
  - Maintenance
  - Continue initial therapy

- Non-transplant Candidates

# Lenalidomide/Bortezomib-Based Rx in NDMM

| Response   | RVD\(^1\)  
n = 66          | RVDD\(^2\)   
n = 72          | VDCR\(^3\)   
n = 48          |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>CR + nCR</td>
<td>40% (57%)*</td>
<td>39%</td>
<td>40%</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>67% (74%)*</td>
<td>67%</td>
<td>58%</td>
</tr>
<tr>
<td>≥PR</td>
<td>100%</td>
<td>96%</td>
<td>88%</td>
</tr>
</tbody>
</table>

* Phase 2 Cohort (n=35)

- Active in pts with Adverse Cytogenetics
- Hematologic toxicity is more severe with addition of Chemo (Cy or doxorubicin)
- Risk of DVT does not appear to be increased over Lenalidomide/dex alone
- Risk of PN moderately increased over Bortezomib alone
- Generally otherwise well tolerated, although TRM seen with VDCR

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RVD: lenalidomide, bortezomib, dexamethasone; RVDD: RVD with pegylated liposomal doxorubicin; VDCR: VRD plus cyclophosphamide (wkly low dose dex with VRd, vs RVD)

Objective: Ph III trial to compare efficacy & safety of Rd with RVd
Eligibility: ≥18 yrs, active MM, PS 0-3.

**Primary Endpoint:** PFS

**Secondary Endpoints:** ORR, OS and Safety

BORT, bortezomib; d, day; DEX, dexamethasone; HSV, herpes simplex virus; ISS, International Staging System; LEN, lenalidomide; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Ph, phase; PS, performance status; pt, patient; Rd, lenalidomide and low-dose dexamethasone; RVd, bortezomib, lenalidomide and low-dose dexamethasone; SCT, stem cell transplant; SWOG, Southwest Oncology Group.

SWOG S0777: PFS and OS

**Progression Free Survival**

- **Treatment**
  - RVd
  - Rd

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVd</td>
<td>242 199 166 135 84 28 8</td>
</tr>
<tr>
<td>Rd</td>
<td>229 173 131 105 68 30 8</td>
</tr>
</tbody>
</table>

- **Median PFS**
  - RVd: 43 months
  - Rd: 30 months

<table>
<thead>
<tr>
<th>HR = 0.712 (0.560, 0.906)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-rank p value = 0.0018 (one sided)</td>
</tr>
</tbody>
</table>

**Overall Survival**

- **Treatment**
  - RVd
  - Rd

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVd</td>
<td>242 227 211 196 132 59 15 0</td>
</tr>
<tr>
<td>Rd</td>
<td>229 212 193 168 115 48 17</td>
</tr>
</tbody>
</table>

- **Median OS**
  - RVd: 75 months
  - Rd: 64 months

<table>
<thead>
<tr>
<th>HR = 0.709 (0.516, 0.973)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-rank p value = 0.025 (two sided)</td>
</tr>
</tbody>
</table>

AE, adverse event; HR, hazard ratio; OS, overall survival; PFS, progression free survival; Rd, lenalidomide plus low dose dexamethasone; RVd, lenalidomide, bortezomib and dexamethasone.

Dorie BGM et al. Lancet. 2017; 389: 519-527
Novel Agent-based Induction Therapies
ASH 2017

<table>
<thead>
<tr>
<th></th>
<th>Thal-based</th>
<th>Len-based</th>
<th>Bort-Based</th>
<th>Bort+IMiD-based</th>
<th>New agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-drug combinations</td>
<td>TD</td>
<td>RD</td>
<td>VD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rd</td>
<td></td>
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<td></td>
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<tr>
<td>3-drug combinations</td>
<td>TAD</td>
<td>RAD</td>
<td>PAD</td>
<td>VTD</td>
<td>*KTD</td>
</tr>
<tr>
<td></td>
<td>CTD</td>
<td>RCD</td>
<td>VCD</td>
<td>RVD</td>
<td>KRd</td>
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<td></td>
<td></td>
<td>BiRD</td>
<td></td>
<td></td>
<td>**IRd</td>
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<tr>
<td>4-drug combinations</td>
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<td></td>
<td></td>
<td>VTDC</td>
<td>***R2V2</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>RVDC</td>
<td>PanRVD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RVDD</td>
<td>MoAbs</td>
</tr>
</tbody>
</table>

Thal = Thalidomide, Len = Lenalidomide, Bortz = Bortezomib
Cfz: carfilzomib, MoAbs – monoclonal antibodies, Pan: panobinostat
***R2V2: RVD + vorinostat
**IRd: lenalidomide, ixazomib (mln 9708), dex
Daratumumab (DARA) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Patients (pts) With Newly Diagnosed Multiple Myeloma (MMY1001): an Open-label, Phase 1b Study (updated ASH 2017)

Andrzej Jakubowiak,1 Ajai Chari,2 Sagar Lonial,3 Brendan Weiss,4 Raymond L. Comenzo,5 Kaida Wu,6 Nushmia Z. Khokhar,6 Jianping Wang,7 Parul Doshi,6 Saad Z. Usmani8

1University of Chicago Medical Center, Chicago, IL; 2Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; 3Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA; 4Abramson Cancer Center and Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; 5Division of Hematology/Oncology, John C. Davis Myeloma and Amyloid Program, Tufts Medical Center, Boston, MA; 6Janssen Research & Development, LLC, Spring House, PA, USA; 7Janssen Research & Development, LLC, Raritan, NJ, USA; 8Levine Cancer Institute/Carolinas HealthCare System, Charlotte, NC, USA.

ClinicalTrials.gov Identifier: NCT01998971
Study Design

Open-label, Multicenter, Phase 1b Study (N = 22)

Eligibility/Treatment
• NDMM
• Transplant eligible and non-eligible
• Treatment duration: ≤13 cycles or until elective discontinuation for ASCT
• No clinically significant cardiac disease; echo required at screening

Dosing Schedule (28-d cycles)

Daratumumab:
• **Split dose**: 8 mg/kg Days 1-2 of Cycle 1
• 16 mg/kg QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter

Carfilzomib:
• 20 mg/m² C1D1
• Escalated to 70 mg/m² C1D8+; **weekly (Days 1, 8, 15)**

Lenalidomide:
• 25 mg; Days 1-21 of each cycle

Dexamethasone: 40 mg/week

Pre- and post-infusion medications:
Dexamethasone 20 mg; Diphenhydramine 25-50 mg; paracetamol 650-1,000 mg; montelukast 10 mg

Endpoints

Primary
• Safety, tolerability

Secondary
• ORR, duration of response, time to response, IRR

Exploratory
• PFS

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Echo, echocardiogram; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; C1D1, Cycle 1 Day 1; C1D8, Cycle 1 Day 8; IRR, infusion-related reaction; C1D3, Cycle 1 Day 3.

*20 mg if >75 y. *On daratumumab dosing days, dexamethasone 20 mg IV was administered as pre-medication on infusion day and 20 mg PO the day after infusion; for DARA, split first dose dexamethasone 20 mg IV was administered as a pre-medication on C1D1 and C1D2; on C1D3, administration of low-dose methylprednisolone (≤20 mg PO) was optional. *Required before first daratumumab dose, optional for subsequent doses.
Response Rate\textsuperscript{a,b}

- Median number of treatment cycles: 11.5 (range, 1.0-13.0)

Depth of response improved with duration of treatment

\textsuperscript{a}5 patients who proceeded to ASCT before C8 and 1 patient who discontinued due to PD at C7 were excluded.

PR, partial response; CR, complete response.
\textsuperscript{b}Response-evaluable population. \textsuperscript{c}Response rate (\geq PR) evaluated by IMWG criteria; M-protein measurements by central lab assessment.
**PFS**

- Median follow-up: 10.8 (range, 4.0-12.5) months
- Overall survival = 100%

12-month PFS rate\(^a\) = 94%

*Kaplan-Meier estimate.*
Conclusions

• DARA + KRd was well tolerated
  – Safety is consistent with previous reports of DARA and KRd
  – Low IRR rates associated with split first dose; no grade 3/4

• Highly effective with 100% ORR
  – 91% ≥VGPR and 43% ≥CR
  – Depth of response improved with duration of treatment

• No adverse impact on stem cell collection (10.4 x 10^6 cells/kg)
  – DARA is feasible as part of induction therapy

Data from this study support further investigation of DARA-KRd in NDMM
**Ixazomib Lenalidomide Dexamethasone: IRd**

Single-arm phase 1/2 study of weekly in NDMM

Primary Endpoint (Phase 2): \(\geq\)VGPR (CR + VGPR)

Patient Characteristics: 65 pts enrolled (15 Phase 1, 50 Phase 2; 23 (35%) discontinued during induction to undergo SCT and 42 (65%) did not receive SCT). 25 (38%) went on to ixazomib maintenance.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (N=65)</th>
<th>Did not receive SCT (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>66 (34–86)</td>
<td>68 (34-86)</td>
</tr>
<tr>
<td>ECOG PS 0/1/2, n (%)</td>
<td>28 (43)/34 (52)/3 (5)</td>
<td>20 (48)/19 (45)/3 (7)</td>
</tr>
<tr>
<td>ISS stage at diagnosis I/II/III, n (%)</td>
<td>28 (43)/28 (43)/9 (14)</td>
<td>17 (40)/18 (43)/7 (17)</td>
</tr>
<tr>
<td>High-risk cytogenetics,* n (%)</td>
<td>5 (8)</td>
<td>3 (7)</td>
</tr>
</tbody>
</table>

Dose and Schedule:
- Phase 1: oral ixazomib standard 3+3 dose escalation**\((1.68–3.95 \text{ mg/m}^2 \text{ weekly})\); Phase 2: oral ixazomib at RP2D from phase 1 (4.0 mg weekly); Single-agent ixazomib maintenance (at last tolerated dose) continued until disease progression or unacceptable toxicity
- **Induction: up to 12 \(\times\) 28-day treatment cycles**
  - 1
  - 8
  - 15
  - 22
  - 28
- **Maintenance**
  - Ixazomib maintenance, days 1, 8, 15, 28-day cycles

**Stem cell collection was allowed after 3 cycles; patients could proceed to SCT after 6 cycles; Mandatory thromboembolism prophylaxis with aspirin 81–325 mg QD or LMWH while on Rd**

*High-risk cytogenetics includes del(17), t(4;14) and t(14;16) abnormalities.
**Based on dose-limiting toxicities in cycle 1 LMWH, low molecular-weight heparin; QD, every day
Ixazomib Lenalidomide dexamethasone: IRd
Single-arm phase 1/2 study of weekly in NDMM

Response Rates:
Best confirmed response (evaluable)

Deepest of response in pts receiving ixazomib
Maintenance (N=25)

MRD evaluation (response-evaluable pts)

*Includes sCR; **Includes nCR (defined per Richardson PG et al, N Engl J Med. 2003;348:2609–17)
**Ixazomib Lenalidomide dexamethasone: IRd**

**Single-arm phase 1/2 study of weekly in NDMM**

**PFS:**

Median follow up of ~56 mos

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**Efficacy Outcomes:**

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>All patients (N=64)</th>
<th>Did not receive SCT (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up for OS, months</td>
<td>56.3</td>
<td>55.2</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>35.4</td>
<td>29.4</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Landmark OS rate, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>2 year</td>
<td>89</td>
<td>87</td>
</tr>
<tr>
<td>4 year</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>Median time to best response ≥ VGPR, months</td>
<td>4.9</td>
<td>6.6</td>
</tr>
<tr>
<td>Median time to best response sCR/CR, months</td>
<td>5.6</td>
<td>5.6</td>
</tr>
</tbody>
</table>

*Patients who received SCT were censored at the time of SCT*

Kumar et al. EHA 2017
Ixazomib Lenalidomide dexamethasone: IRd
Single-arm phase 1/2 study of weekly in NDMM

Quality of life: Mean EORTC QLQ-C30 scores in phase 2 pts who did not receive SCT (N=36)
Ixazomib Lenalidomide Dexamethasone: IRd
Phase 1/2 study of twice-weekly ixazomib + Rd in NDMM

Primary Endpoint (Phase 2): ≥VGPR (CR + VGPR)

Patient Characteristics: 64 pts enrolled (14 Phase 1, 50 Phase 2; 20 (31%) withdrew during induction to undergo SCT and 41 (64%) did not receive SCT); 3 (5%) withdrew during induction for reasons other than SCT but then went on to receive SCT. 18 (28%) went on to ixazomib maintenance.

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<td>53/44/4</td>
<td>51/46/2</td>
</tr>
<tr>
<td>ISS stage at diagnosis I/II/III, %</td>
<td>48/34/4</td>
<td>46/37/2</td>
</tr>
<tr>
<td>High-risk cytogenetics,* %</td>
<td>9</td>
<td>15</td>
</tr>
</tbody>
</table>

Dose and Schedule: Phase 1: oral ixazomib standard 3+3 dose escalation**(3.0 or 3.7 mg twice weekly); Phase 2: oral ixazomib at RP2D from phase 1 (3.0 mg twice weekly); Single-agent ixazomib maintenance (at last tolerated dose) continued until disease progression or unacceptable toxicity

Induction: up to 16 × 21-day treatment cycles

1
4
8
11
21

Maintenance

Ixazomib maintenance
D 1, 4, 8, 11
21-day cycles

Lenalidomide

Dex was dosed at 20 / 10 mg in cycles 1–8 / 9–16
Stem cell collection was allowed after 4 cycles; patients could proceed to autologous SCT after 8 cycles
Mandatory thromboembolism prophylaxis with aspirin 81–325 mg QD or LMWH while on Rd

*High-risk cytogenetics includes del 17, t(4;14) and t(14;16) abnormalities.

