WELCOME & INTRODUCTIONS
Multiple Myeloma: Understanding My Treatment Options

Welcome to LLS Community
We are a community of blood cancer patients, survivors and caregivers. We’re here to support you, give you trusted information and resources, and help you feel connected. No one should have to face a blood cancer diagnosis alone.

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Program will begin shortly

THE CHANGING LANDSCAPE OF MYELOMA TREATMENT
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Duarte, CA
DISCLOSURES
Multiple Myeloma: Understanding My Treatment Options

Consultant:
- Celgene, Janssen, Adaptive

Speakers Bureau:
- Celgene, Takeda

History of Myeloma

- 3300 BC - Pre-Columbian America
- 3200-500 BC - Egyptian mummies – Thebe
- 200-1300 AD - American Indian Skeletons
- 11th-15th Century AD - Iceland
First descriptions...

Sarah Newbury, 39 F

- 1840: Severe back pain while stooping
- April 1842: Fractured femurs
- April 15, 1844: St. Thomas Hospital
- Rx: Orange peel infusion, rhubarb pills, arrow-root, mutton chop, wine, a pint of Porter and opiates
- April 20, 1844: Death

Solly S, Med Chir Trans Lond 27:435, 1844

Sarah Newbury: Autopsy

- Multiple fractures
- Thorax reduced in size with compression of lungs
- Bone marrow: Modena red with round or oval cells with 1 or 2 nuclei

The disease began with a “morbid action of the blood vessels in which the earthy matter of the bone marrow is absorbed and thrown out by the kidneys in the urine”

Samuel Solly, 1844
Myeloma

- MM is characterized by
  - Excessive numbers of abnormal plasma cells in the bone marrow
  - Overproduction of intact monoclonal immunoglobulins (IgG, IgA, IgD, or IgE) or Bence-Jones protein (free antibody light chains) and concomitant drop in other immunoglobulins

Serum Protein Electrophoresis

- Normal
- Monoclonal Protein in Myeloma

Reproduced with permission from the Multiple Myeloma Research Foundation Web site. Available at: http://www.multiplemyeloma.org/about_myeloma/index.html

Kyle RA and Rajkumar SV. Cecil Textbook of Medicine, 22nd Edition, 2004
Immunofixation to Determine Type of Monoclonal Protein

IgG kappa M protein

Lambda Light Chains

Clinical Manifestations of Symptomatic Multiple Myeloma

- Renal compromise (30%)
- Neuropathy (33%)
- Infection (15%)
- Hypercalcemia (15% to 20%)
- Bone pain (75% to 80%)
- Lytic lesions (70%)
- Anemia (70%)

Initial Diagnostic Evaluation

<table>
<thead>
<tr>
<th>Evaluation</th>
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<tbody>
<tr>
<td><strong>History and physical</strong></td>
</tr>
<tr>
<td>Blood workup</td>
</tr>
<tr>
<td>CBC with differential and platelet counts</td>
</tr>
<tr>
<td>BUN, creatinine</td>
</tr>
<tr>
<td>Electrolytes, calcium, albumin, LDH</td>
</tr>
<tr>
<td>Serum quantitative immunoglobulins</td>
</tr>
<tr>
<td>Serum protein electrophoresis and immunofixation</td>
</tr>
<tr>
<td>β2-M</td>
</tr>
<tr>
<td>Serum free light chain assay</td>
</tr>
<tr>
<td>Urine</td>
</tr>
<tr>
<td>24-hr protein</td>
</tr>
<tr>
<td>Protein electrophoresis (quantitative Bence-Jones protein)</td>
</tr>
<tr>
<td>Immunofixation electrophoresis</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Skeletal survey</td>
</tr>
<tr>
<td>Unilateral bone marrow aspirate and biopsy evaluation with immunohistochemistry or flow cytometry, cytogenetics, and FISH</td>
</tr>
<tr>
<td>MRI and PET/CT as clinically indicated</td>
</tr>
</tbody>
</table>

Induction Therapy

- Combination therapy with 3 drugs is standard for fit patients, true also for patients with renal failure
- Ongoing trials are investigating 4-drug combinations
- Which three drugs?
- Goal of therapy; MRD?
SWOG S0777: Study Design

Eight 21-day cycles of VRd
Bortezomib 1.3 mg² IV
Days 1, 4, 8, and 11
Lenalidomide 25 mg/day PO
Days 1–14
Dexamethasone 20 mg/day PO
Days 1, 2, 4, 5, 8, 9, 11, 12

Rd maintenance
until PD, toxicity,
or withdrawal

Lenalidomide 25 mg
PO days 1–21
Dexamethasone 40 mg
PO days 1, 8, 15, 22

Six 28-day cycles of Rd
Lenalidomide 25 mg/day PO
Days 1–21
Dexamethasone 40 mg/day PO
Days 1, 8, 15, 22

- All patients received aspirin 325 mg/day
- VRd patients received HSV prophylaxis

SWOG study was not specifically conducted in elderly patients with newly diagnosed MM

VRD lite: Bz SQ/w & Rd × 9 c followed by 6 BzR consolidation resulted in ORR of 86% (66% ≥ VGPR).
Median PFS: 35 m; median OS: not reached

