Disease Biology – Screening

Quads vs Triplets

BCMA Targets

Non-BCMA Targets

Updates in AL Amyloidosis
Disease Biology

• iStopMM (Iceland Screens, Treats or Prevents MM)
  • Overall results (#156)
  • High prevalence of SMM (#156)
  • No increased COVID with MGUS (#154)
  • New FreeLite reference levels (#542)

• PROMISE
  • Screening data for 2,960 subjects (#152)
Disease Biology: iStopMM

- All Iceland residents born before 1976

Aims:
- Evaluate the impact of MGUS screening
- Obtain evidence for optimal work-up and follow-up
- Integrate biological, imaging, and germline genetic markers in risk models for progression
- Evaluate the impact of screening on quality of life
- Biobanking
- Evaluate the effect of early detection and early treatment
Disease Biology: iStopMM

- All Iceland residents born before 1976
- 54% (80,759) agreed to participate
- 93% (75,422) screened
- 4.9% (3,725) overall prevalence of MGUS
  - 2.3% ages 40-59
  - 6.2% ages 60 – 79
  - 12.9% ages 80 - 103
Disease Biology: iStopMM

At 3y follow-up

- Active screening identifies a significantly higher number of individuals with full blown malignancies and smoldering disease

- The authors advise against systematic screening in healthy individuals
Disease Biology: iStopMM

SMM Prevalence

Of the total 75,422 patients screened (51% of target population)
- 3,725 were randomized
- BMBx completed in 1,503
- 180 diagnosed with SMM

Study Arm 3 (1,279 individuals) used to estimate prevalence of SMM
- 10.8% had SMM (prevalence of 0.53%: 95% CI 0.49 - 0.57%)
- 1/3 of patients had intermediate or high risk SMM (based on the 2/20/20 Mayo risk stratification model)
Disease Biology: PROMISE

Screened 2211 individuals from PROMISE and 5411 from MGH biobank

- 2439 Black individuals
- 3866 non-Black with a family hx
- 631 control (non-Black, no family hx)

High risk population
- African-American
- First Degree relative with plasma cell dyscrasia

Screening
- SPEP and IFX
- sFLC
- Mass spec

Positive Result

MGUS
Follow q6m-1y

SMM
Monitor q3-6m

Negative Result

Follow until Progression

Yearly Follow Up with re-screen every 3 years

Prevalence of MGUS = 10%
- Among individuals > 50, MGUS incidence: 10% in controls, 17% among Black individuals, 13% among non-Black with a family hx

Higher rate of MGUS detection by mass spec

https://www.enroll.promisestudy.org/
# Quadruplet Therapy for NDMM

<table>
<thead>
<tr>
<th>Study</th>
<th>Induction</th>
<th>ASCT</th>
<th>Consolidation</th>
<th>Maintenance</th>
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<tbody>
<tr>
<td>GRIFFIN (phase 2)</td>
<td>Dara-RVd vs RVd</td>
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<td>sCR rate at end of post-ASCT consolidation</td>
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<td>GMMG-HD7 (phase 3)</td>
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<td>MASTER (phase 2)</td>
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<td>Dara-KRd (by MRD status)*</td>
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<td>GMMG-HD6 (phase 3)</td>
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Quad Therapy for NDMM: GRIFFIN UPDATE

**Induction: Cycles 1-4**
- **D-VRd in 21-day cycles**
  - D: 16 mg/kg IV D1, 8, 15
  - V: 1.3 mg/m² SC D1, 4, 8, 11
  - R: 25 mg PO D1-14
  - d: 20 mg PO D1, 2, 8, 9, 15, 16
  - (n = 104)

- **VRd in 21-day cycles**
  - V: 1.3 mg/m² SC D1, 4, 8, 11
  - R: 25 mg PO D1-14
  - d: 20 mg PO D1, 2, 8, 9, 15, 16
  - (n = 103)

**Consolidation: Cycles 5-6†**
- **D-VRd in 21-day cycles**
  - D: 16 mg/kg IV D1
  - VRd: as in induction

**Maintenance: Cycles 7-32‡**
- **D-R in 28-day cycles**
  - D: 16 mg/kg IV D1 Q4W or Q8W
  - R: 10 mg PO D1-21 of C7-9 and 15 mg PO D1-21 of C10+§

Transplant-eligible adults with ND MM;
- ECOG PS ≤2;
- CrCl ≥30 mL/min*
- (N = 207)

*Lenalidomide dose was adjusted in patients with CrCl ≤50 mL/min. †Consolidation began 60-100 days after transplant. ‡Patients completing maintenance phase were permitted to continue single-agent lenalidomide. §15 mg administered only if tolerable.