**Based on dose-limiting toxicities in cycle 1
Open-label, non-randomized phase 1/2 study of twice-weekly ixazomib + Rd in NDMM

Response Rates:

Best confirmed response (evaluable)

Evolution of response in pts receiving ixazomib Maintenance (N=18)

Best confirmed response: high risk patients

MRD evaluation (response-evaluable pts)


Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>All patients (N=62)</th>
<th>Did not receive SCT (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD evaluation, n (%)</td>
<td>27 (44)</td>
<td>20 (51)</td>
</tr>
<tr>
<td>Best response of sCR/CR, n</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Achieved MRD-negative status, n (% of patients with sCR/CR)</td>
<td>8 (80)</td>
<td>8 (89)</td>
</tr>
</tbody>
</table>

*High-risk cytogenetic abnormalities include del(17), t(4;14), and t(14;16)†
† Patient withdrew consent after achieving CR and could not be followed up

Richardson et al. EHA 2017
Open-label, non-randomized phase 1/2 study of twice-weekly ixazomib + Rd in NDMM

PFS:
Median follow up of ~47 mos

Efficacy Outcomes:

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>All patients (N=62)</th>
<th>Did not receive SCT (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up for OS, months</td>
<td>46.9</td>
<td>47.0</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>24.9</td>
<td>24.9</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Landmark OS rate, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>2 year</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>3 year</td>
<td>91</td>
<td>86</td>
</tr>
<tr>
<td>Median time to best response ≥VGPR, months*</td>
<td>3.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Median time to best response sCR/CR, months*</td>
<td>4.2</td>
<td>4.2</td>
</tr>
</tbody>
</table>

*In patients achieving these levels of response
NE, not estimable
Open-label, non-randomized phase 1/2 study of twice-weekly ixazomib + Rd in NDMM

Quality of life: Mean EORTC QLQ-C30 scores in phase 2 pts who did not receive SCT (N=31)
Data from a pooled analysis of phase 2 study pts who did not undergo ASCT and received ixazomib maintenance show promising PFS, an increase in depth of response during maintenance.

Efficacy and Safety of Long-term Ixazomib Maintenance Therapy in Patients (Pts) with Newly Diagnosed Multiple Myeloma (NDMM) Not Undergoing Transplant: an Integrated Analysis of Four Phase 1/2 Studies (Dimopoulos, Abstract 902.)

- 28 (23%) pts improved their response during ixazomib maintenance.

Ixazomib is only indicated for RRMM in Japan.

Dimopoulos M et al., ASH2017 Abstract 902.
Data from a pooled analysis of phase 2 study pts who did not undergo ASCT and received ixazomib maintenance show promising PFS, an increase in depth of response during maintenance.

Study design:
- Pts from 4 studies of weekly/twice-weekly ixazomib (C16005, twice-weekly IRd; C16008, weekly IRd; C16006, weekly/twice-weekly IMP; C16020, weekly ICd) who completed induction without PD and, in the IRd studies, were not withdrawn for ASCT, could receive single-agent ixazomib maintenance.

Results:
- N=121, median age 72 years (range 34–90)
- Median duration of ixazomib maintenance was 10.6 months (9.9 – 26.7 mo in individual studies)

2-yr PFS estimate for patients with high-risk cytogenetics (n=12) was 51% (18-77) from study entry and 56% (24-79) from the start of maintenance.

Ixazomib is only indicated for RRMM in Japan.

Dimopoulos M et al., ASH2017 Abstract 902.
All-oral IRd as induction prior to and consolidation after ASCT, followed by single-agent ixazomib maintenance, is well tolerated, convenient, and effective

Ixazomib-Lenalidomide-Dexamethasone (IRd) Combination before and after Autologous Stem Cell Transplantation (ASCT) Followed By Ixazomib Maintenance Is a Safe and Effective Strategy in Patients with Newly Diagnosed Multiple Myeloma (NDMM): A Phase 2 Study from the Intergroupe Francophone Du Myélome (IFM)

Study overview:
- 42 NDMM pts ≤66 years (median age 60 years)
- 3 x 28-day cycles of ixazomib 4.0 mg (days 1, 8, and 15), lenalidomide 25 mg (days 1–21), and dexamethasone 40 mg (days 1, 8, 15, and 22)
- Melphalan 200 mg/m² and ASCT
- Consolidation with 2 cycles of IRd and 6 additional cycles without dexamethasone (IR)
- Maintenance with 13 x 28-day cycles of ixazomib 4.0 mg (days 1, 8, and 15)

Endpoints:
- Primary: CR rate post-consolidation
- Other: PFS, OS, safety

Results:
- Median follow-up 24 months:
  - 2-year PFS was 83%
  - 2-year OS was 95%
- 32/37 (86%) pts and 26/31 (84%) pts completed the planned cycles of consolidation and maintenance, respectively
- 5 pts discontinued due to adverse events; rash n=3 (during induction, late consolidation, and maintenance, n=1 each), thrombocytopenia n=1 (before maintenance), infection n=1 (during maintenance)
- No renal or liver toxicity and no cardiac failure or ischemic heart disease was reported

Complete Response rates

<table>
<thead>
<tr>
<th>Induction</th>
<th>ASCT</th>
<th>Early consolidation (2 cycles IRd)</th>
<th>Late consolidation (6 cycles IR)</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>19</td>
<td>32</td>
<td>36</td>
<td>48</td>
</tr>
</tbody>
</table>

Moreau P et al., ASH2017 abstract 2021
Updated data from a phase 2 study of ixazomib plus lenalidomide as maintenance therapy post-ASCT supports the long-term feasibility of this treatment approach in pts with NDMM

Update on a Phase II Study of Ixazomib with Lenalidomide As Maintenance Therapy Following Autologous Stem Cell Transplant in Patients with Multiple Myeloma

Study design:
• Endpoints: PFS, ORR, safety, incidence of second primary malignancies (SPMs)

Results:
• 29 pts had an improvement in their best overall response from their baseline response
• 22 pts had grade 1/2 PN and 6 pts had grade 3 PN
• 3 pts were diagnosed with SPMs while on maintenance (post-ASCT); breast ductal carcinoma in situ, n=1, and squamous cell carcinoma of the skin, n=2

Patel et al., ASH2017 Abstract 437
Updated data from a phase 2 study of ixazomib plus lenalidomide as maintenance therapy post-ASCT supports the long-term feasibility of this treatment approach in pts with NDMM

Update on a Phase II Study of Ixazomib with Lenalidomide As Maintenance Therapy Following Autologous Stem Cell Transplant in Patients with Multiple Myeloma

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26 (41)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Elevated aspartate aminotransferase</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Elevated alanine aminotransferase</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Elevated alkaline phosphatase</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Elevated total bilirubin</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Rash</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Lung infection</td>
<td>16 (25)</td>
</tr>
<tr>
<td>Influenza</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

**Results**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, months</td>
<td>37.8</td>
</tr>
<tr>
<td>Pts remaining on therapy, n (%)</td>
<td>34 (53)</td>
</tr>
<tr>
<td>Medium no. of cycles received, n (range)</td>
<td>28 (1–51)</td>
</tr>
<tr>
<td>Best response, %</td>
<td></td>
</tr>
<tr>
<td>sCR</td>
<td>7.8</td>
</tr>
<tr>
<td>CR</td>
<td>26.5</td>
</tr>
<tr>
<td>VGPR</td>
<td>53</td>
</tr>
<tr>
<td>PR</td>
<td>10.9</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>NR</td>
</tr>
<tr>
<td>Median PFS in pts with high-risk cytogenetics</td>
<td>NR</td>
</tr>
<tr>
<td>Estimated 2-year PFS, %</td>
<td>81</td>
</tr>
<tr>
<td>Discontinuation rate, n (%)</td>
<td>30 (47)</td>
</tr>
<tr>
<td>Reasons:</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>16 (53)</td>
</tr>
<tr>
<td>Principal investigator discretion</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Consent withdrawal</td>
<td>11 (37)</td>
</tr>
</tbody>
</table>

**Key messages**

- Findings demonstrate the long-term feasibility of post-ASCT maintenance therapy with IR, with similar incidence of AEs vs historical data for lenalidomide alone, manageable hematologic AEs, PN was mostly grade ≤2 (grade 3, n=6) and no other unexpected toxicities
- Based on clinical experience, the protocol was amended in Aug 2013 to reduce the starting dose of ixazomib to 3.0 mg, aligned with the dosing schedule of the phase 3 TOURMALINE-MM3 study

Patel et al., ASH 2017 Abstract 437
**Key eligibility criteria:**
- Transplant-ineligible NDMM
- ECOG 0-2
- Creatinine clearance ≥40 mL/min
- No peripheral neuropathy grade ≥2

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

**1:1 Randomization (N = 706)**

**VMP × 9 cycles (n = 356)**
- Bortezomib: 1.3 mg/m² SC
  - Cycle 1: twice weekly
  - Cycles 2-9: once weekly
- Melphalan: 9 mg/m² PO on Days 1-4
- Prednisone: 60 mg/m² PO on Days 1-4

**D-VMP × 9 cycles (n = 350)**
- Daratumumab: 16 mg/kg IV
  - Cycle 1: once weekly
  - Cycles 2-9: every 3 weeks
  - Same VMP schedule

**D**
- Cycles 10+
- 16 mg/kg IV
  - Every 4 weeks: until PD

**Follow-up for PD and survival**

**Primary endpoint:**
- PFS

**Secondary endpoints:**
- ORR
- ≥VGPR rate
- ≥CR rate
- MRD (NGS; 10⁻⁵)
- OS
- Safety

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

NDMM, newly diagnosed multiple myeloma; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; EU, European Union; VMP, bortezomib/melphalan/prednisone; SC, subcutaneously; PO, orally; D, daratumumab; IV, intravenously; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; OS, overall survival.
**Efficacy: PFS**

- **HR, 0.50** (95% CI, 0.38-0.65; *P* <0.0001)
- Median (range) follow-up: 16.5 (0.1-28.1) months
- Consistent PFS treatment benefit across subgroups

50% reduction in the risk of progression or death in patients receiving D-VMP
Efficacy: ORR\textsuperscript{a} and MRD (NGS; 10\textsuperscript{-5} Threshold)

Significantly higher ORR, ≥VGPR, and ≥CR with D-VMP

\textgreater3\text{-}fold higher MRD-negativity rate with D-VMP

\begin{itemize}
\item ORR, overall response rate; VMP, bortezomib/melphalan/prednisone; D, daratumumab; CR, complete response; VGPR, very good partial response; PR, partial response; sCR, stringent complete response. MRD, minimal residual disease; NGS, next-generation sequencing using clonoSEQ version 2.0 (Adaptive). \textsuperscript{b}\textsuperscript{c}Intent-to-treat population. \textsuperscript{d}P value was calculated with the use of the Cochran–Mantel–Haenszel chi-square test. \textsuperscript{e}P <0.0001.
\end{itemize}
STaMINA: ASCT + RVd vs Tandem ASCT

Study Design

- Primary endpoint: PFS
- Secondary endpoints: OS, response rates (particularly ≥ VGPR), the rate of CR conversion for pts not in CR, toxicity and infections after each intervention and long term, the rate of nonadherence, Tx-related mortality, QoL

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*a* Pts must have received ≥ 2 cycles of systemic therapy within 2-12 months of initial Tx. *b* Bortezomib 1.3 mg/m^2^ d1, 4, 8, 11; Lenalidomide 15 mg d1-15; Dexamethasone 40 mg d1, 8, 15; 21 days per cycle. *c* LEN maintenance x 3 years amended to LEN maintenance until PD in 2014 amendment after report of CALGB 100104. ASCT, autologous stem cell transplant; CR, complete response; d, day; LEN, lenalidomide; MEL, melphalan; MM, multiple myeloma; OS, overall survival; pt, patient; PD, progressive disease; PFS, progression-free survival; pt, patient; QoL, quality of life; RVd, lenalidomide, bortezomib, dexamethasone; Tx, treatment; VGPR, very good partial response.

Stadtmauer E et al. ASH 2016; Oral Presentation and Abstract LBA-1
**STaMINA: ASCT + RVd vs Tandem ASCT**

*Primary Endpoint: Progression-Free Survival*

- At 38 mos follow-up, PFS was similar across all 3 Tx arms

![Graph showing progression-free survival](image)

38 Month Estimate and 95% CI
- **Auto/Auto:** 56.5 (49.4, 62.9)
- **Auto/RVD:** 56.7 (50.0, 62.8)
- **Auto/Maint:** 52.2 (45.4, 58.6)

<table>
<thead>
<tr>
<th>N at risk</th>
<th>Months from Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto/Auto 247</td>
<td>200 153 87</td>
</tr>
<tr>
<td>Auto/RVD 254</td>
<td>215 172 99</td>
</tr>
<tr>
<td>Auto/Maint 257</td>
<td>213 158 80</td>
</tr>
</tbody>
</table>

- PFS in high risk pts was similar to standard risk group across all arms

ASCT, autologous stem cell transplant; Auto, autologous stem cell transplant; Maint, maintenance; PFS, progression-free survival; RVd, lenalidomide, bortezomib, dexamethasone; Tx, treatment.
STaMINA: ASCT + RVd vs Tandem ASCT

Overall Survival

- At 38 mos follow-up, OS was similar across all 3 Tx arms
Lenalidomide Maintenance After High-Dose Melphalan and Autologous Stem Cell Transplant in Multiple Myeloma: A Meta-Analysis of Overall Survival

Michel Attal,1 Antonio Palumbo,2 Sarah A. Holstein,3 Valérie Lauwers-Cances,1 Maria Teresa Petrucci,4 Paul Richardson,5 Cyrille Hulin,6 Patrizia Tosi,7 Kenneth C. Anderson,5 Denis Caillot,8 Valeria Magarotto,9 Philippe Moreau,10 Gerald Marit,11 Zhinuan Yu,12 Philip L. McCarthy13

1Institut Universitaire du Cancer, Toulouse-Oncopole, France; 2The Myeloma Unit, Department of Hematology, University of Turin, Turin, Italy; 3Roswell Park Cancer Institute, Buffalo, NY; 4University La Sapienza, Rome, Italy; 5Dana-Farber Cancer Institute, Boston, MA; 6Bordeaux Hospital University Center (CHU), Bordeaux, France; 7Seràgnoli Institute of Hematology and Medical Oncology, Bologna University, Bologna, Italy; 8Dijon University Hospital Center, Dijon, France; 9University of Torino, Torino, Italy; 10University Hospital Hôtel-Dieu, Nantes, France; 11Centre Hospitalier Universitaire, Bordeaux, France; 12Celgene Corporation, Summit, NJ; 13Blood and Marrow Transplant Program, Roswell Park Cancer Institute, Buffalo, NY

LEN Maintenance After ASCT in MM: OS Analysis

Hazard Ratios by study

ASCT, autologous stem cell transplant; CTL, control; HR, hazard ratio; LEN, lenalidomide; MM, multiple myeloma; OS, overall survival.