Durie B et al. Blood. 2015;126 Abstract25
Trial design

NDMM patients, transplant-eligible and younger than 65 years

Endpoint 1: VGPR rate after induction

4x KCd
K: 30 mg²/m² d 1,2,9,15-16
C: 800 mg²/m² d 1,8,14
R: 20 mg d 1-21
R: 25 mg d 1-21
R: 30 mg d 1,2,9,15-16,22-23

4x KRd
K: 30 mg²/m² d 1,2,9,15-16
R: 20 mg d 1-21
R: 30 mg d 1,2,9,15-16,22-23

Single ASCT

Intensification with high-dose melphalan followed by autologous stem-cell rescue

Endpoint 2: VGPR, sCR, MRD rate pre-maintenance

4x KCd
K: 20 mg²/m² d 1,2,9,15-16
C: 300 mg²/m² d 1,8,14
R: 20 mg d 1-21
R: 29 mg d 1,2,9,15-16,22-23

4x KRd
K: 30 mg²/m² d 1,2,9,15-16
R: 20 mg d 1-21
R: 29 mg d 1,2,9,15-16,22-23

R1
KRd: 1:1:1

R2
1:1

KR
K: 30 mg²/m² d 1,2,9,15-16
R: 15 mg d 1-21
R: 13 mg d 1-21

Pre-maintenance response rate and MRD negativity

ITT analysis

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>P value*</th>
</tr>
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<tbody>
<tr>
<td>2VGPR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRd ASCT vs KCd ASCT</td>
<td>2.53</td>
<td>0.004</td>
</tr>
<tr>
<td>KRd12 vs KCd ASCT</td>
<td>2.11</td>
<td>0.015</td>
</tr>
<tr>
<td>sCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRd ASCT vs KCd ASCT</td>
<td>1.65</td>
<td>0.035</td>
</tr>
<tr>
<td>KRd12 vs KCd ASCT</td>
<td>1.00</td>
<td>0.048</td>
</tr>
</tbody>
</table>

MRD neg (10⁻⁵) *

<p>| | | |</p>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>KRd ASCT vs KCd ASCT</td>
<td>2.02</td>
<td>0.009</td>
</tr>
<tr>
<td>KRd12 vs KCd ASCT</td>
<td>1.73</td>
<td>0.042</td>
</tr>
</tbody>
</table>

*ORs: Patients whose samples were not available (~10%) were considered as positive. Adjusted for ISS, age, FISH, LDH.

^Pre-maintenance response rate and MRD negativity

10² mg²/m² d 1-2, cycle 1 only. ‘A tolerated 10 mg²/m² d 1-2, every 28 days up to 2 years for patients who have started the maintenance treatment from 6 months before the approval of lenalidomide 25 mg²/m² d 1-28 (lenalidomide 25 mg²/m² d 1-28).’
Persistent 1-year MRD negativity rate

"Second-generation flow cytometry", sensitivity 10⁻⁵

For KRd_ASCT 10 pts evaluable for persistent MRD negativity at 1 year have R-ISS not available due to missing FISH or LDH data
For KRd_12 11 pts evaluable for persistent MRD negativity at 1 year have R-ISS not available due to missing FISH or LDH data


All evaluable patients (N=72)

KRd_ASCT

1-year Persistent
MRD neg
90%

KRd_12

All evaluable patients (N=64)

1-year Persistent
MRD neg
78%

Persistent 1-year MRD negativity rate

Selected 4-Drug Combinations Being Studied in Newly Diagnosed Myeloma

<table>
<thead>
<tr>
<th>4-Drug Combo</th>
<th>4th Drug</th>
<th>Selected supportive trials, NCT#</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRd-Dara</td>
<td>daratumumab (CD38 MAb)</td>
<td>Janssen, NCT03652064, NCT03412565, NCT02874742; EMN, NCT03710603</td>
</tr>
<tr>
<td>VRd-Isa</td>
<td>isatuximab (CD38 MAb)</td>
<td>Heidelberg, NCT03617731; IMROZ, NCT03319667</td>
</tr>
<tr>
<td>VRd-Elo</td>
<td>elotuzumab (SLAMF7 MAb)</td>
<td>DFCI, NCT02375555; Heidelberg, NCT02495922</td>
</tr>
<tr>
<td>KRd-Dara</td>
<td>daratumumab (CD38 MAb)</td>
<td>MMY1001, NCT01998971; MSKCC, NCT03290960, Chicago, NCT03500445</td>
</tr>
<tr>
<td>KRd-Isa</td>
<td>isatuximab (CD38 MAb)</td>
<td>Tubingen, NCT03104842</td>
</tr>
<tr>
<td>KRd-Elo</td>
<td>elotuzumab (SLAMF7 MAb)</td>
<td>Chicago, NCT02969837</td>
</tr>
<tr>
<td>IRd-Dara</td>
<td>daratumumab (CD38 MAb)</td>
<td>Toulouse, NCT03669445; Mayo, NCT03012800</td>
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</table>

VRd, bortezomib, lenalidomide, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; IRd, ixazomib, lenalidomide, dexamethasone
Daratumumab

Current/Ongoing Phase 3 Trials

- RRMM
  - D-Rd (POLLUX) & D-Vd (CASTOR)
  - D-Pd (APOLLO)* & D-Kd (CANDOR)*
- NDMM non-transplant
  - D-VMP (ALCYONE) & D-Rd (MAIA)
  - D-VRd (CEPHEUS)*
- NDMM transplant
  - D-VTd Part 1 (CASSIOPEIA)
  - D-VRd (PERSEUS)*
  - D-R maintenance (AURIGA)*

CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; ADCP, antibody-dependent cellular phagocytosis; RRMM, relapsed/refractory multiple myeloma; D, daratumumab; R, lenalidomide; d, dexamethasone; V, bortezomib; P, pomalidomide; K, carfilzomib; NDMM, newly diagnosed multiple myeloma; MP, melphalan and prednisone; T, thalidomide.