After 24 mo of maintenance therapy D-VRd followed by D-R maintenance continued to show significant improvement in sCR and depth of response vs VRd followed by R maintenance¹
- Patients with sCR after 24-mo maintenance: 66.0% vs 47.4% (P = .0096)
- Patients with MRD negativity after 24-mo maintenance at 10⁻⁵ threshold: 64.4% vs 30.1% (P < .0001); at 10⁻⁶ threshold: 35.6% vs 14.6% (P = .0007)
- MRD negativity rates for D-VRd treated patients were consistent in all subgroups of patients, including those with high risk features.
Quad Therapy for NDMM: GMMG-HD7

**Induction (3 x 6-Wk Cycles)**

- Isatuximab 10 mg/kg*
- Bortezomib 1.3 mg/m²†
- Lenalidomide 25 mg†
- Dexamethasone 20 mg†

(n = 331)

**Maintenance (4-Wk Cycles)**

- Isatuximab 10 mg/kg‡ +
- Lenalidomide 10 → 15 mg§
- Dexamethasone 20 mg||

**HDT ASCT**

- Lenalidomide 10 → 15 mg§
- Dexamethasone 20 mg||

**3 yr or PD**

- Cycle 1: D1, 8, 15, 22; Cycles 2-3: D1, 15, 29.
- Cycle 4+: D1.
- Days 1-28. Increase dose to 15 mg after 3 mos
- Dexamethasone D1, 8, 15, 22 in C1.

**Adults with NDMM who are eligible for HDT and ASCT (N = 662)**

**Addition of isatuximab to VRd produced superior rates of MRD negativity vs VRd alone**

- MRD-negative rate at end of 18-wk induction: 50.1% vs 35.6%

**The benefit of adding isatuximab was seen across all patient subgroups**

**Trial ongoing, including analyses of second randomization after ASCT of isatuximab + lenalidomide vs lenalidomide alone as maintenance therapy**

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*Cycle 1: D1, 8, 15, 22, 29; cycles 2-3: D1, 15, 29.
†Bortezomib D1, 4, 8, 11, 22, 25, 29, 32; lenalidomide Days 1-14 and 22-35; dexamethasone D1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, 33.
‡Data cutoff: April 2021.
§Days 1-28. Increase dose to 15 mg after 3 mos
||Dexamethasone D1, 8, 15, 22 in C1.

Quad Therapy for NDMM: IFM 2018-01

- 95.2% of patients responded (measured after 1y of maintenance therapy), Over half of patients achieved CR or sCR
- 39.5% of patients achieved MRD negativity to 10^{-6}, 51.4% at 10^{-5}
- Responses (including MRD negativity) deepened over time

Quad Therapy for NDMM: MASTER UPDATE

86% of patients achieved a CR or better

80% of patients achieved MRD negativity (10x^-5), 66% achieved MRD negativity at 10x^-6

Responses deepened with each phase of treatment and were similar in patients with 0, 1, or 2+ high-risk genetic abnormalities

ASCT increased the rates of MRD negativity following induction therapy, benefitting patients with highest-risk disease features

Nearly all patients with no or only 1 high-risk genetic abnormality and confirmed MRD negativity had no disease progression or MRD resurgence since stopping therapy

* 24 and 72 weeks after completing therapy

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**Quad Therapy: Dara-KRd**

- Daratumumab 16 mg/m² days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m² Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22

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**Induction**

Dara-KRd x 4

**AHCT**

MRD (MRD-SURE) - Treatment-free observation and MRD surveillance*

**Consolidation**

Dara-KRd x 4

MRD (MRD-SURE) - Treatment-free observation and MRD surveillance*

**Consolidation**

Dara-KRd x 4

MRD (MRD-SURE) - Treatment-free observation and MRD surveillance*

**Lenalidomide Maintenance**

* MRD assessment by NGS

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BCMA Targets for Relapsed Disease

Current FDA Approved Therapies

**Belantamab mafodotin** (DREAMM-2 trial) [FDA approval 8/5/20]
- ORR 32% (7% with CR/sCR, 11% with VGPR), median DoR 11mo
  - Common AE of keratopathy, generally reversible
  - **ASH 2021 Updates** DREAMM-5: Belantamab + Feladilimab (Inducible T-cell Co-Stimulator Agonist): ORR 52%
    - ALGONQUIN: Bela + Pd
    - DREAMM-9: Bela + RVd in transplant-ineligible, NDMM – alternative dosing schedules

**Idecabtagene vicleucel** (KarMMa) [FDA approval 3/26/21]
- ORR 73%, ORR 81% in patients who received the highest target dose

**Ciltacabtagene autoleucel** (JNJ-4528, CARTITUDE-1) [FDA approval 2/28/22]
- 1y follow-up: ORR 97% (sCR 67%), PFS 77%, OS 89%
  - **ASH 2021 Update** 2y follow-up: ORR 98% (sCR 83%), PFS 60.5%, OS 74%
BCMA Targets: CARTITUDE-1

Ciltacabtagene autoleucel: 2 BCMA-targeting single-domain antibodies intended to boost avidity plus a 4-1BB costimulatory domain.