ASH 2017: Lenalidomide Maintenance Significantly Improves Outcomes Compared to Observation Irrespective of Cytogenetic Risk: Results of the Myeloma XI Trial

Graham Jackson1, Faith E Davies2, Charlotte Pawlyn3,5, David Cairns4, Alina Striha4, Anna Hockaday4, Inga Sakauskiene4, John R Jones3,5, Bhuvan Kishore6, Mamta Garg7, Cathy Williams8, Kamaraj Karunanithi9, Jindriska Lindsay10, Matthew W Jenner11, Gordon Cook12, Martin F Kaiser3,5, Mark T Drayson13, Roger G Owen14, Nigel H. Russell8, Walter M Gregory4 and Gareth J. Morgan2

1)Department of Haematology, University of Newcastle, Newcastle Upon Tyne; 2)Myeloma Institute, University of Arkansas for Medical Sciences, Little Rock, AR; 3)The Institute of Cancer Research, London 4)Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, Leeds; 5)Department of Haematology, The Royal Marsden Hospital NHS Foundation Trust, London; 6)Heart of England Foundation Trust, Birmingham; 7)Leicester Royal Infirmary, Leicester; 8)Centre for Clinical Haematology, Nottingham University Hospital, Nottingham; 9)University Hospital of North Midlands, Stoke on Trent; 10)Kent and Canterbury NHS Trust, Canterbury; 11)Department of Haematology, University Hospital Southampton NHS Foundation Trust, Southampton; 12)Leeds Institute of Cancer and Pathology, University of Leeds, Leeds; 13)Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham; 14)St James's University Hospital, Leeds

On behalf of the Myeloma XI Trial Management Group and NCRI Haem-Onc CSG
Myeloma XI

Study objective:
• To determine the efficacy and safety of lenalidomide continued to disease progression.

Study design:
• Phase III, multicentre, open label, parallel group, randomised controlled trial.
• Newly diagnosed symptomatic myeloma patients of all ages.
• Randomisation at 3 months post ASCT (TE) or at maximum response (TNE).
• Primary endpoints: PFS and OS.
Myeloma XI

Induction

**NDMM**
Treated on Myeloma XI induction protocols

Maintenance

**Lenalidomide**
10mg/day, days 1-21/28

Observation

\[N=1971 \quad TE = 1248, \quad TNE = 723\]
Median follow up: 30.6 months (IQR 17.9-50.7)

Exclusion criteria

- Failure to respond to lenalidomide as induction IMiD or progressive disease
- Previous or concurrent active malignancies

TE: transplant eligible
TNE: transplant non-eligible
Lenalidomide improved response during maintenance

**All:**

Median Time to Improved Response [95%CI]
- Obs. (n=667) NR
- Len. (n=902) NR

HR: 1.94 95%CI [1.21, 3.12]
Logrank P = 0.0127

Est. [95%CI]
- Obs. (%) 4.6 [6.3, 2.9]
- Len. (%) 9.4 [11.4, 7.3]

Number at risk
- Obs. 663 351 184 83 36 12 1
- Len. 892 570 313 152 82 30 2

**MRD results will be presented by Ruth de Tute / Roger Owen**

**Monday, December 11th, 7:00PM Abstract no. 904**

**TE:**

Median Time to Improved Response [95%CI]
- Obs. (n=385) NR
- Len. (n=538) NR

HR: 3.70 95%CI [1.55, 8.82]
Logrank P = 9e-04

Est. [95%CI]
- Obs. (%) 3.2 [5.8, 0.6]
- Len. (%) 8.3 [11.3, 5.2]

Number at risk
- Obs. 281 118 48 17 8 2
- Len. 362 229 129 60 26 12

**TNE:**

Median Time to Improved Response [95%CI]
- Obs. (n=282) NR
- Len. (n=364) NR

HR: 2.29 95%CI [1.52, 3.45]
Logrank P < 0.0001

Est. [95%CI]
- Obs. (%) 4.6 [6.3, 2.9]
- Len. (%) 9.4 [11.4, 7.3]

Number at risk
- Obs. 663 351 184 83 36 12 1
- Len. 892 570 313 152 82 30 2

Improved response = achievement of VGPR/CR

TE: transplant eligible
TNE: transplant non-eligible
Transplant eligible pathway

Lenalidomide improved PFS from 30 to 57 months, hazard ratio of 0.47

Median PFS [95% CI]

<table>
<thead>
<tr>
<th></th>
<th>Median PFS [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lenalidomide (n=730)</strong></td>
<td>56.9m [49.7, ∞]</td>
</tr>
<tr>
<td><strong>Observation (n=518)</strong></td>
<td>30.1m [25.2, 32.4]</td>
</tr>
</tbody>
</table>

HR : 0.48 95% CI [0.40, 0.58]
Log-Rank P < 0.0001

PFS: progression-free survival
### Subgroup analysis

Across both pathways lenalidomide improved PFS from 20 to 39 months, Hazard ratio of 0.46

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Level</th>
<th>Observation n/N</th>
<th>Lenalidomide n/N</th>
<th>HR [ 95%CI ]</th>
<th>P. (het)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>336/527</td>
<td>294/696</td>
<td>0.49 (0.42, 0.57)</td>
<td>0.3148</td>
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<tr>
<td>Female</td>
<td></td>
<td>197/307</td>
<td>162/441</td>
<td>0.42 (0.34, 0.52)</td>
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<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=65 years</td>
<td></td>
<td>219/421</td>
<td>164/596</td>
<td>0.47 (0.39, 0.58)</td>
<td>0.7848</td>
</tr>
<tr>
<td>&gt;65 years</td>
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<td>314/413</td>
<td>292/541</td>
<td>0.45 (0.39, 0.53)</td>
<td></td>
</tr>
<tr>
<td><strong>ISS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td></td>
<td>131/239</td>
<td>97/327</td>
<td>0.37 (0.28, 0.49)</td>
<td>0.7142</td>
</tr>
<tr>
<td>Stage II</td>
<td></td>
<td>229/349</td>
<td>182/439</td>
<td>0.47 (0.38, 0.57)</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td></td>
<td>138/192</td>
<td>149/291</td>
<td>0.51 (0.41, 0.65)</td>
<td></td>
</tr>
<tr>
<td><strong>Induction therapy</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>CTD/CTDa</td>
<td></td>
<td>242/344</td>
<td>224/430</td>
<td>0.53 (0.44, 0.64)</td>
<td>0.0809</td>
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<tr>
<td>RCD/RCDa</td>
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<td>262/373</td>
<td>207/473</td>
<td>0.42 (0.35, 0.51)</td>
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<tr>
<td>CCRD</td>
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<td>29/117</td>
<td>25/234</td>
<td>0.35 (0.20, 0.60)</td>
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<tr>
<td><strong>Response before maintenance</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CR or VGPR</td>
<td></td>
<td>433/706</td>
<td>371/947</td>
<td>0.52 (0.45, 0.59)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PR or MR</td>
<td></td>
<td>95/117</td>
<td>74/171</td>
<td>0.25 (0.18, 0.34)</td>
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</tr>
<tr>
<td>NC or PD</td>
<td></td>
<td>3/6</td>
<td>5/8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>t(4,14)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td></td>
<td>32/32</td>
<td>25/51</td>
<td>0.35 (0.20, 0.60)</td>
<td>0.3297</td>
</tr>
<tr>
<td>Absent</td>
<td></td>
<td>199/295</td>
<td>173/396</td>
<td>0.44 (0.36, 0.55)</td>
<td></td>
</tr>
<tr>
<td><strong>del(17p)</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td></td>
<td>21/24</td>
<td>20/37</td>
<td>0.71 (0.35, 1.45)</td>
<td>0.4259</td>
</tr>
<tr>
<td>Absent</td>
<td></td>
<td>210/303</td>
<td>178/410</td>
<td>0.43 (0.35, 0.52)</td>
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</tr>
<tr>
<td><strong>1q gain</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td></td>
<td>84/107</td>
<td>84/162</td>
<td>0.46 (0.33, 0.62)</td>
<td>0.4553</td>
</tr>
<tr>
<td>Absent</td>
<td></td>
<td>147/220</td>
<td>114/285</td>
<td>0.39 (0.31, 0.51)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td>533/834</td>
<td>456/1137</td>
<td>0.46 (0.41, 0.53)</td>
<td></td>
</tr>
</tbody>
</table>

PFS: progression-free survival
Transplant eligible pathway

Lenalidomide improved 3 yr OS from 80.2% to 87.5%, hazard ratio of 0.69

3 yr OS:

- Lenalidomide (n=1137): 87.5% [84.3, 90.7]
- Observation (n=834): 80.2% [76.0, 84.4]

HR: 0.69 95% CI [0.52, 0.93]
Log-Rank P = 0.0130

OS: overall survival
### Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Level</th>
<th>Observation</th>
<th>Lenalidomide</th>
<th>HR [ 95%CI ]</th>
<th>P. (het)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>58/327</td>
<td>65/459</td>
<td>0.86 (0.60, 1.22)</td>
<td>0.0243</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>40/191</td>
<td>19/271</td>
<td>0.42 (0.24, 0.74)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt;=65 years</td>
<td>80/406</td>
<td>65/577</td>
<td>0.68 (0.49, 0.95)</td>
<td>0.8075</td>
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<tr>
<td>Age</td>
<td>&gt;65 years</td>
<td>18/112</td>
<td>19/153</td>
<td>0.74 (0.38, 1.43)</td>
<td></td>
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<tr>
<td>ISS</td>
<td>Stage I</td>
<td>28/180</td>
<td>21/251</td>
<td>0.64 (0.36, 1.14)</td>
<td>0.4784</td>
</tr>
<tr>
<td>ISS</td>
<td>Stage II</td>
<td>35/206</td>
<td>37/266</td>
<td>0.86 (0.54, 1.38)</td>
<td></td>
</tr>
<tr>
<td>ISS</td>
<td>Stage III</td>
<td>31/101</td>
<td>22/157</td>
<td>0.51 (0.30, 0.89)</td>
<td></td>
</tr>
<tr>
<td>Induction therapy</td>
<td>CTD</td>
<td>43/194</td>
<td>40/236</td>
<td>0.81 (0.53, 1.25)</td>
<td>0.5242</td>
</tr>
<tr>
<td>Induction therapy</td>
<td>RCD</td>
<td>47/207</td>
<td>31/260</td>
<td>0.57 (0.36, 0.90)</td>
<td></td>
</tr>
<tr>
<td>Response before maintenance</td>
<td>CR or VGPR</td>
<td>81/449</td>
<td>70/626</td>
<td>0.73 (0.53, 1.00)</td>
<td>0.7076</td>
</tr>
<tr>
<td>Response before maintenance</td>
<td>PR or MR</td>
<td>15/60</td>
<td>11/93</td>
<td>0.48 (0.22, 1.06)</td>
<td></td>
</tr>
<tr>
<td>Response before maintenance</td>
<td>NC or PD</td>
<td>1/4</td>
<td>1/4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(4,14)</td>
<td>Present</td>
<td>10/24</td>
<td>12/42</td>
<td>0.65 (0.28, 1.52)</td>
<td>0.8304</td>
</tr>
<tr>
<td>t(4,14)</td>
<td>Absent</td>
<td>35/177</td>
<td>25/229</td>
<td>0.57 (0.34, 0.96)</td>
<td></td>
</tr>
<tr>
<td>del(17p)</td>
<td>Present</td>
<td>7/13</td>
<td>10/25</td>
<td>0.44 (0.14, 1.36)</td>
<td>0.6927</td>
</tr>
<tr>
<td>del(17p)</td>
<td>Absent</td>
<td>38/188</td>
<td>27/246</td>
<td>0.55 (0.34, 0.91)</td>
<td></td>
</tr>
<tr>
<td>1q gain</td>
<td>Present</td>
<td>17/58</td>
<td>24/104</td>
<td>0.70 (0.36, 1.33)</td>
<td>0.287</td>
</tr>
<tr>
<td>1q gain</td>
<td>Absent</td>
<td>28/143</td>
<td>13/167</td>
<td>0.43 (0.22, 0.84)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>98/518</td>
<td>84/730</td>
<td>0.69 (0.52, 0.93)</td>
<td></td>
</tr>
</tbody>
</table>

OS: overall survival
Conclusions

• Treatment with lenalidomide until disease progression resulted in a highly significant improvement in PFS for newly diagnosed myeloma patients of all ages.

• Overall survival was prolonged in transplant eligible patients.

• The benefit was attenuated in transplant non-eligible patients by subsequent treatment regimens.

• There was no evidence of an increase in mutational instability or significant toxicity with lenalidomide maintenance.

• Lenalidomide maintenance is effective irrespective of cytogenetic risk status.
**DETERMINATION**

**DFCI 10-106 / IFM DFCI 2009 / BMT CTN 1304**

Delayed vs. Early Transplant with Revlimid Maintenance and Antimyeloma Triple therapy

---

**Objectives**

1) Compare progression-free survival between Arm A and Arm B for patients with newly diagnosed symptomatic MM
2) Evaluate the impact of lenalidomide maintenance given until progression

**Eligibility**

- Multiple myeloma diagnosis based on IMF 2003 Diagnostic Criteria
- Diagnostic assessments w/in 21 days of protocol therapy
- Age 18 to 65 years

---

**REGISTRATION**

---

**INITIAL THERAPY**

- Lenalidomide + bortezomib + dexamethasone (RVD)
- 1 Cycle (21 days)

---

**RANDOMIZATION**

- Stratify according to:
  - ISS stage (stage I, II or III)
- Cytogenetics: standard vs. high-risk vs FISH failures. High-risk is defined as presence of del(17p), or t(4;14), or t(14;16) using FISH.