Direct on-tumor actions may contribute to rapid response1-6

Immunomodulatory actions may contribute to deep & durable response7-9

GRiffin (NCT02874742): Randomized Phase

- Phase 2 study of D-RVd vs RVd in transplant-eligible NDMM, 35 sites in US with enrollment from 12/2016 and 4/2018

Key eligibility criteria:
- Transplant-eligible NDMM
- 18-70 years of age
- ECOG score 0-2
- Cr Cl ≥ 30 ml/min

Endpoints & statistical assumptions

Primary endpoint: sCR (by end of consolidation); 1-sided alpha of 0.1
80% power to detect 15% improvement (50% vs 35%), N = 200

Secondary endpoints: MRD (NGS 10-5), CR, ORR (VGPR)

D-RVd, daratumumab-lenalidomide/bortezomib/dexamethasone; RVd, lenalidomide/bortezomib/dexamethasone; NDMM, newly diagnosed multiple myeloma; US, United States; ECOG, Eastern Cooperative Oncology Group; CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; ADCP, antibody-dependent cellular phagocytosis; RRMM, relapsed/refractory multiple myeloma; D, daratumumab; R, lenalidomide; d, dexamethasone; V, bortezomib; P, pomalidomide; K, carfilzomib; NDMM, newly diagnosed multiple myeloma; Cr Cl, creatinine clearance; IV, intravenously; PO, orally; SC, subcutaneously; G-CSF, granulocyte colony-stimulating factor; D-R, daratumumab-lenalidomide; Q4W, every 4 weeks; Q8W, every 8 weeks; sCR, stringent complete response; MRD, minimal residual disease; NGS, next-generation sequencing; CR, complete response; ORR, overall response rate; VGPR, very good partial response.
### Most Common TEAEs

<table>
<thead>
<tr>
<th></th>
<th>D-RVd (n = 99)</th>
<th>RVd (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td><strong>Hematologic, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>48 (49)</td>
<td>32 (32)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>43 (43)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>34 (34)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Anemia</td>
<td>32 (32)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>30 (30)</td>
<td>23 (23)</td>
</tr>
<tr>
<td><strong>Non-hematologic, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>61 (62)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Peripheral neuropathy\</td>
<td>58 (59)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>53 (54)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>46 (47)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>46 (47)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>46 (47)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>39 (39)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>39 (39)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Cough</td>
<td>38 (38)</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>32 (32)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>32 (32)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Infusion-related reactions</strong></td>
<td>41 (41)</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

- Any-grade infections occurred in 81 (82%) patients in the D-RVd arm and 56 (55%) patients in the RVd arm; grade 3/4 infections were similar between groups (17 [17%] patients each)
- Pneumonia occurred in 10 (10%) patients in the D-RVd arm and 9 (9%) patients in the RVd arm

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**The impact of myeloma treatment**

- High complete response rates with current therapy
- Minimal residual disease (MRD)
- Ongoing treatment

Adapted from: "Iceberg" by Created by Uwe Kils (iceberg) and User:Wiska Bodo (sky). – (Work by Uwe Kils) http://www.ecoscope.com/iceberg/
Consequences of MRD

leads to relapse

Adapted from: "Iceberg" by Created by Uwe Kilis (iceberg) and User:Wiska Bodo (sky). — (Work by Uwe Kilis) http://www.ecoscope.com/iceberg/.

Determination Trial (IFM 2009):
Newly Diagnosed Multiple Myeloma

Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma

Determination Trial (IFM 2009): Newly Diagnosed Multiple Myeloma

Median PFS: 36 mo
4-year OS: 82%

Arm A: additional 5 VRd cycles
1 year maintenance

VRd (3 cycles)

Arm B: MEL 200, then 2 VRd cycles
1 year maintenance

Median PFS: 50 mo
4-year OS: 81%

IFM 2009 Follow-Up Study: Focus on MRD

At median follow-up of 55 months, median PFS for MRD-negative patients not reached vs 29 months for MRD-positive patients

MRD neg obtained in 30% (73/245) with VRd + transplant and 20% (54/264) with VRd alone

Perrot A et al. Blood. 2018;Sep 24 [Epub ahead of print].
What is the definition and objectives of maintenance?

- Therapy administered for a prolonged period to maintain the response previously achieved
- Maintenance therapy must
  - Be convenient
  - Be safe and well tolerated long term
  - Not prevent the use, or reduce the efficacy, of other future treatments
- **Objective**: To eliminate MRD or maintain the absence of MRD, reduce the risk of relapse, and finally prolong PFS and OS

Maintenance for Everyone
What are the options to maintain the response after ASCT?

- Thalidomide
- Bortezomib
- Lenalidomide
- Other agents

Maintenance With Thalidomide

- Benefit in OS in the long-term follow-up
- Compromises important aspects of QoL
  - Worsening of cognitive function, dyspnea, swollen legs, constipation, thirst, dry mouth, balance problems
  - Improving appetite and sleep
- High incidence of neuropathy
  - 70% of patients treated for 12 months

Maintenance With Bortezomib

The above clinical regimens are not approved by regulatory authorities. This information is just to discuss maintenance treatment research evolution.