---

**ARM A**

- **RVD q 21 days (2 cycles)**
- Collection of peripheral blood stem cells (PBSCs) using cyclophosphamide and filgrastim or G-CSF type granulocyte® or equivalent
- RVD q 21 days (5 cycles)
- Maintenance Lenalidomide q28 days (until disease progression)

---

**ARM B**

- **RVD q 21 days (2 cycles)**
- Collection of peripheral blood stem cells (PBSCs) using cyclophosphamide and filgrastim or G-CSF type granulocyte® or equivalent
- Autologous stem cell transplant
  - Melphalan: infused over two days or as a single infusion
  - Re-infusion of PBSCs
- RVD q 21 days (2 cycles)
- Maintenance Lenalidomide q28 days (until disease progression)

---

- **Study treatment provided free of charge to all study participants**
- **BMT CTN accrual credit provided to all BMT CTN centers**

Protocol Chair: PG Richardson: paul.richardson@dfci.harvard.edu
Protocol Coordinator: A Zeytoonjian: andreaA_zeytoonjian@dfci.harvard.edu
BMT CTN Project Manager: Ann Foley, MA, CCRP: afoley@nmipd.org

To view the entire protocol, go to www.bmtctn.net. Posted to http://clinicaltrials.gov/ as NCT01208662

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Ph.III: IFM/DFCI 2009 Study (US and France)  
Newly Diagnosed MM (N=1,420)

- **Induction**
  - **RVDx3**
  - **CY (3g/m2)**
  - **Mobilization**
    - Goal: $5 \times 10^6$ cells/kg
  - **Melphalan 200mg/m^2* + ASCT**
  - **RVD x 2**

- **Consolidation**
  - **RVD x 5**
  - **CY (3g/m2)**
  - **Mobilization**
    - Goal: $5 \times 10^6$ cells/kg
  - **RVDx3**

- **Maintenance**
  - **Lenalidomide**

- **Randomise**

- **Calibration**

- **MRD @ CR**

**Richardson et al, ASH 2016**
Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma

Michel Attal, M.D., Valerie Lauwers-Cances, M.D., Cyrille Hulin, M.D., Xavier Leleu, M.D., Denis Caillot, M.D., Martine Escoffre, M.D., Bertrand Arnulf, M.D., Margaret Macro, M.D., Karim Belhadj, M.D., Laurent Garderet, M.D., Murielle Roussel, M.D., Catherine Payen, M.D., Claire Mathiot, M.D., Jean P. Fermand, M.D., Nathalie Meuleman, M.D., Sandrine Rollet, M.S., Michelle E. Maglio, B.S., Andrea A. Zeytoonjian, B.S., Edie A. Weller, Ph.D., Nikhil Munshi, M.D., Kenneth C. Anderson, M.D., Paul G. Richardson, M.D., Thierry Facon, M.D., Hervé Avet-Loiseau, M.D., Jean-Luc Harousseau, M.D., and Philippe Moreau, M.D., for the IFM 2009 Study*
# Phase III: IFM 2009: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RVD-Alone Group</th>
<th>Transplantation Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 350)</td>
<td>(N = 350)</td>
</tr>
<tr>
<td><strong>Median Age (Range), yr.</strong></td>
<td>59 (29-66)</td>
<td>60 (30-60)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>208 (59)</td>
<td>214 (61)</td>
</tr>
<tr>
<td><strong>Type of myeloma, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>209 (60)</td>
<td>223 (64)</td>
</tr>
<tr>
<td>IgA</td>
<td>71 (20)</td>
<td>73 (21)</td>
</tr>
<tr>
<td>Light Chain</td>
<td>57 (16)</td>
<td>46 (13)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (4)</td>
<td>8 (2)</td>
</tr>
<tr>
<td><strong>ISS, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>115 (33)</td>
<td>118 (34)</td>
</tr>
<tr>
<td>II</td>
<td>170 (49)</td>
<td>171 (49)</td>
</tr>
<tr>
<td>III</td>
<td>65 (19)</td>
<td>61 (17)</td>
</tr>
<tr>
<td><strong>B2M, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5mg/l</td>
<td>169 (48)</td>
<td>178 (51)</td>
</tr>
<tr>
<td>&gt;3.5mg/l</td>
<td>181 (52)</td>
<td>172 (49)</td>
</tr>
<tr>
<td><strong>Cytogenetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(4:14)</td>
<td>26/256</td>
<td>28/259</td>
</tr>
<tr>
<td>del 17p</td>
<td>15/256</td>
<td>16/258</td>
</tr>
<tr>
<td>t (14:16)</td>
<td>6/256</td>
<td>6/258</td>
</tr>
<tr>
<td>t (4:14) or t(14:16) or del 17p</td>
<td>44/256</td>
<td>46/259</td>
</tr>
</tbody>
</table>

ISS, international staging system; RVD, lenalidomide, bortezomib, dexamethasone.

Phase III: IFM 2009: PFS & OS Curves

- Data cut off 1\textsuperscript{st} Sep 2015

PFS, progression free survival; OS, overall survival; RVD, lenalidomide, bortezomib, dexamethasone.

## Phase III: IFM 2009: Response to Treatment

### Table 2. Response to Treatment.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RVD-Alone Group (N = 350)</th>
<th>Transplantation Group (N = 350)</th>
<th>Adjusted P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response during the study — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>169 (48)</td>
<td>205 (59)</td>
<td>0.02</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>101 (29)</td>
<td>102 (29)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>70 (20)</td>
<td>37 (11)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>10 (3)</td>
<td>6 (2)</td>
<td></td>
</tr>
<tr>
<td>Complete response — no. (%)</td>
<td>169 (48)</td>
<td>205 (59)</td>
<td>0.03</td>
</tr>
<tr>
<td>Complete response or very good partial response — no. (%)</td>
<td>270 (77)</td>
<td>307 (88)</td>
<td>0.001</td>
</tr>
<tr>
<td>Minimal residual disease not detected during the study — no./ total no. with complete or very good partial response (%)‡</td>
<td>171/265 (65)</td>
<td>220/278 (79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Responses were assessed according to the International Uniform Response Criteria for Multiple Myeloma. Percentages may not total 100 because of rounding.
† P values were adjusted for multiplicity with the use of the Holm procedure to control the family-wise error rate at 0.05.
‡ Minimal residual disease was detected by means of flow cytometry. As a result of decisions made by the patient or the investigator, 5 patients in the RVD-alone group and 29 patients in the transplantation group were not tested.

RVD, lenalidomide, bortezomib, dexamethasone.

### Phase III: IFM 2009: Subgroup Analyses of PFS

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Transplantation</th>
<th>RVD Alone</th>
<th>Hazard Ratio (95% CI) for Progression or Death</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Patients</strong></td>
<td>2095</td>
<td>2095</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Transplantation</strong></td>
<td>126/196</td>
<td>85/185</td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>Age 18–59 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 60–65 yr</td>
<td>85/154</td>
<td>72/165</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Male</td>
<td>129/208</td>
<td>102/214</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>82/142</td>
<td>55/136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of multiple myeloma</td>
<td></td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>IgG</td>
<td>133/209</td>
<td>96/223</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA</td>
<td>38/71</td>
<td>39/73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light chain</td>
<td>31/57</td>
<td>17/46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>International Staging System stage</td>
<td></td>
<td></td>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td>I</td>
<td>60/115</td>
<td>44/118</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>107/170</td>
<td>81/171</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>44/65</td>
<td>32/61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetic risk at screening</td>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>Standard risk</td>
<td>122/212</td>
<td>83/213</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>32/44</td>
<td>31/46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test failure</td>
<td>57/94</td>
<td>43/91</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PFS, progression free survival; RVD, lenalidomide, bortezomib, dexamethasone.

### Phase III: IFM 2009: Adverse Events

<table>
<thead>
<tr>
<th>Grade 3 / 4 AEs in ≥2%</th>
<th>RVD-Alone Group (N = 350)</th>
<th>Transplantation Group (N = 350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>166 (47.4)</td>
<td>322 (92.0)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12 (3.4)</td>
<td>52 (14.9)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>31 (8.9)</td>
<td>69 (19.7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>50 (14.3)</td>
<td>291 (83.1)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>5 (1.4)</td>
<td>25 (7.1)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0</td>
<td>59 (16.9)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>10 (2.9)</td>
<td>15 (4.3)</td>
</tr>
<tr>
<td>Cytolytic hepatitis</td>
<td>11 (3.1)</td>
<td>7 (2.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (2.0)</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (0.3)</td>
<td>13 (3.7)</td>
</tr>
<tr>
<td>Infections</td>
<td>31 (8.9)</td>
<td>71 (20.3)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>42 (12.0)</td>
<td>45 (12.9)</td>
</tr>
<tr>
<td>Rash</td>
<td>7 (2.0)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Any thromboembolic event*</td>
<td>13 (3.7)</td>
<td>19 (5.4)</td>
</tr>
</tbody>
</table>

AE, adverse event; RVD, lenalidomide, bortezomib, dexamethasone.

**IFM 2009: Causes of Mortality (9/2015)**

<table>
<thead>
<tr>
<th></th>
<th>RVD arm N=48</th>
<th>Transplant N=54</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myeloma, n (%)</strong></td>
<td>40/48 (83%)</td>
<td>35/54 (65%)</td>
</tr>
<tr>
<td><strong>Toxicity, n (%)</strong></td>
<td>4/48 (8%)</td>
<td>9*/54 (16%)</td>
</tr>
<tr>
<td><strong>SPM (AML/MDS)</strong></td>
<td>1/48 (2%)</td>
<td>6/54 (11%)</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>3/48 (6%)</td>
<td>4/54 (7%)</td>
</tr>
</tbody>
</table>

* Included 5 transplant related deaths

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; RVD, lenalidomide, bortezomib, dexamethasone; SPM, second primary malignancies.

• Progression-free survival was prolonged in patients who were MRD negative versus those who were MRD positive (adjusted hazard ratio, 0.30; 95% confidence interval, 0.23 to 0.37; P<0.001).

• Overall survival was prolonged in patients who were MRD negative versus those who were MRD positive (adjusted hazard ratio, 0.34; 95% confidence interval, 0.22 to 0.51; P<0.001).

MRD, minimal residual disease; OS, overall survival; PFS, progression free survival.
Key Targets in MM 2017

Genomic abnormalities:
- Target and Overcome Mutations
- Critical Role of Combination Therapy
- Evolving Position and Timing of ASCT

Excess Protein Production:
- Target Protein Degradation

Immune Suppression:
- Restore anti-MM immunity
Targeting the Ubiquitin Proteasome System In MM; The Central Role of Proteasome Inhibition (PI)

Deubiquitylating Enzymes (DUBs)
- P5091 target USP-7
- bAP15 target USP-14/UCHL5

UB enzymes E1, E2 and E3-UB-Ligases

Poly-ubiquitinated proteins (proteasome substrates)

Six Protease activities
- β5, β5i
- β1, β1i
- β2, β2i

Degraded protein

26S PROTEASOME

ATPases/ Cdc48

Potential Therapeutic Targets

Immunoproteasome

Adapted from Lawasut, P, Chauhan D, Hideshima T, Richardson PG et al. IMW 2013
Phase III ASPIRE Study: KRd vs. Rd (n=792)

Primary endpoint = PFS; OS update ASH 2017

<table>
<thead>
<tr>
<th></th>
<th>KRd (n = 396)</th>
<th>Rd (n = 396)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥PR)</td>
<td>87.1%</td>
<td>66.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥CR</td>
<td>31.8%</td>
<td>9.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

• Median follow-up for KRd: 32.3 months

Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma

A. Keith Stewart, M.B., Ch.B., S. Vincent Rajkumar, M.D., Meletios A. Dimopoulos, M.D., Tamás Masszi, M.D., Ph.D., Ivan Špíčka, M.D., Ph.D., Albert Oriol, M.D., Roman Hafez, M.D., Ph.D., Laura Rosiñoł, M.D., Ph.D., David S. Siegel, M.D., Ph.D., Georgi G. Mihaylov, M.D., Ph.D., Vesselina Goranova-Marinova, M.D., Ph.D., Péter Rajnics, M.D., Ph.D., Aleksandr Suvorov, M.D., Ruben Niesvizky, M.D., Andrezej Jakubowiak, M.D., Ph.D., Jesus F. San-Miguel, M.D., Ph.D., Heinz Ludwig, M.D., Michael Wang, M.D., Vladimir Maisnar, M.D., Ph.D., Jiri Minarik, M.D., Ph.D., William I. Bensinger, M.D., Maria-Victoria Mateos, M.D., Ph.D., Dina Ben-Yehuda, M.D., Vishal Kukreti, M.D., Naseem Zojwalla, M.D., Margaret E. Tonda, Pharm.D., Xinquan Yang, Ph.D., Biao Xing, Ph.D., Philippe Moreau, M.D., and Antonio Palumbo, M.D., for the ASPIRE Investigators®

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ixazomib (MLN 9708) – a first in class oral proteasome inhibitor (PI)

• Ixazomib is the first oral proteasome inhibitor to be studied in the clinic
  – Ixazomib is a peptide boronic acid proteasome inhibitor that has a distinct physicochemical structure and pharmacology compared to bortezomib
  – Preclinical studies indicated synergy with lenalidomide

• An early-phase study of ixazomib plus lenalidomide-dexamethasone (IRd) in newly diagnosed MM:
  – Substantial activity (overall response rate 92%)
  – Tolerable and manageable safety profile, enabling long-term treatment

• Rationale for the phase 3 TOURMALINE-MM1 study assessing IRd (vs. placebo) plus lenalidomide-dexamethasone in patients with relapsed and/or refractory MM
  – IRd: first all-oral triplet regimen containing a proteasome inhibitor and an immunomodulatory drug

Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma


TOURMALINE-MM1 Study Design

Randomization
722 patients

R/R MM Patients

1:1

Ixazomib – Lenalidomide - Dexamethasone
- Ixazomib 4 mg PO Days 1, 8, 15
- Lenalidomide* 25 mg PO Days 1–21
- Dexamethasone 40 mg PO Days 1, 8, 15 and 22
- Repeat every 28 days until disease progression

Placebo - Lenalidomide - Dexamethasone
- Placebo PO Days 1, 8, 15
- Lenalidomide *25 mg PO Days 1–21
- Dexamethasone 40 mg PO Days 1, 8, 15 and 22
- Repeat every 28 days until disease progression

Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

Select inclusion/exclusion criteria:
- Relapsed and/or refractory MM
- Measurable disease
- Received one to three prior therapies
- ECOG PS 0–2
- Cannot be refractory to proteasome inhibition or lenalidomide

Primary endpoint
PFS

Key secondary endpoints
OS, OS in patients with del (17p)

Secondary endpoints
ORR, CR + VGPR, DOR, TTP, PFS in pts with high-risk cytogenetic abnormalities, AEs

Final PFS analysis: Significant, 35% improvement in PFS with IRd vs placebo-Rd

Hazard ratio, 0.74 (95% CI, 0.59 – 0.94) P = 0.01

No. at Risk
Ixazomib group
Placebo group

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>No. of Events of Progression or Death</th>
<th>Median Progression-free Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo group</td>
<td>157</td>
</tr>
<tr>
<td></td>
<td>Ixazomib group</td>
<td>129</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>20.6</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>14.7</td>
</tr>
<tr>
<td>4</td>
<td></td>
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<td>12</td>
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<tr>
<td>14</td>
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<td>16</td>
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<tr>
<td>18</td>
<td></td>
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<tr>
<td>20</td>
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<tr>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Outcomes by Cytogenetic Risk Group

<table>
<thead>
<tr>
<th>ORR, %</th>
<th>≥VGPR, %</th>
<th>≥CR, %</th>
<th>Median PFS, months</th>
<th>Median TTP, months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRd</td>
<td>Placebo-Rd</td>
<td>IRd</td>
<td>Placebo-Rd</td>
</tr>
<tr>
<td>All patients</td>
<td>78.3*</td>
<td>71.5</td>
<td>48.1*</td>
<td>39</td>
</tr>
<tr>
<td>Standard-risk patients</td>
<td>80</td>
<td>73</td>
<td>51</td>
<td>44</td>
</tr>
<tr>
<td>All high-risk patients</td>
<td>79*</td>
<td>60</td>
<td>45*</td>
<td>21</td>
</tr>
<tr>
<td>Patients with del(17p)†</td>
<td>72</td>
<td>48</td>
<td>39</td>
<td>15</td>
</tr>
<tr>
<td>Patients with t(4;14) alone</td>
<td>89</td>
<td>76</td>
<td>53</td>
<td>28</td>
</tr>
</tbody>
</table>

In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics.
- Median duration of response with IRd vs placebo-Rd was 20.5 vs 11.3 months in high-risk and NE vs 15.0 months in standard-risk patients.
- At a pre-planned analysis for OS (median follow-up ~23 months in the overall study population), OS data were not mature.
- In the IRd vs placebo-Rd arms, 37/199 (19%) vs 47/216 (22%) patients in the standard-risk group, and 15/75 (20%) vs 24/62 (39%) patients in the high-risk group had died.

*p<0.05 for comparison between regimens. †Alone or in combination with t(4;14) or t(14;16). Data not included on patients with t(14;16) alone due to small numbers (n=7).

# PFS in High-risk and Standard-risk Patients.

<table>
<thead>
<tr>
<th></th>
<th>Number of events</th>
<th>Median, months</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ixazomib-Rd</td>
<td>26</td>
<td>21.4</td>
<td>0.543</td>
<td>0.021</td>
</tr>
<tr>
<td>Placebo-Rd</td>
<td>35</td>
<td>9.7</td>
<td>(0.321-0.918)</td>
<td></td>
</tr>
<tr>
<td><strong>Standard-risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ixazomib-Rd</td>
<td>63</td>
<td>20.6</td>
<td>0.640</td>
<td>0.007</td>
</tr>
<tr>
<td>Placebo-Rd</td>
<td>91</td>
<td>15.6</td>
<td>(0.462-0.888)</td>
<td></td>
</tr>
</tbody>
</table>

Log-rank test

Number of patients at risk:

**High-risk**
- Ixazomib-Rd: 75, 74, 70, 66, 62, 59, 57, 52, 45, 42, 40, 34, 26, 22, 21, 18, 14, 13, 9, 7, 3, 2, 1, 0, 0
- Placebo-Rd: 62, 58, 56, 52, 49, 47, 43, 36, 28, 26, 23, 20, 18, 14, 11, 8, 6, 5, 3, 2, 2, 0, 0, 0

**Standard-risk**
- Ixazomib-Rd: 199190183175168157151142138133121106, 81, 64, 60, 50, 34, 29, 19, 14, 10, 4, 3, 1, 0
- Placebo-Rd: 216200190179169164153144136130119, 96, 76, 57, 49, 42, 32, 25, 14, 11, 8, 3, 2, 0, 0

※High-risk: del (17p), t (4;14), and/or t (14;16)

Avet-Loiseau H et al., *Blood*. 2017
PFS in Expanded High-risk Patients

Number of patients at risk:

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ixazomib-Rd</td>
<td>155146139130122114109101 93 89 77 66 50 40 39 34 27 25 14 12 6 3 2 0 0 0 0</td>
</tr>
<tr>
<td>Placebo-Rd</td>
<td>154143135126116112102 90 79 74 66 53 43 30 24 18 14 11 7 4 3 1 0 0 0 0</td>
</tr>
</tbody>
</table>

※Expanded high-risk: Any of del(17p), t(4;14), t(14;16), or 1q21 amplification

Number of events | Median, months | HR (95% CI) | p value |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ixazomib-Rd</td>
<td>62</td>
<td>17.5</td>
<td>0.664 (0.474-0.928)</td>
</tr>
<tr>
<td>Placebo-Rd</td>
<td>83</td>
<td>11.1</td>
<td></td>
</tr>
</tbody>
</table>

Log-rank test

Avet-Loiseau H et al., *Blood*. 2017
Cumulative best responses over time in the ITT population

There is a gap between efficacy in clinical trials and effectiveness in the real-world for pts with RRMM *Pl-IMiD combinations*

Real-world and clinical trial data in relapsed/refractory multiple myeloma (RRMM): evaluating treatment duration and comparing effectiveness and efficacy

Literature review of real-world RRMM data published in the past 10 years (n=47)

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Phase 3 clinical studies</th>
<th>Median PFS/TTNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Real-world reports</td>
</tr>
<tr>
<td></td>
<td>All regimens combined</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Not applicable</td>
<td>6–15.1</td>
</tr>
<tr>
<td>Pl doublet / PI-based‡</td>
<td>Btz: 6.2–9.4</td>
<td>Btz: 5.7–11.9</td>
</tr>
<tr>
<td></td>
<td>Cbz: 14.9–22.2</td>
<td>Cbz: 3.2–9.4</td>
</tr>
<tr>
<td>Pl-alkylator triplet</td>
<td>12–18.4§</td>
<td>16.2</td>
</tr>
<tr>
<td>Injectable Pl-immunomodulatory drug triplet</td>
<td>18.3–29.6</td>
<td>9.4–12.7</td>
</tr>
<tr>
<td>Oral Pl-immunomodulatory drug triplet</td>
<td>17.5–20.6</td>
<td>19.2</td>
</tr>
<tr>
<td>Len doublet / len-based‡</td>
<td>11.1–18.4</td>
<td>6.6–21</td>
</tr>
</tbody>
</table>

Richardson PG et al., ASH2017 Abstract 3149
There is a gap between efficacy in clinical trials and effectiveness in the real-world for pts with RRMM

*Other regimens*

Real-world and clinical trial data in relapsed/refractory multiple myeloma (RRMM): evaluating treatment duration and comparing effectiveness and efficacy

Literature review of real-world RRMM data published in the past 10 years (n=47)

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Phase 2 / 3 clinical studies</th>
<th>Real-world reports</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior therapies</td>
<td>DOT</td>
</tr>
<tr>
<td>Pom-dex</td>
<td>5</td>
<td>4.9</td>
</tr>
<tr>
<td>K-Pom-dex</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Pano-Vd</td>
<td>1–3</td>
<td>5</td>
</tr>
<tr>
<td>Daratumumab-based</td>
<td>4–5</td>
<td>4</td>
</tr>
</tbody>
</table>

Richardson PG et al., ASH2017 Abstract 3149
Targeting Peptidase - Melflufen is a peptidase enhanced therapy with an alkylating payload

1. Amino-peptidases highly over expressed in multiple myeloma (MM) cells

2. Lipophilic melflufen rapidly traverses cell membranes

3. Amino-peptidase potentiated release of hydrophilic alkylating moieties

4. Hydrophilic alkylating moieties trapped inside the cell

5. Melflufen and hydrophilic alkylating moieties binds directly to DNA

Peptidase enhanced activity in MM cells results in:

- Approx. 50-fold higher intra-cellular exposure in MM cells\(^1,5\)
- Approx. 50-fold higher anti-MM potency\(^1,2,5\)
- Alkylation of DNA with limited or no induction of DNA repair\(^3,5\)
- Strong anti-angiogenic properties \(^1,4,5\)
- Therapeutic index of 20 - 40 (MM cells compared with peripheral blood mononuclear cells)\(^1,5\)

O-12-M1 study - Melflufen Phase 2 in RR MM
(Richardson PG et al, ASH 2017)

• RRMM pts with ≥ 2 prior lines of therapy, including lenalidomide and bortezomib
• Disease progression while on therapy or within 60 days of last dose
• Primary end point: ORR according to IMWG criteria

• Phase 1 determined the MTD of melflufen to be 40 mg given i.v. monthly in combination with oral dexamethasone 40 mg weekly (28-day cycles)
• Phase 2 enrolled 45 patients who received 227 doses of melflufen
• Melflufen demonstrated rapid and durable response activity in heavily pre-treated RR MM patients (IMiD and PI exposed and disease progression while on therapy or within 60 days of last dose in their last line of therapy) in RR MM.
• The ORR was 41% and CBR is 65% with median PFS of 5.7 months, and median OS of 20.7 months

• Favorable tolerability - hematologic toxicity was common but clinically manageable, non-hematologic AEs were infrequent
Mateos MV et al ASH 2017: Horizon Study
Rationale

- Clear lack of treatment options in the patient group
- Data suggest considerable clinical benefit of melflufen treatment in patients that are single (IMiD or PI), double (IMiD and PI) and even triple (IMiD, PI and alkylator) refractory
- Side effect profile in this group seems similar as expected for alkylators

=> Melflufen may offer a meaningful benefit with acceptable toxicity profile for patients with heavily pre-treated disease and refractory to pomalidomide and/or daratumumab.
Horizon Treatment schedule

28 day cycles until disease progression

Screening

TREATMENT

Day 1
- 40 mg Melflufen
- 40* mg Dex

Days 8, 15 and 22
- 40* mg Dex

Follow up for PFS and OS for up to 24 months

*Patients over the age of 75 receive 20 mg Dex
2007 MM BJ Kappa
42 years old
- Thal-Dex → CR
  + ASCT
- Bort-Dex x6 → CR
  + 2nd ASCT
- Len – Dex x 20
- VTD x2
- DCEP x 2
- Pom-Dex
- VBCMP/VBAD → SD
  + Allo – SCT
  (June’15)

BJ (mg/dl)

FLCK (mg/L)

Melflufen

Up to 21,000

CS1-ADC

Dara

Pom Bort-Dex

Elo -LD

0 1000 2000 3000 4000 5000 6000 7000 8000 9000 10000
7/15/15 10/23/15 1/31/16 5/10/16 8/18/16 11/26/16 3/6/17 6/14/17 9/22/17 12/31/17

BJ (mg/dl)

FLCK (mg/L)
Waterfall plot of best M-protein change (N=30)

Data cut-off 13 Nov 2017
Swim-lane plot (N=30)

Data cut-off 13 Nov 2017
Safety and tolerability (N=38)

- Grade 3/4 treatment-related AEs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade 3 or 4, n (%)</th>
<th>Grade 4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-related AE</td>
<td>22 (58)</td>
<td>15 (39)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>17 (45)</td>
<td>12 (32)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>15 (39)</td>
<td>9 (24)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3 (8)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (21)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>3 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>2 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data cut-off 13 Nov 2017
Safety and tolerability (N=38)

- Melflufen-related SAEs

<table>
<thead>
<tr>
<th>ADVERSE EVENT TERM</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any melflufen-related SAE</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Soft tissue infection</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Data cut-off 13 Nov 2017
**Melflufen ongoing or planned studies in RR MM**

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Type</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>HORIZON Phase 3</td>
<td>Ongoing randomized comparative study comparing melflufen to standard of care in late-stage RRMM.</td>
</tr>
<tr>
<td>2017</td>
<td>OCEAN Phase 2</td>
<td>Ongoing single arm multi-refractory study.</td>
</tr>
<tr>
<td>2018</td>
<td>HORIZON Phase 1/2</td>
<td>- Triple combination study comparing melflufen to standard of care.</td>
</tr>
<tr>
<td></td>
<td>ANCHOR Phase 3</td>
<td>Recruitment ongoing H2H melflufen vs pomalidomide.</td>
</tr>
<tr>
<td>2019</td>
<td>HORIZON Phase 1/2</td>
<td>recruitment ongoing.</td>
</tr>
<tr>
<td>2020</td>
<td>ANCHOR Phase 3</td>
<td>Planned FPI Q4-17.</td>
</tr>
</tbody>
</table>

**Questions and Comments:**

- **QUESTION ASKED**
  - How does melflufen compare to standard of care in late-stage RRMM?
  - How does melflufen work in RRMM patients with limited treatment options?
  - How is melflufen dosed in triple combinations in RRMM?

- **COMMENT**
  - Recruitment ongoing H2H melflufen vs pomalidomide.
  - Recruitment ongoing for pomalidomide- and/or daratumumab-refractory patients.
  - Planned FPI Q4-17 combination with bortezomib or daratumumab.
Summary: ASH 2017

- Melflufen shows promising activity in this heavily pretreated patient population where patients have a median of 6 prior lines of therapy.