Tourmaline MM3 Trial: Ixazomib vs Placebo Following ASCT in NDMM Patients (2 years)

Ixazomib as maintenance
- 28% reduction in the risk of progression/death with ixazomib maintenance
- Upgraded the responses and increased conversions to MRD negativity over control
- Resulted in a favorable safety profile, including an absence of risk of second primary malignancies and low rates of peripheral neuropathy


Meta-Analysis Evaluating the Role of Len as Maintenance After ASCT

Target population of patients with NDMM who received LEN maintenance or placebo/no maintenance after ASCT

Relapse is the hallmark of multiple myeloma

- Definitions
- Relapse from CR / Biochemical Progression / Clinical Relapse
- Biological Correlates
- Choosing when to treat
- Risk Stratification of Relapse

### Definitions – Relapse

- From CR
  - Mainly used for clinical trials
  - Reappearance of serum or urine M-protein by immunofixation or electrophoresis or abnormal FLC ratio
  - Development of ≥5% plasma cells in BM
  - Any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

- Clinical relapse
  - New CRAB findings
  - New plasmacytomas or bone lesions (fractures do not necessarily count)
  - Increasing size of existing plasmacytomas (≥50%)
  - Hyperviscosity related to paraprotein

*Kumar et al, Lancet Oncol, 2017*
Definitions – Progression

- Increase of 25% from lowest confirmed response value in one or more of:
  - Serum M-protein (absolute increase must be ≥0.5 g/dL)
  - Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL
  - Urine M-protein (absolute increase must be ≥200 mg/24 h)
  - Light chain disease: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL)

- Non-secretory: 25% increase in bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%)

- Appearance of a new lesion(s), ≥50% increase from nadir

- ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

Kumar et al, Lancet Oncol, 2017

Multiclonal disease with spatial and temporal heterogeneity

Rasche L et al Nature Communications 8, Article number: 268(2017)
Indications for treatment

- Clinical relapse (CRAB or plasmacytomas)
- Significant biochemical progression without clinical relapse
  - Doubling of the M-component in two consecutive measurements separated by 2 months with the reference value of 5 g/L, (=0.5 g/dL) or
  - In two consecutive measurements any of the following increases:
    - the absolute levels of serum M protein by ≥10 g/L (=1.0g/dL), or
    - an increase of urine M protein by ≥500 mg per 24 hours, or
    - an increase of involved FLC level by ≥20 mg/dL (= 200 mg/L) (plus an abnormal FLC ratio) or 25% increase (whichever is greater)

Selecting Treatment for Relapsed/Refractory Myeloma: General Principles

- Duration of initial response defines biology
- Triplet (2 active classes + dexamethasone) preferred over doublet
  - With ≥ 1 agent from a new or nonrefractory class
- Consider disease risk, PS, age, and comorbidities when selecting therapy and optimal doses
  - Consider BM biopsy at each relapse to assess risk
- Take into account prior and residual toxicities
- Treat to maximum response and maintain on ≥ 1 agent until progression or tolerability
### Phase III Lenalidomide-Based Therapy for R/R Myeloma

<table>
<thead>
<tr>
<th>Trial</th>
<th>ORR, %</th>
<th>≥ CR, %</th>
<th>≥ VGPR, %</th>
<th>Median PFS, Mos</th>
<th>Median OS, Mos</th>
<th>Median F/u (OS), Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPIRE: KRd vs Rd[1]</td>
<td>87 vs 67</td>
<td>32 vs 9</td>
<td>70 vs 40</td>
<td>26.3 vs 16.6</td>
<td>HR: 0.69</td>
<td>48.3 vs 40.4</td>
</tr>
<tr>
<td>TOURMALINE-MM1: IxaRd vs Rd[2]</td>
<td>78 vs 72</td>
<td>14 vs 7</td>
<td>48 vs 39</td>
<td>20.6 vs 14.7</td>
<td>HR: 0.74</td>
<td>NR</td>
</tr>
<tr>
<td>POLLUX: DRd vs Rd[3-5]</td>
<td>93 vs 76</td>
<td>57 vs 23</td>
<td>80 vs 49</td>
<td>44.5 vs 17.5</td>
<td>HR: 0.44</td>
<td>NR vs NR</td>
</tr>
<tr>
<td>ELOQUENT-2: ERd vs Rd[6,7]</td>
<td>79 vs 66</td>
<td>5 vs 9</td>
<td>36 vs 30</td>
<td>19.4 vs 14.9</td>
<td>HR: 0.73</td>
<td>48.3 vs 39.6</td>
</tr>
</tbody>
</table>