- In the reported data set, 97% of patients have rapid disease progression while on previous therapy or within 60 days of last dose, 100% of patients have stopped responding or are refractory to lenalidomide and PIs, 100% of patients are refractory to pomalidomide or daratumumab and 62% of patients are refractory to pomalidomide and daratumumab.

- Thrombocytopenia and neutropenia are as expected the most common AEs, and non-hematologic AEs are infrequent.

- The ORR and CBR of 27% and 33% respectively are encouraging and patient recruitment continues.
Key Targets in MM 2017

Genomic abnormalities:
- Target and overcome mutations
- Critical Role of Combination Therapy
- Evolving Position and Timing of ASCT

Excess Protein Production:
- Target Protein degradation

Immune Suppression:
- Restore anti-MM immunity
Restoring Immune function

Immunomodulatory drugs, other small molecules (e.g. HDACi’s)

Monoclonal antibodies

Checkpoint inhibitors

Vaccines

Cellular therapies
**Options for 2\textsuperscript{nd}+ Relapse**

Comparison of Pom-Dex Trials (& Combinations)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MM-003\textsuperscript{1}</th>
<th>STRATUS (MM-010)\textsuperscript{2}</th>
<th>Pom-Dex vs Pom-Cyclo-Dex\textsuperscript{3}</th>
<th>Pom-Btz-Dex\textsuperscript{4}</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>302</td>
<td>682</td>
<td>36</td>
<td>47</td>
</tr>
<tr>
<td>Population</td>
<td>Failed Bort &amp; Len &amp; refr to last line</td>
<td>At least 2 prior lines &amp; Len-refractory</td>
<td>1-4 prior lines &amp; Len-refractory</td>
<td></td>
</tr>
<tr>
<td>ORR, %</td>
<td>31</td>
<td>32.6</td>
<td>39</td>
<td>65</td>
</tr>
<tr>
<td>≥VGPR, %</td>
<td></td>
<td></td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>PFS, months</td>
<td>4.0</td>
<td>4.6</td>
<td>4.4</td>
<td>9.5</td>
</tr>
<tr>
<td>OS, months</td>
<td>13.1\textsuperscript{5}</td>
<td>11.9</td>
<td>16.8</td>
<td>NR</td>
</tr>
</tbody>
</table>

### Other Pom/dex Combinations

<table>
<thead>
<tr>
<th>Regimen</th>
<th>POM + Vd&lt;sup&gt;1&lt;/sup&gt;</th>
<th>K + POMdex&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Ixa + POMdex&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Dara + POMdex&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Isa+ POMdex&lt;sup&gt;5&lt;/sup&gt;</th>
<th>MOR202+ POMdex&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM 1–4 mg PO D1–14 + BORT 1 mg/m² IV or 1.3 mg/m² IV or SC C1-8: D1,4,8,11; C9+: D1,8 + LoDex 20 mg (&gt;75 y: 10 mg) C1-8: D1,2,4,5,8,9,11,12; C9+: D1,2,8,9 (n = 34) †</td>
<td>Carfilzomib 20/27/36 mg/m² D1,2,15,16 + POM 3 or 4 mg/day D1–21 + Dex QW 40 mg C1–4 (20 mg C5–8) (n = 46)&lt;sup&gt;‡&lt;/sup&gt; The same combination but K weekly (n = 57)</td>
<td>Ixazomib 3 or 4 mg D1,8,15 + POM 4 mg/day D1–21 + Dex 40 mg D1,8,15,22 (&gt;75 y: 20 mg) (All, n = 32; Ixa 4 mg, n = 25)</td>
<td>Daratumumab 16 mg/kg C1–2 QW; C3–6 Q2W; C7–13 or until PD Q4W + POM 4 mg/day D1–21 + Dex 40 mg (&gt;75 y: 20 mg) (n = 98)</td>
<td>Isatuximab 10 mg/Kg IV C1 QW; Q2W thereafter + POM 4 mg/day D1–21 + Dex 40 mg (&gt;75 y: 20 mg) (n = 14)</td>
<td>MOR202 at dose of 4, 8, 16 mg/kg QW + POM 4 mg/day D1–21 + Dex 40 mg (&gt;75 y: 20 mg) (n = 11)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study phase</th>
<th>I</th>
<th>I/II</th>
<th>I/II</th>
<th>I</th>
<th>I/II</th>
<th>I/II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior lines of therapy, n</td>
<td>1–4</td>
<td>1–5 including PI and Len</td>
<td>≥2 (2–13)</td>
<td>4.5 (2-11)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Refractory to Len, n (%)</td>
<td>All patients were Len-refractory</td>
<td>40 (87)/41(72)</td>
<td>32 (100); 25 (100)</td>
<td>87 (89)</td>
<td>15(75)</td>
<td>11(100)</td>
</tr>
<tr>
<td>Refractory to PI, n (%)</td>
<td>All pts were PI-exposed (but not refractory)</td>
<td>NR</td>
<td>20 (63); 15 (60)*</td>
<td>74 (76)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

| ORR, % | 65 | 64/64 | 44 | 71 | 64 | 56 |
| Median (range) | 7.4 (4.4–9.6) months | NR | 56 (28-160) months | NR | 4 months | - |
| DOR | NR | 12.9/9.2 months | NR | 6-m rate = 66% | - | - |
| Median PFS, months | NR | NR | NR | NR | NR | NR |

Monoclonal Antibodies Kill MM Through Multiple Mechanisms

**DIRECT EFFECTS**
- Interferes with survival or delivers myeloma-killing substances

**INDIRECT EFFECTS**
- Labels myeloma cells for killing by complement
- Labels myeloma cells for killing by NK cells
- Activates T cells by taking the brakes off

Adapted from Richardson PG, ASH 2016
Elotuzumab: Immunostimulatory Mechanism of Action

• Elotuzumab is an immunostimulatory monoclonal antibody that recognises SLAMF7, a protein highly expressed by myeloma and natural killer cells

• Elotuzumab causes myeloma cell death via a dual mechanism of action

ADCC = antibody-dependent cell-mediated cytotoxicity; SLAMF7 = signaling lymphocytic activation molecule F7

Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma

Sagar Lonial, M.D., Meletios Dimopoulos, M.D., Antonio Palumbo, M.D., Darrell White, M.D., Sebastian Grosicki, M.D., Ph.D., Ivan Spicka, M.D., Adam Walter-Croneck, M.D., Philippe Moreau, M.D., Maria-Victoria Mateos, M.D., Ph.D., Hila Magen, M.D., Andrew Belch, M.D., Donna Reece, M.D., Meral Bekzac, M.D., Andrew Spencer, M.D., Heather Oakervee, M.D., Robert Z. Orlowiski, M.D., Masafumi Taniwaki, M.D., Christoph Röllig, M.D., Hermann Einsele, M.D., Ka Lung Wu, M.D., Anil Singhal, Ph.D., Jesus San-Miguel, M.D., Morio Matsumoto, M.D., Jessica Katz, M.D., Ph.D., Eric Bleickardt, M.D., Valerie Poulart, M.Sc., Kenneth C. Anderson, M.D., and Paul Richardson, M.D., for the ELOQUENT-2 Investigators

Phase III ELOQUENT-2 Study: ERd vs. Rd (n=646)

- **Median follow-up:** 24.5 months

### Table: Overall Response Rate and ≥CR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERd</td>
<td>19.4 months</td>
</tr>
<tr>
<td>Rd</td>
<td>14.9 months</td>
</tr>
</tbody>
</table>

### Graph: Probability of PFS

- Probability of PFS (PFS) vs. Months
- Median PFS: 19.4 months for ERd vs. 14.9 months for Rd
- HR 0.70 (95% CI, 0.57-0.85) P<0.001

### Table: Overall Response Rate and ≥CR

<table>
<thead>
<tr>
<th></th>
<th>ERd (n=321)</th>
<th>Rd (n=325)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥PR)</td>
<td>79%</td>
<td>66%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥CR*</td>
<td>4%</td>
<td>7%</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Complete response rates in the ERd group may be underestimated owing to interference from the presence of therapeutic antibody in results on immunofixation and serum protein electrophoresis assays

AE, adverse event; CI, confidence interval; CR, complete response; ERd, elotuzumab, lenalidomide, low-dose dexamethasone; NR, not reported; ORR, overall response rate; PR, partial response; Pts, patients; Rd, lenalidomide, low-dose dexamethasone; Yr, year

Overall Survival: Elotuzumab Rd vs Rd

HR = 0.78 95%CI: (0.63-0.96)

Median OS
- ELd: 483 mos (95%CI: 403-544)
- Ld: 396 mos (95%CI: 333-454)

Patients at risk
- ELd: 321 patients at risk at 1-year, 308 at 2-year, 303 at 3-year, 296 at 4-year
- Ld: 325 patients at risk at 1-year, 288 at 2-year, 283 at 3-year, 270 at 4-year

Dimopoulos et al, EHA 2017
Daratumumab (DARA)

- Human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory MoA\(^1\).
- Approved as monotherapy in many countries for heavily pretreated RRMM.
- Approved in combination with standard of care regimens in RRMM after ≥1 prior therapy in the USA, EU, and other countries.
- DARA induces rapid, deep and durable responses in combination with a PI (bortezomib) or an IMiD (lenalidomide) in RRMM\(^2,3\).

MoA, mechanism of action; RRMM, relapsed/refractory multiple myeloma; CDC, cellular dependent cytotoxicity; ADCC, antibody dependent cellular cytotoxicity; ADCP, antibody dependent cellular phagocytosis; MDSC, myeloid-derived suppressor cell.

Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma


Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

On daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2; RRMM, relapsed or refractory multiple myeloma; ISS, international staging system; R, lenalidomide; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; TTP, time to progression; MRD, minimal-residual disease.

**POLLUX: Study Design**

Multicentre, randomised (1:1), open-label, active-controlled phase 3 study

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**DRd (n = 286)**

- Daratumumab 16 mg/kg IV
  - qw in Cycles 1-2, q2w in Cycles 3-6, then q4w until PD
- R 25 mg PO
  - Days 1-21 of each cycle until PD
- d 40 mg PO
  - 40 mg weekly until PD

**Rd (n = 283)**

- R 25 mg PO
  - Days 1-21 of each cycle until PD
- d 40 mg PO
  - 40 mg weekly until PD

**Primary endpoint**

- PFS

**Secondary endpoints**

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

**Statistical analyses**

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

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**Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg\(^a\), paracetamol, and an antihistamine**

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*On daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2; RRMM, relapsed or refractory multiple myeloma; ISS, international staging system; R, lenalidomide; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; TTP, time to progression; MRD, minimal-residual disease.*

Updated Efficacy; ASH 2016

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

Responses continue to deepen in the DRd group with longer follow-up

HR, hazard ratio; CI, confidence interval; sCR, stringent complete response; PR, partial response.
Note: PFS = ITT population; ORR = response-evaluable population.

HR: 0.37 (95% CI, 0.28-0.50; \( P < 0.0001 \))

ORR, %
- DRd: 93%
- Rd: 76%

≥CR: 46%
- DRd: 23
- Rd: 12

≥VGPR: 78%
- DRd: 32
- Rd: 25

≥VGPR: 45%

Usmani SZ et al, ASH 2016. Oral Presentation and Abstract 1151
Conclusions

• DRd significantly improved outcomes for patients with myeloma
  – 63% reduction in risk of progression or death for DRd vs. Rd
  – Similar findings observed across all analyses in the 1 to 3 prior lines population

• More patients achieve deeper responses including MRD negativity with DRd

• DRd is superior to Rd regardless of time since last therapy refractoriness to last line of therapy or cytogenetic risk

These data support the use of DRd for patients who received ≥1 prior therapy regardless of risk status or refractoriness to prior Tx
### Lenalidomide-based Studies in RR MM

<table>
<thead>
<tr>
<th>POLLUX DRd vs Rd</th>
<th>ASPIRE KRd vs Rd$^1$</th>
<th>ELOQUENT-2 ERd vs Rd$^{2,3}$</th>
<th>TOURMALINE-MM1 NRd vs Rd$^4$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS HR (95% CI)</strong></td>
<td>0.37 ( (0.27-0.52) )</td>
<td>0.69 ( (0.57-0.83) )</td>
<td>0.74 ( (0.59-0.94) )</td>
</tr>
<tr>
<td>ORR</td>
<td>93%</td>
<td>87%</td>
<td>78%</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>76%</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>≥CR</td>
<td>43%</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td>Duration of response, mo</td>
<td>NE</td>
<td>28.6</td>
<td>20.7</td>
</tr>
<tr>
<td><strong>OS HR (95% CI)</strong></td>
<td>0.64 ( (0.40-1.01) )</td>
<td>0.79 ( (0.63-0.99) )</td>
<td>0.77 ( (0.61-0.97) )</td>
</tr>
</tbody>
</table>


K, carfilzomib; E, elotuzumab; N, ixazomib.
Phase III CASTOR Study: DVd vs. Vd (n=498)$^{1,2}$

Updated Efficacy at ASH 2016$^2$

<table>
<thead>
<tr>
<th></th>
<th>DVd (n=240)</th>
<th>Vd (n=234)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥PR)</td>
<td>84%</td>
<td>63%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥CR</td>
<td>26%</td>
<td>10%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>


**Table 1:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVd</td>
<td>Not reached</td>
</tr>
<tr>
<td>Vd</td>
<td>7.1 months</td>
</tr>
</tbody>
</table>

**Figure 1:**

- 12-month PFS$^a$
- Median follow-up: 13 months
- Kaplan-Meier estimate
- AE, adverse event; CI, confidence interval; CR, complete response; DVd, daratumumab, bortezomib, low-dose dexamethasone; HR, hazard ratio; ORR, overall response rate; PFS, progression free survival; PR, partial response; URTI, upper respiratory tract infection; Vd, bortezomib, dexamethasone

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$^a$ Kaplan-Meier estimate

AE, adverse event; CI, confidence interval; CR, complete response; DVd, daratumumab, bortezomib, low-dose dexamethasone; HR, hazard ratio; ORR, overall response rate; PFS, progression free survival; PR, partial response; URTI, upper respiratory tract infection; Vd, bortezomib, dexamethasone
Conclusions