### Phase III PI-Based Therapy for R/R Myeloma

<table>
<thead>
<tr>
<th>Trial</th>
<th>ORR, %</th>
<th>≥ CR, %</th>
<th>≥ VGPR, %</th>
<th>Median PFS, Mos</th>
<th>Median OS, Mos</th>
<th>Median F/u (OS), Mos</th>
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<tbody>
<tr>
<td>ENDEAVOR: Kd vs Vd[1]</td>
<td>77 vs 63</td>
<td>13 vs 6</td>
<td>54 vs 29</td>
<td>18.7 vs 9.4</td>
<td>HR: 0.53</td>
<td>NR vs 24.3</td>
</tr>
<tr>
<td>CASTOR: D/Vd vs Vd[2,3]</td>
<td>84 vs 63</td>
<td>29 vs 10</td>
<td>62 vs 29</td>
<td>16.7 vs 7.1</td>
<td>HR: 0.31</td>
<td>NR</td>
</tr>
<tr>
<td>PANORAMA-1: PanOvd vs Vd[4,5]</td>
<td>61 vs 55</td>
<td>11 vs 6</td>
<td>28 vs 16</td>
<td>12.0 vs 8.1</td>
<td>HR: 0.63</td>
<td>40 vs 36</td>
</tr>
<tr>
<td>Elotuzumab (phase II) E/Vd vs Vd[6]</td>
<td>66 vs 63</td>
<td>4 vs 4</td>
<td>36 vs 27</td>
<td>9.7 vs 6.9</td>
<td>HR: 0.72</td>
<td>NR</td>
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<tr>
<td>MMY1001 (phase I) DKd vs Kd[7]</td>
<td>84 vs 63</td>
<td>27</td>
<td>71</td>
<td>NR (1-yr PFS: 71%)</td>
<td>NR (1-yr OS: 62%)</td>
<td>12.0</td>
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Pomalidomide-Based Salvage Therapy for R/R Myeloma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>Primary Endpoint</th>
<th>ORR, %</th>
<th>≥ VGPR, %</th>
<th>Median PFS, Mos</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pom/Dex (N = 302) [1] Phase III trial vs HD Dex</td>
<td>R/R; ≥ 2 lines of tx including len and bzt</td>
<td>PFS</td>
<td>31 vs 10</td>
<td>6 vs &lt; 1</td>
<td>4.0 vs 1.9</td>
<td>12.7 vs 8.1</td>
</tr>
<tr>
<td>Bortezomib + Pom/Dex (N = 559) [2] Phase III trial vs HD</td>
<td>1-3 lines of tx with len exposure; prior PI ok</td>
<td>PFS</td>
<td>82 vs 50</td>
<td>53 vs 18</td>
<td>11 vs 7</td>
<td>NR</td>
</tr>
<tr>
<td>Carfilzomib + Pom/Dex (N = 57) [3]</td>
<td>R/R to most recent bc; 1-3 lines of tx; len refractory</td>
<td>MTD, PR rate</td>
<td>62</td>
<td>23</td>
<td>10.3</td>
<td>NR (1 yr: 67%)</td>
</tr>
<tr>
<td>Daratumumab + Pom/Dex (N = 103) [4]</td>
<td>R/R; ≥ 2 lines of tx, including len and bzt</td>
<td>MTD</td>
<td>60</td>
<td>42</td>
<td>8.8</td>
<td>17.5</td>
</tr>
<tr>
<td>Ixazomib + Pom/Dex (N = 32) [5]</td>
<td>1-5 lines of tx, including len and PI; len refractory</td>
<td>MTD activity</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Elotuzumab + Pom/Dex (N = 60) [6] Phase II trial vs Pom/Dex</td>
<td>≥ 2 lines of tx including IMiD and PI; refractory to last tx</td>
<td>PFS</td>
<td>53 vs 26</td>
<td>20</td>
<td>10.3 vs 4.8</td>
<td>--</td>
</tr>
</tbody>
</table>


Myeloma therapy

Slide credit: clinicaloptions.com
Continuing Evolution of Multiple Myeloma Treatment: Selected New Classes and Targets 2018–2020

Mechanisms of Relapse

- Increased frequency of T reg
- Increased CD38 expression on T regs
- A proliferating ligand (APRIL) promotes T regs viability
- APRIL upregulates genes involved in immunosuppression
- Cell adhesion mediated immunoresistance
Schematic overview of immunotherapeutic options in multiple myeloma.

Ab: antibody; allo-SCT: allogeneic stem cell transplantation; CAR T-cells: chimeric antigen receptor T-cells; DLI: donor lymphocyte infusion; IMiDs: immunomodulatory drugs; NK: natural killer; PD-1: programmed death receptor 1; PD-L1: programmed death ligand 1; SLAMF7: signaling lymphocytic activation molecule family 7.


Immunomodulatory Agents

- Bind cereblon leading to degradation of Ikaros and Aiolos downregulation of IRF-4 and C-Myc
- Ikaros and Aiolos repress IL-2 transcription
- Activation of T cells and NK cells
- 1990 Thalidomide
- 2006 Lenalidomide approved
- 2013 Pomalidomide (2 prior lines of therapy)
- 2020 CC-220
CC-220

- Iberdomide (CC-220; IBER) is a novel cereblon (CRBN) E3 ligase modulator (CELMoD) that:
  - Has a 20-fold higher binding affinity to CRBN than lenalidomide (LEN) or pomalidomide (POM)\(^6\)
  - Induces more efficient degradation of target proteins, including Ikaros and Aiolos, than LEN or POM\(^6\)
  - Has in vitro antmyeloma and immune co-stimulatory activity on T and natural killer (NK) cells\(^7\)
  - Synergizes with other SoC agents in myeloma, including increasing apoptosis in MM cell lines treated with bortezomib (BORT) and enhancing the antibody-dependent cellular cytotoxicity (ADCC) activity of daratumumab (DARA)\(^8,9\)

Antibodies

- Potential targets
- CD38
- CD138
- Slam F7
Elotuzumab: Immunostimulatory Mechanisms of Action