• PFS benefit continues to be maintained with DVd over time

• DVd is superior to Vd regardless of prior lines of therapy

• Largest magnitude of benefit with DVd is observed in patients with 1 prior line of therapy
  – 78% reduction in risk of progression or death for DVd versus Vd

• More patients in DVd achieved deeper responses with longer follow-up
  – Higher CR and MRD-negative rates
  – MRD negativity translated into longer PFS

• DVd is superior to Vd regardless of cytogenetic risk or time since last therapy

• No new safety signals were reported

These data further support the use of this newly approved regimen of DVd in RRMM, with most benefit in patients with 1 prior line of therapy

CR, complete response; DVd, daratumumab, bortezomib, low-dose dexamethasone; MRD, minimal residual disease; Vd, bortezomib, dexamethasone.
## Proteasome Inhibitor-based Studies in RR MM

<table>
<thead>
<tr>
<th></th>
<th>Daratumumab DVd vs Vd</th>
<th>Carfilzomib Kd vs Vd(^1)</th>
<th>Panobinostat PVd vs Vd(^2,3)</th>
<th>Elotuzumab EVd vs Vd(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS HR (95% CI)</strong></td>
<td>0.39 (0.28-0.53)</td>
<td>0.53 (0.44-0.65)</td>
<td>0.63 (0.52-0.76)</td>
<td>0.72 (0.59-0.88)</td>
</tr>
<tr>
<td>PFS, median mo</td>
<td>NE</td>
<td>18.7</td>
<td>12.0</td>
<td>9.7</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>59%</td>
<td>54%</td>
<td>28%</td>
<td>36%</td>
</tr>
<tr>
<td>≥CR</td>
<td>19%</td>
<td>13%</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>Duration of response, mos</td>
<td>NE</td>
<td>21.3</td>
<td>13.1</td>
<td>11.4</td>
</tr>
<tr>
<td><strong>OS HR (95% CI)</strong></td>
<td>0.77 (0.47, 1.26)</td>
<td>0.79 (0.58-1.08)</td>
<td>0.94 (0.78-1.14)</td>
<td>0.61 (0.32-1.15)</td>
</tr>
</tbody>
</table>

DARA Plus Rd or Vd in RRMM: Updated PFS (ASCO 2017)

**POLLUX (ITT)**
Median follow-up: 25.4 months

- 24-month PFS\(^a\) 68%
- Median PFS: 17.5 mos
- HR, 0.41 (95% CI, 0.31-0.53; \(P<0.0001\))

**CASTOR (1 prior line)**
Median follow-up: 19.4 months

- 18-month PFS\(^a\) 68%
- Median PFS: 7.9 mos
- HR, 0.19 (95% CI, 0.12-0.29; \(P<0.0001\))

SOC, standard of care; ITT, intent-to-treat; DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.

\(^a\)Kaplan-Meier estimates.

Exploratory analyses based on clinical cut-off: January 11, 2017 for CASTOR; March 7, 2017 for POLLUX.

PFS According to MRD Status at $10^{-5}$

- Lower risk of progression in MRD-negative patients
- PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care

Avet-Loiseau al, ASH 2016
Efficacy by Cytogenetic Risk Status for Daratumumab With Lenalidomide and Dex or Bortezomib and Dex in Relapsed or Refractory Multiple Myeloma

- First prospective assessment of cytogenetic status by NGS in phase 3 studies
- DARA plus standard of care showed significant benefit in both high-risk and standard-risk patients in terms of PFS, ORR, and MRD-negative rates
- In high-risk patients, MRD negativity was achieved only with DARA
- Preliminary data indicate possible OS benefit of DARA; longer follow-up is needed

San Miguel et al, EHA 2017
Where Do We Envision Using Daratumumab?

Will we use daratumumab as Rituximab is used in NHL?
DARA – Future Considerations and Next Steps

• Better understanding of the immunomodulatory effects of Dara combination regimens: ASH 2017
• While significantly number of pts achieve MRD neg, durability and significance of MRD is still not known: ASH 2017
• Combo of Dara plus RVD, KRD with ASCT under evaluation (GRiffin and others)
• Stem cell harvest is not impacted by DARA plus RVd, KRd or VTD, but the ph3 studies will determine this for sure…
• How will Dara plus PD-1/PDL-1 data look? Early data suggests synergy with favorable safety: ASH 2017
• Can Dara be combined with CAR-T and/or anti-BCMA?
• Alcyone (D-VMP) and Maia (DRD): data anticipated 2017/2018
• Dara SC + hylauridanase in smaller volumes: ASH 2017
Phase Ib Study of Isatuximab+Pom+dex in RRMM

Modes of action of isatuximab

**Tumor cell targeting**

**Immunomodulatory**

**Innate immunity**

**Apoptosis**

**CD38 inhibition**

**NK/Mφ activation**

**Immune-depletion**

**Adenosine inhibition**

ADCC/CP, antibody-dependent cellular cytotoxicity/phagocytosis; CDC, complement-dependent cytotoxicity; Mφ, macrophage; MDSC, myeloid-derived suppressor cell; NK, natural killer cell; Pom, pomalidomide; RRMM, relapsed refractory multiple myeloma.

Richardson P et al. *ASH 2016. Poster Presentation and Abstract 2123*
Reductions in paraprotein levels were recorded in the majority of patients.

Waterfall plot of best percentage change in paraprotein levels

Post-baseline paraprotein data were not available for one patient in the 5 mg/kg cohort. QW, weekly; Q2W, once every 2 weeks.
Phase Ib Study of Isatuximab+Pom+dex in RRMM (n=20)

Time on treatment by best confirmed response (at least PR)

- Seven patients who achieved at least PR remained on treatment at data cutoff.

CR, complete response; PR, partial response; QW, weekly; Q2W, once every 2 weeks; VGPR, very good partial response.

Richardson P et al. *ASH 2016. Poster Presentation and Abstract 2123*
Author's Conclusions

• The combination of isatuximab with Pom/Dex is generally well tolerated in patients with RRMM
  • The AEs observed are generally consistent with the known safety profiles of the individual agents

• IARs were all Gr 1/2 in intensity and tended to occur with the first infusion.

• The PK parameters of isatuximab do not appear to be affected by Pom/Dex co-administration.

• The combination of isatuximab with Pom/Dex was clinically active in this heavily pretreated patient population
  • Confirmed ORR was 64%; confirmed ORR with isatuximab 10 mg/kg was 67%
  • Confirmed ORR in IMiD-refractory patients was 64%

• The MTD for this combination was not reached at the highest isatuximab dose level tested; 10 mg/kg was the selected dose for the expansion cohort based on these preliminary clinical, efficacy, safety, and PK data

• A global Phase III study of isatuximab plus Pom/Dex is planned to start in 2016

AEs, adverse events; Dex, dexamethasone; IARs, infusion adverse reactions; MTD, maximum tolerated dose; ORR, overall response rate; PK, pharmacokinetic; Pom, pomalidomide; RRMM, relapsed refractory multiple myeloma.

Richardson P et al. ASH 2016. Poster Presentation and Abstract 2123
ASH 2017: 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, Nikoletta Lendvai², Rakesh Popat³, Peter M. Voorhees⁴, Brandi Reeves⁵, Edward N. Libby⁶, Paul G. Richardson⁷, Larry D. Anderson Jr⁸, Heather J. Sutherland⁹, Kwee Yong³, Axel Hoos¹⁰, Michele M. Gorczyca¹⁰, Soumi Lahiri¹⁰, Zangdong He¹⁰, Daren Austin¹⁰, Joanna Opalinska¹⁰, Adam D. Cohen¹¹

¹Princess Margaret Cancer Centre Toronto, Ontario, Canada; ²Memorial Sloan-Kettering Cancer Center, New York, NY, USA; ³University College London Hospitals NHS Foundation Trust, London, UK; ⁴Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA; ⁵Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA; ⁶University of Washington, Seattle WA, USA; ⁷Dana-Farber Cancer Institute, Boston, MA, USA; Canada; ⁸University of Texas Southwestern, Dallas, TX, USA; ⁹Vancouver General Hospital, Vancouver, BC, Canada; ¹⁰GlaxoSmithKline, USA/UK; ¹¹Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA
**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

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

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![Diagram showing mechanisms of action](image)

**GSK2857916**

<table>
<thead>
<tr>
<th><strong>Toxin</strong></th>
<th>MMAF (non-cell permeable, highly potent auristatin)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Afucosylation</strong></td>
<td>Enhanced ADCC</td>
</tr>
<tr>
<td><strong>Linker</strong></td>
<td>Stable in circulation</td>
</tr>
</tbody>
</table>

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

**Part 1 completed**

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03</td>
<td>n=1</td>
</tr>
<tr>
<td>0.06</td>
<td>n=1</td>
</tr>
<tr>
<td>0.12</td>
<td>n=4</td>
</tr>
<tr>
<td>0.24</td>
<td>n=4</td>
</tr>
<tr>
<td>0.48</td>
<td>n=4</td>
</tr>
<tr>
<td>0.96</td>
<td>n=3</td>
</tr>
<tr>
<td>1.92</td>
<td>n=4</td>
</tr>
<tr>
<td>3.4</td>
<td>n=3</td>
</tr>
<tr>
<td>4.6</td>
<td>n=6</td>
</tr>
</tbody>
</table>

**N=38**

**Additional dose evaluation**

**n=8**

**Part 2 ongoing**

**Cohort 1**: 3.4 mg/kg (enrollment completed)  **N=35**

**Cohort 2**: 3.4 mg/kg (enrollment ongoing)  **N=6/10**

DREAMM-1 Part 2: Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Part 2 (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (min, max)</td>
<td>60 (46–75)</td>
</tr>
<tr>
<td>Females/males, %</td>
<td>51/49</td>
</tr>
<tr>
<td>≥5 prior lines, n (%)</td>
<td>20 (57)</td>
</tr>
<tr>
<td>ASCT</td>
<td>31 (89)</td>
</tr>
<tr>
<td><strong>IMiDs</strong></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>35 (100)</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>33 (94)</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>21 (60)</td>
</tr>
<tr>
<td><strong>Refractory to IMiD</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32 (91)</td>
</tr>
<tr>
<td><strong>PI</strong></td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>35 (100)</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>34 (97)</td>
</tr>
<tr>
<td><strong>Refractory to PI</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34 (97)</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>14 (40)</td>
</tr>
<tr>
<td><strong>Refractory to daratumumab</strong></td>
<td>13 (37)</td>
</tr>
<tr>
<td><strong>Refractory to IMiD/PI</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31 (89)</td>
</tr>
<tr>
<td><strong>Refractory to IMiD/PI and prior daratumumab</strong></td>
<td>12 (34)</td>
</tr>
<tr>
<td>Cytogenetics risk, n (%)*</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>20 (58)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (43)</td>
</tr>
<tr>
<td>Missing</td>
<td>11 (31)</td>
</tr>
</tbody>
</table>

*Patients with any of the following genetic abnormalities were considered high risk: t(4:14), del3; del17, t(14:16), t(14:20) or gain 1q. Multiple categories per subject possible: total may exceed 100%.

ASCT, autologous stem cell transplant; IMiD, immunomodulator; PI, proteasome inhibitor.
DREAMM-1 Part 2: Maximum % Reduction in M-Protein or Free Light Chain from Baseline

ORR = 21/35 (60%; 95% CI: 42.1%, 76.1%)
• 1 sCR, 2 CR, 15 VGPR, 3 PR

*One patient with a VGPR had a <90% reduction in serum M-protein due to missing laboratory data, which was confirmed by investigators as too small to quantify after the data cut-off

Cl, confidence interval; CR, complete response; FLC, free light chain; M-protein, myeloma protein; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response
DREAMM-1 Part 2: Efficacy – Overall Response Rate

<table>
<thead>
<tr>
<th></th>
<th>sCR</th>
<th>CR</th>
<th>VGPR</th>
<th>PR</th>
<th>NE</th>
<th>ORR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 2 (N=35)</td>
<td>3 (n=1)</td>
<td>6 (n=2)</td>
<td>43 (n=15)</td>
<td>9 (n=3)</td>
<td>9 (n=3)</td>
<td>60 (n=21)</td>
</tr>
<tr>
<td>Prior daratumumab (N=14)</td>
<td>7 (n=1)</td>
<td>0</td>
<td>21 (n=3)</td>
<td>14 (n=2)</td>
<td>14 (n=2)</td>
<td>43 (n=6)</td>
</tr>
<tr>
<td>Refractory to both IMiD and PI (N=31)</td>
<td>3 (n=1)</td>
<td>6 (n=2)</td>
<td>42 (n=13)</td>
<td>6 (n=2)</td>
<td>10 (n=3)</td>
<td>58 (n=18)</td>
</tr>
<tr>
<td>Refractory to IMiD, PI and prior daratumumab (N=12)</td>
<td>8 (n=1)</td>
<td>0</td>
<td>25 (n=3)</td>
<td>8 (n=1)</td>
<td>17 (n=2)</td>
<td>42 (n=5)</td>
</tr>
</tbody>
</table>

Note: subjects with NE discontinued treatment after one or two doses
*Any discrepancies in % due to rounding error

CR, complete response; IMiD, immunomodulator; NE, not evaluable; ORR, overall response rate; PI, proteasome inhibitor; PR, partial response; sCR, stringent complete response; VGPR, very good partial response
Median duration of follow-up was 6.6 months

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response
DREAMM-1 Part 2: Efficacy – Progression-free Survival and duration of response

Number of subjects
- Progressed or died: 15 (43%)
- Censored, f/u ended: 3 (9%)
- Censored, f/u ongoing: 17 (49%)

Progression-free survival (months)
- Q1 (95% CI): 2.3 (0.7, 6.8)
- Median (95% CI): 7.9 (3.1, -)
- Q3 (95% CI): N/A

Number of subjects
- Progressed or died: 4 (19%)
- Censored, f/u ended: 0
- Censored, f/u ongoing: 17 (81%)

Duration of response (months)
- Q1 (95% CI): 6.7 (1.6, -)
- Median (95% CI): N/A
- Q3 (95% CI): N/A

CI, confidence interval; f/u, follow-up; N/A, not available; Q, quartile
Conclusions

– Median time of follow-up was 6.6 months; the study is ongoing with the Part 2 cohort still receiving therapy

– GSK2857916 resulted in an ORR of 60% in heavily pre-treated patients with MM
  – 51% of patients in Part 2 had VGPR or better

– Median PFS was 7.9 months and DOR was not estimable as only 4 responders had progressed at the time of the data cut-off. The 25th percentile for DOR is 6.7 months.

– GSK2857916 was well tolerated and side effects were manageable
  – Thrombocytopenia and corneal events emerged as the most frequent AEs and reasons for dose modification
  – IRRs occurred in only 23% of patients and without pre-medication; no IRRs occurred on subsequent infusions

– The target and therapeutic mechanisms of action differentiate GSK2857916 from currently approved drugs in MM

– Additional monotherapy and combination studies are planned

DOR, duration of response; IRR, infusion-related reaction; MM, multiple myeloma; ORR, overall response rate; PFS, progression-free survival; VGPR, very good partial response
Harnessing the Immune System to Fight Myeloma:

Types of Immunotherapy, Immuno-Oncology

Passive

Monoclonal antibodies

Direct effects

Antigen

Monoclonal antibody

Myeloma cell

CDC

C1q

MAC

Cell death

Fc receptor

ADCC

Lysis

NK cell

Active

Chimeric antigen receptor (CAR) T cells

1. Extract WBCs from patient

2. Modify and expand cells in lab

3. Infuse MM-targeted cells back to patient

Vaccines (therapeutic not preventive)

Richardson PG et al, ASH 2017
Myeloma CAR therapy: ASH 2017

- Multiple promising targets:
  - CD19, CD138, **CD38**, CD56, kappa, Lewis Y, CD44v6, **CS1 (SLAMF7)**, BCMA

- Functional CAR T cells can be generated from MM patients

- CAR T and NK cells have in vitro and in vivo activity against MM

- Clinical trials underway
  - Anecdotal prolonged responses but no robust efficacy data available yet

- Many questions remain about CAR design:
  - optimal co-stimulatory domains
  - optimal vector
  - optimal dose and schedule
  - need for chemotherapy
  - Perhaps ‘cocktails’ of multiple CARs or CARs + chemotherapy will be required for best outcomes
### CAR T Cells in Development for Myeloma 2017

<table>
<thead>
<tr>
<th>Institution</th>
<th>α-CD19-BBz</th>
<th>α-Kappa-28z</th>
<th>α-CD138-28z</th>
<th>α-BCMA-28z</th>
<th>α-BCMA-BBz</th>
<th>α-BCMA-BBz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Institution</strong></td>
<td>Penn</td>
<td>Baylor</td>
<td>Chinese PLA General Hospital</td>
<td>NCI</td>
<td>Penn</td>
<td>bluebird bio</td>
</tr>
<tr>
<td><strong>scFV Clone</strong></td>
<td>FMC63</td>
<td>CRL-1758</td>
<td>NK-92</td>
<td>11D5-3</td>
<td>ND</td>
<td>bb2121</td>
</tr>
<tr>
<td><strong>scFV Origin</strong></td>
<td>Murine</td>
<td>Murine</td>
<td>Murine</td>
<td>Murine</td>
<td>Human</td>
<td>Humanized</td>
</tr>
<tr>
<td><strong>Gene Transfer System</strong></td>
<td>Lentivirus</td>
<td>Retrovirus</td>
<td>Lentivirus</td>
<td>Retrovirus</td>
<td>Lentivirus</td>
<td>Lentivirus</td>
</tr>
<tr>
<td><strong>Intracellular Domain</strong></td>
<td>4-1BB ICD-CD3zeta</td>
<td>CD28 ICD-CD3zeta</td>
<td>CD28 ICD-CD3zeta</td>
<td>CD28 ICD-CD3zeta</td>
<td>4-1BB ICD-CD3zeta</td>
<td>4-1BB ICD-CD3zeta</td>
</tr>
<tr>
<td><strong>Patients Treated</strong></td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>12</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td><strong>Dose(s)</strong></td>
<td>1e7-5e7 CARTs/pt</td>
<td>0.2-2e8 CARTs/m2</td>
<td>0.44-1.5e7 CARTs/kg</td>
<td>0.3-9e6 CARTs/kg</td>
<td>1e7-5e8 CARTs/pt</td>
<td>5-80e7 CARTs/pt</td>
</tr>
<tr>
<td><strong>Best Response (number of patients)</strong></td>
<td>CR (1), VGRP (6), PR (2), PD (2)</td>
<td>SD (5), NR (3)</td>
<td>SD (4), PD (1)</td>
<td>Stringent CR (1), VGRP (2), PR (1), SD (8)</td>
<td>Stringent CR (1), VGRP (1), SD (1), MR (2), PD (1)</td>
<td>Stringent CR (2), VGRP (1), PR (4), SD (1), PD (1)</td>
</tr>
<tr>
<td><strong>Reference(s)</strong></td>
<td>25</td>
<td>27</td>
<td>26</td>
<td>28</td>
<td>29</td>
<td>ASH 2016 Abstract</td>
</tr>
</tbody>
</table>
Safety and Efficacy of B-Cell Maturation Antigen (BCMA)-Specific Chimeric Antigen Receptor T cell (CART-BCMA) with Cyclophosphamide Conditioning for Refractory Multiple Myeloma (MM)


ASH 2017
Study design

- **Cohort 1**: $1 - 5 \times 10^8$ CAR+ T cells (n=3-6) → expansion
- **Cohort 2**: Cytox 1.5 g/m² + $1 - 5 \times 10^7$ CAR+ T cells (n=3-6) → expansion
- **Cohort 3**: Cytox 1.5 g/m² + $1 - 5 \times 10^8$ CAR+ T cells (n=3-6) → expansion

4 week delay between subjects

- **24 treated**
  - 9 in cohort 1: $1 - 5 \times 10^8$ CART-BCMA (no lymphodepleting chemo)
  - 5 in cohort 2: Cytox + $1 - 5 \times 10^7$ CART-BCMA
  - 10 in cohort 3: Cytox + $1 - 5 \times 10^8$ CART-BCMA

- All successfully manufactured at least minimum target dose
  - 1 required 2 collections
  - Median transduction efficiency=17.4% (7.5 – 33.3%)

- 20/24 got 100% of planned dose
  - 4 got 40% due to fevers/CRS on day 2
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Cohort 1 (n=9)</th>
<th>Cohort 2 (n=5)</th>
<th>Cohort 3 (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytokine release syndrome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grade</td>
<td>8 (89%)</td>
<td>3 (60%)</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Penn Grade 3/4</td>
<td>3 (33%)</td>
<td>0 (0%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Toci/Siltux used</td>
<td>4 (44%)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td><strong>Neurotoxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grade</td>
<td>3 (33%)</td>
<td>0 (0%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>2 (22%)</td>
<td>0 (0%)</td>
<td>1 (10%)</td>
</tr>
</tbody>
</table>
- Responses: ≥PR in 11/24 (47%)
  - 4 ongoing at 3+, 3+, 6+ and 24+ months
  - 1-5 x10^8 dose more active
  - Not clearly associated with baseline BCMA expression or sBCMA concentration
- Decreased BCMA expression may be escape mechanism
CRB-401 Phase 1 Study in Relapsed / Refractory Multiple Myeloma

• Objectives: Determine preliminary safety and efficacy and recommended phase 2 dose

ASH 2017

9 U.S. Clinical Sites, 1 Centralized Manufacturing Site
bb2121 is a second-generation CAR construct targeting BCMA, consisting of autologous T cells transduced with a lentiviral vector encoding a novel CAR incorporating an anti-BCMA scFv, a 4-1BB costimulatory motif to promote proliferation and persistence, and a CD3ζ T cell activation domain.
CRB-401 Study Design and Status

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

Leukapheresis
Screening

bb2121 manufacturing Manufacturing (10 days) + release
bb2121 infusion

1st Response Assessment (Wk 4)

Sample collection for T cell expansion & collection

Day 0

Flu 30 mg/m^2
Cy 300 mg/m^2
Days -5,-4,-3

BM BX (Wk 2)
BM BX (Wk 4)

Study Status (Escalation)

Cells Collected
N=24

Dosed
N=21

Evaluable for Response
N=21

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
Neurotoxicity includes the preferred terms: depressed level of consciousness, confusional state, bradyphrenia.

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Overall n (%)</th>
<th>Grade 3 or higher n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome</td>
<td>15 (71)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>5 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18 (86)</td>
<td>18 (86)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (52)</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Anemia</td>
<td>14 (67)</td>
<td>12 (57)</td>
</tr>
</tbody>
</table>
Dose Escalation: Cytokine Release Syndrome

- **CRS generally manageable**
  - Mostly Grade 1-2
  - 2 patients with Grade 3 CRS that resolved in 24 hours
  - 4 patients received tocilizumab, 1 with steroids
- **Cytokine elevation highest in pts with Grade 3 CRS**

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

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

- **IFNγ**
- **IL-6**
- **TNFα**
- **CRP**
Reversible Life Threatening Grade 4 Neurotoxicity (PRESS) Associated with Rapid Myeloma Response in One Patient with Low BCMA Expression (Expansion Cohort)
• 17/18 (94%) ORR at active doses ⭐️
• 9/10 evaluable patients MRD negative
• Durable ongoing responses over 1 year
• Median PFS not reached in active dose cohorts
  – 4 patients progressed
  – Median follow up 40 weeks
Clinical Response: Deepening of Response over Time (ASH 2017)

Dose Escalation: Cohorts $\geq 150 \times 10^6$ CAR T Cells (N=18)

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

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

Objective Response Rate
Subjects Treated in Escalation – Cohorts $\geq 150 \times 10^6$

| ORR=100% | 27 | ≥CR | 27% |
| ORR=94%  | 56 | ≥CR | 56% |
| ≥VGPR 74% | 47 | ≥VGPR | 74% |
| ≥VGPR 89% | 33 | ≥VGPR | 89% |
| PR       |   | PR |     |

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

04 MAY 2017 (N=15) 02 OCT 2017 (N=18)
NR, not reached
Preliminary Characteristics of Patients Who Progressed

- No evidence of BCMA expression loss at disease progression (N = 3 evaluable)
- Progression to date is independent of:
  - Tumor burden
  - bb2121 dose
  - CRS
  - bb2121 persistence

<table>
<thead>
<tr>
<th>Subject</th>
<th>Tumor Burden*</th>
<th>Dose (10^6 CAR T cells)</th>
<th>Best Response</th>
<th>Time to progression (mos)</th>
<th>% CD138+ cells expressing BCMA by IHC (Prescreen / PD)</th>
<th>CRS (Max Grade)</th>
<th>Detectable Vector at Last Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Low</td>
<td>450</td>
<td>VGPR</td>
<td>11</td>
<td>80% / 60%</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>Low</td>
<td>150</td>
<td>VGPR</td>
<td>6</td>
<td>80% / 10%</td>
<td>No events</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>High</td>
<td>450</td>
<td>VGPR</td>
<td>9</td>
<td>80% / NE</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td>19</td>
<td>Low</td>
<td>150</td>
<td>SD</td>
<td>1</td>
<td>50% / 40%</td>
<td>No events</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Tumor Burden*
MM 2017: Integration and Impact of Novel Agents

• Innovations (PIs, IMiDs) to date have produced significant improvements in PFS, OS: recent approvals (e.g. Carfilzomib, Ixazomib, HDACi, MoAbs) will augment this, with the next wave of therapies agnostic to mutational thrust

• Baseline immune function appears a key barrier to success and is targetable (e.g. use of PD1/PDL1 blockade)

• MoAbs (Elo, DARA, ISA, MOR 202) active in high risk disease, represent true new novel mechanisms, as well as other immuno-therapeutics (e.g. checkpoint inhibitors, vaccines)

• New insights to mechanisms of drug action (e.g. IMiDs, Ixazomib, Marizomib, Panobinostat, AC 241) will further expand therapeutic opportunities

• Numerous other small molecule inhibitors, targeted chemotherapeutics show promise (e.g. HDACi’s, CXCR4, BCL, AKT, CDK, HSP 90, Nuclear Transport, KSP, BET bromodomain proteins/Myc, DUBs, MEK, melflufen) – with nelfinavir, venetoclax, melflufen and selexinor showing promise moving forward into advanced phase studies

• Further refinement of prognostics and MRD will guide therapy
The Impact Of Novel Therapies in MM ~ Case Report

2009 –
Patient DG, age 62 years
High Risk IgG kappa MM
DSS 3, ISS 2,
Elevated LDH
17 del positive ,
13 del positive (by FISH) PMH – HTN, nil else.

RD + Zometa => RVD (VGPR) Well tolerated, minimal PN (G1)

2010 ASCT (CY – HDM) (CR)
R/Z maintenance

2011 PD – RVD (PR)

2012 PD – PomVD (VGPR)

2013 PD (aggressive relapse with extra-medullary disease) DARA [501] 16 mg/kg (CR) to present (> 4 years) “Best I have ever felt since prior to diagnosis”
Continuing Evolution of Multiple Myeloma Treatment: Selected New Classes and Targets 2016-2017

1st Generation Novel Agents

- Lenalidomide
- Thalidomide
- Bortezomib
- Bortezomib + Doxil

2nd Generation Novel Therapies/Immunotherapy

- Carfilzomib
- Pomalidomide
- Panobinostat
- Elotuzumab
- Ixazomib
- Daratumumab
- Isatuximab*

3rd Generation IMiDs*

- Melflufen*
- Selexinor*
- Venetoclax*
- Nelfinavir*

Not yet FDA-approved for MM; available in clinical trials

*Not yet FDA-approved for MM
Ongoing MM Collaborative Model for Rapid Translation From Bench to Bedside

Pharmaceuticals

Advocacy
MMRF/C; IMF
IMWG; LLS
IMS

Academia

Progress and Hope

NIH
NCI

FDA
EMEA

22 new FDA-approved drugs/combos/indications in last 14 yrs