The immunomodulatory drug pomalidomide may synergize with elotuzumab through multiple mechanisms to increase the killing of MM cells

4. Pazina T et al, EHA 2018 [PS1277].

NK
MM
Macrophage-mediated ADCP of MM cells

NK-cell activation through SLAMF7

MM cells tagged for recognition; mediation of cell death via ADCC

ADCC, antibody-dependent cell cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; FcγR, Fc gamma receptor; NK, natural killer; SLAMF7, signaling lymphocytic activation molecule F7

CD38 targeting

- Daratumumab FIRST ONE
  - Human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action

- Approved
  - As monotherapy in many countries for heavily pretreated RRMM
  - In combination with standard of care regimens in RRMM after ≥1 prior therapy in many countries

- Efficacy
  - Daratumumab induces rapid, deep, and durable responses in combination with a PI (bortezomib) or an IMiD (lenalidomide) in RRMM

RRMM, relapsed or refractory multiple myeloma; CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; ADCP, antibody-dependent cellular phagocytosis; PI, proteasome inhibitor; IMiD, immunomodulatory drug.
### RRMM: Daratumumab: 1-3 prior lines

#### POLLUX and CASTOR Study Designs

Open-label, multicenter, randomized (1:1), active-controlled, phase 3 studies in RRMM patients with ≥1 prior line of therapy

<table>
<thead>
<tr>
<th>POLLUX</th>
<th>CASTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRd (n = 286)</strong></td>
<td><strong>Dvd (n = 251)</strong></td>
</tr>
<tr>
<td>D 16 mg/kg IV</td>
<td>D 16 mg/kg IV</td>
</tr>
<tr>
<td>Every week: Cycles 1-2</td>
<td>Every week: Cycles 1-3</td>
</tr>
<tr>
<td>Every 2 weeks: Cycles 3-6</td>
<td>Every 3 weeks: Cycles 4-8</td>
</tr>
<tr>
<td>Rd group 283</td>
<td>Dvd group 251</td>
</tr>
<tr>
<td>R 25 mg PO (similar to Rd alone)</td>
<td>V 1.3 mg/m² SC (similar to Vd alone)</td>
</tr>
<tr>
<td>Days 1-21 of each cycle until PD</td>
<td>d 22 mg (similar to Vd alone)</td>
</tr>
<tr>
<td>d 40 mg weekly until PD</td>
<td>for 8 cycles</td>
</tr>
</tbody>
</table>

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**Patient characteristics**
- Median age: 63 years
- Prior therapy: 2

**Median PFS, mo**
- DRd group: 286 months
  - All patients: 16.7 months
  - 1 prior therapy: 27.0 months
- Rd group: 283 months
  - All patients: 7.1 months
  - 1 prior therapy: 7.9 months

---

**Efficacy and safety in elderly patients was similar to that of the overall population in both trials**

New Kids on the Block

Global phase 3 pivotal study of isatuximab with Pd in RRMM - Study design

RRMM
≥2 prior lines with Len and PI
No prior therapy with pomalidomide

Isa-Pd
Isa: 10mg/kg on day 1, 8, 15, 22 in cycle 1 subsequently on day 1, 15
P: 4mg on days 1-21 of 28-day cycle
d: 40mg (20mg for ≥ 75yr) on day 1, 8, 15, 22

Primary Endpoint:
PFS (IRC)
Key secondary endpoints:
ORR, OS

Sample size calculation:
~300 patients required to detect an HR of 0.6 with 90% power and 1-sided type 1 error of 2.5%

Treatment until PD or unacceptable AEs

ICARIA-MM is the 1st randomized phase 3 trial adding a CD38 antibody to the Pd backbone
Preliminary Results From a Phase 1b Study of TAK-079, an Investigational Anti-CD38 Monoclonal Antibody (mAb) in Patients With Relapsed/Refractory Multiple Myeloma (RRMM)

Amrita Y. Krishnan, MD1, Krina K Patel, MD, MS2, Parameswaran Hari, MBBS, MD3, Sundar Jagannath, MD4, Ruben Niesvizky, MD5, Rebecca W Silbermann, MD5, Deborah Berg, RN, MSN5, Jianchang Lin, PhD6, Eric R Fedyk, PhD6, Antonio Palumbo, MD7, and Keith E Stockerl-Goldstein, MD8

1City of Hope, Duarte, CA; 2Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; 3Medical College of Wisconsin, Milwaukee, WI; 4Tisch Cancer Institute / Multiple Myeloma Program, Mount Sinai School of Medicine, New York, NY; 5Division of Hematology & Medical Oncology, Weill Cornell Medical College, New York, NY; 6Knight Cancer Institute, Oregon Health & Science University, Portland, OR; 7Takeda Pharmaceutical Company, Cambridge, MA; 8Washington University School of Medicine, St. Louis, MO

Therapeutic Hypothesis: Target Cell Selectivity Enhances Depletion

TAK-079 binds minimally to RBCs and platelets, focusing activity on high density CD38+ targets, leading to enhanced target cell depletion1. This profile could translate into differentiated efficacy and safety.

1. Fedyk et al. ASH 2019 abstract/poster 3136
RBCs, red blood cells
**Time on Study by Dose and Best Response**

Clinical activity occurred early and was durable

<table>
<thead>
<tr>
<th>Dose cohort</th>
<th>Prior Dose</th>
<th>C0</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
<th>C7</th>
<th>C8</th>
<th>C9</th>
<th>C10</th>
<th>C11</th>
<th>C12</th>
<th>C13</th>
<th>C14</th>
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</table>

Data cut-off: 1 Oct 2019

**BCMA Targeting**

- Antibody drug conjugates
- CAR T
- Bispecific T-cell Engagers
GSK-ADC: DREAMM1 Phase 2 Part 2

- Study BMA117159: DRiving Excellence in Approaches to Multiple Myeloma (DREAMM)-1
- Secondary objectives: safety and tolerability, MTD, recommended Phase 2/Part 2 dose

Premedication:
- Prophylactic steroid eye drops before each dose
- Premedication for infusion reactions not permitted with first dose and not mandated at subsequent doses

Population:
- Relapsed, refractory MM
- Undergone stem cell transplant (if eligible)
- Prior treatment with ≥3 classes of alkylators, proteasome inhibitors and immunomodulators (if eligible)
- Progression on, or within 60 days of completion of the last therapy and measurable disease with at least one of the following:
  - Serum M-protein ≥0.5 g/dL
  - Urine M-protein ≥200 mg/24 h
  - Serum FLC assay: involved FLC level ≥5 mg/dL and an abnormal serum FLC ratio (<0.26 or >1.65)
  - Biopsy proven plasmacytoma (measured within 28 days of screening)

GSK-ADC: DREAMM1 Phase 2 Part 2:
- Results at 3.4 mg/kg IV Q3 Wk

Updated Results
- ORR 60%
  - 2 sCR
  - 3 CR
  - 14 VGPR
  - 2 PR
- PFS: 12 months
- DOR: 14.3 months
- D/PI/IMiD refractory
  - PFS 6.2 m

89% Double refractory;
34% double + Dara refractory
29% Cyto High-risk

Trudel et al. Ash 2017

AMG-420 – Phase I Study Bispecific

Study Schematic / Objectives

- First-in-human (FIH) phase 1 dose escalation study* of AMG 420 for up to 10 cycles, depending on response.
- Single-patient cohorts [0.2-1.6 μg/day (d)] were followed by cohorts of 3-6 patients (3.2-800 μg/d).
- Objectives of this phase 1 study of AMG 420 in patients with relapsed and/or refractory (R/R) MM included:
  - Assessing safety and tolerability per CTCAE 4.03
  - Determining the maximum tolerated dose (MTD)
  - Assessing anti-tumor activity

* NCT02514239. EOT, end of treatment. FU, follow-up. IP, investigational product.
Median 4 PLT: ~25% Dara
~31% Double Refractory

AMG-420 – Phase I Study

Responding Patients

Unless PD was the last response indicated, patients were responding at last evaluation.

As of Apr 8, 2019. CR, complete response. EOT, end of treatment. PD, progressive disease. PR, partial response.
CC-93269-MM-001 PHASE 1 TRIAL (NCT03486067): STUDY DESIGN

Key Eligibility Criteria
- RRMM after ≥ 3 prior regimens
- Progressive disease within 60 days of last regimen
- No prior BCMA-directed therapy

Dose Schedule
Cycle (all 28-day cycles)

<table>
<thead>
<tr>
<th>Screening</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
<th>C7</th>
<th>C8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>received</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1–3: Days 1, 8, 15, and 22</td>
<td>C6–8: Days 1 and 15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All doses administered via IV over 2 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Part A: Dose Escalation
- Stage 1: Fixed doses
- Stage 2: Step-up in dose on C1D8

Part B: Cohort Expansion

Endpoints
Primary: Safety including DLTs, AEs, NTG, and MTD
Secondary: Preliminary efficacy including MRD, PK, ADA, and PD endpoints

CYTOKINE RELEASE SYNDROME

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with a CRS event, n (%)</td>
<td>23 (76.7)</td>
</tr>
<tr>
<td>After first dose</td>
<td>23 (76.7)</td>
</tr>
<tr>
<td>After second dose</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>After third dose</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Maximum CRS grade, n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15 (50.0)</td>
</tr>
<tr>
<td>2</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Time to onset, median (range), d</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (1–9)</td>
</tr>
<tr>
<td>Duration, median (range), d</td>
<td>2 (1–6)</td>
</tr>
<tr>
<td>Tocilizumab use, n (%)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>Corticosteroid use, n (%)</td>
<td>22 (73.3)</td>
</tr>
</tbody>
</table>

Maximum Reported CRS Grade by Starting Dose

- Dexamethasone prophylaxis was administered to patients receiving ≥ 6 mg (Cohorts 5–9)
- In Cohort 7 (6–10 mg), 1 patient experienced grade 3 (6 mg) followed by grade 5 CRS (10 mg); contributing factors included myeloma progression with extensive extramedullary disease, and concomitant infection

**Bispecific T-cell engagers/antibodies under study for MM**

**City of Hope**

- **NCT03145181**  
  Dose Escalation Study of JNJ-64007957, a Humanized BCMA CD3 DuoBody Antibody, in Participants with Relapsed or Refractory Multiple Myeloma

- **NCT03399799**  
  Dose Escalation Study of JNJ-64407564 in Participants with Relapsed or Refractory Multiple Myeloma

- **NCT03275103**  
  Dose Escalation Study of BFCR4350A in Participants with Relapsed or Refractory Multiple Myeloma

**non-City of Hope**

- **NCT02514239**  
  Phase I Dose Escalation of i.v. BI 836909 Monotherapy in Last Line Multiple Myeloma Patients

- **NCT03836053**  
  Assessment of AMG 420 in Subjects with Relapsed and/or Refractory Multiple Myeloma

- **NCT03173430**  
  Pilot Study of Blinatumomab in Combination with Salvage Autologous Stem Cell Transplantation for Patients with Refractory Multiple Myeloma
Bispecific T-cell engagers/antibodies under study for MM

**non-City of Hope**

<table>
<thead>
<tr>
<th>NCT03269136</th>
<th>Phase 1 Study of PF-06863135, a BCMA-CD3 Bispecific Ab, in Relapsed/Refractory Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03933735</td>
<td>A Study of TNB-383B in Subjects with Relapsed or Refractory Multiple Myeloma</td>
</tr>
<tr>
<td>NCT03275103</td>
<td>Study of ISB 1342, a CD38/CD3 Bispecific Antibody, in Subjects with Previously Treated Multiple Myeloma</td>
</tr>
<tr>
<td>NCT04108195</td>
<td>A Study of Subcutaneous Daratumumab Regimens in Combination with Bispecific T Cell Redirection Antibodies for the Treatment of Participants with Multiple Myeloma</td>
</tr>
<tr>
<td>NCT03761108</td>
<td>First in Human (FIH) Study of REGN5458 in Patients with Relapsed or Refractory Multiple Myeloma</td>
</tr>
<tr>
<td>NCT04083534</td>
<td>First in Human (FIH) Study of REGN5459 in Patients with Relapsed or Refractory Multiple Myeloma (MM)</td>
</tr>
</tbody>
</table>

**CAR T Cells**

- BCMA targeting
- Slam F7 targeting
- BCMA CD38
JNJ-4528: BCMA-targeted CAR T-Cell Therapy

- JNJ-68284528 (JNJ-4528) is a structurally differentiated chimeric antigen receptor T (CAR-T) cell therapy
  - Contains a CD3ζ signaling domain and 4-1BB costimulatory domain
  - 2 BCMA-targeting single domain antibodies designed to confer avidity
  - Identical to the CAR construct used in the LEGEND-2 study

- LEGEND-2 (N = 74): Phase 1 investigator-initiated study conducted in China
  - High, deep, and durable overall response and manageable safety in R/R MM

Zhao et al. JHO 2018;11(1):141; Xu et al. PNAS 2019;116(19):9543; BCMA=B-cell maturation antigen; MM=multiple myeloma; R/R=relapsed/refractory; VH=variable heavy chain

CARTITUDE-1: Overall Response Rate

- ORR and depth of response were independent of BCMA expression on MM cells at baseline
- Median time to first response = 1 mo (1 – 3)
- Median time to ≥CR = 1 mo (1 – 9)

PR or better; Independent Review Committee-assessed; *No patient had stable disease or progressive disease as best response. CR=complete response; ORR=overall response rate; PR=partial response; sCR=stringent complete response; VGPR=very good partial response
**CARTITUDE-1: Duration of Response**

- Of 29 patients, 27 are progression-free at median 6-month follow-up.

**Building the CS1 CAR T Cell at City of Hope**

1. **CS1 CAR**
2. **scFv-Fc**
3. Serum-free medium
4. Purified harvest medium after 2 days
5. 201 NKS 120 NKS 19 NKS 11 NKS 31 NKS 21 NKS 17 NKS
6. CS1 CAR
CS1 CAR T Cells Efficiently Kill Multiple Myeloma

Conclusions
Myeloma 2020; immune directed

- Immune environment contributes to relapse
- New drugs immune targeting
- Sequencing?
- Cost?
Q&A SESSION
Multiple Myeloma: Understanding My Treatment Options

• Ask a question by phone:
  – Press star (*) then the number 1 on your keypad.

• Ask a question by web:
  – Click “Ask a question”
  – Type your question
  – Click “Submit”

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

LLS EDUCATION & SUPPORT RESOURCES

• Information Specialists
  Master’s level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  – EMAIL: infocenter@LLS.org
  – TOLL-FREE PHONE: 1-800-955-4572

• Caregiver Support: www.LLS.org/caregiver

• Free Education Booklets: www.LLS.org/booklets

• Free Telephone/Web Programs: www.LLS.org/programs

• Live, weekly Online Chats: www.LLS.org/chat

• LLS Community: www.LLS.org/community
LLS EDUCATION & SUPPORT RESOURCES

- **LLS Podcast, *The Bloodline with LLS***
  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: [www.thebloodline.org](http://www.thebloodline.org)

- **Education Videos**
  Free education videos about survivorship, treatment, disease updates and other topics: [www.LLS.org/educationvideos](http://www.LLS.org/educationvideos)

- **Patti Robinson Kaufmann First Connection Program**
  Peer-to-peer program that matches newly diagnosed patients and their families: [www.LLS.org/firstconnection](http://www.LLS.org/firstconnection)

- **Free Nutrition Consults**
  Telephone and email consultations with a Registered Dietitian: [www.LLS.org/nutrition](http://www.LLS.org/nutrition)

- **What to Ask**
  Questions to ask the treatment team: [www.LLS.org/whattoask](http://www.LLS.org/whattoask)

- **Other Support Resources**
  LLS Community, discussion boards, blogs, support groups, financial assistance and more: [www.LLS.org/support](http://www.LLS.org/support)

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THANK YOU

We have one goal: A world without blood cancers