- Of 113 patients enrolled, 97 received cilta-cel; median administered dose: $0.71 \times 10^6$ (0.51-0.95 $\times 10^6$) CAR+ viable T-cells/kg
- **Primary endpoint:** safety and RP2D (phase Ib), efficacy (phase II)

BCMA Targets: CARTITUDE-1, 2y follow-up

- sCR rates deepened over time
  - 67% at median 1-yr follow-up
  - 83% at median 2-yr follow-up
- Median time to first response: 1 mo (range: 0.9-10.7)
- Median time to best response: 2.6 mo (range: 0.9-17.8)
- Median time to ≥CR: 2.9 mo (range: 0.9-17.8)
- Median DoR: NE (range: 21.8-NE)
- Percentage of patients remaining progression-free at 2 yr was 60.5%

*ORR assessed by independent review committee.
# Bispecific Antibodies for RRMM

<table>
<thead>
<tr>
<th>Agent</th>
<th>Elranatamab</th>
<th>Teclistamab</th>
<th>REGN5458</th>
<th>Cevostamab</th>
<th>Talquetemab</th>
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<tbody>
<tr>
<td>Target</td>
<td>BCMA x CD3</td>
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<td>FcRH5 x CD3</td>
<td>GPRC5D x CD3</td>
</tr>
<tr>
<td>Dosing</td>
<td>sc weekly</td>
<td>sc weekly</td>
<td>iv q2w</td>
<td>iv q3w</td>
<td>sc weekly</td>
</tr>
<tr>
<td># patients *</td>
<td>55</td>
<td>169</td>
<td>73</td>
<td>161 *</td>
<td>55 at 2 RP2D *</td>
</tr>
<tr>
<td>Median # prior rx</td>
<td>6 (2-15)</td>
<td>5 (2-14)</td>
<td>5 (2-17)</td>
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<tr>
<td>ORR, %</td>
<td>69</td>
<td>65</td>
<td>75</td>
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<td>CR or better, %</td>
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<td>29</td>
<td>16</td>
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<td>16</td>
</tr>
<tr>
<td>Med DoR</td>
<td>Not reported</td>
<td>Not reached</td>
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<td>CRS, all grades (G3/4), %</td>
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<td>Neurotox, all grades (G3/4), %</td>
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<td>Abstract #</td>
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*included patients with prior BCMA tx
## Bispecific Antibodies for RRMM

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<tr>
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<th>MagnetisMM-1 (Ph 1)</th>
<th>MajesTEC-1 (Ph 1/2)</th>
<th>Ph1</th>
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<th>MonumenTAL-1 (Ph 1)</th>
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BCMA x CD3: REGN5458

Patients with MM who are R/R to ≥3 lines of prior therapy including an IMiD, a PI, and an anti-CD38 Ab, or double refractory to an IMiD and PI with PD on/after anti-CD38 Ab; nonsecretory MM allowed (N = 73)

**Primary objectives:** safety, tolerability, DLTs, RP2D

**Secondary objectives:** ORR, DoR, PFS, MRD status, and OS

<table>
<thead>
<tr>
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<th>Part 2: Dose Expansion</th>
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<tbody>
<tr>
<td>DL1: 3 mg (n = 4)*</td>
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<tr>
<td>DL2: 6 mg (n = 10)*</td>
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<td>DL3: 12 mg (n = 10)*</td>
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<td>DL4: 24 mg (n = 10)*</td>
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<td>DL5: 48 mg (n = 7)*</td>
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<td>DL6: 96 mg (n = 8)*†</td>
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<td>DL7: 200 mg (n = 12)†</td>
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<td>DL8: 400 mg (n = 8)†</td>
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<td>DL9: 800 mg (n = 4)†</td>
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*1 dose-level specific step-up dose. †5-mg and 25-mg step-up doses.
**BCMA x CD3: REGN5458**

- 51% ORR for all enrolled patients
- 86% ≥VGPR and 43% ≥CR among all responders
- For patients achieving CR/sCR (with available data), 4/10 negative at MRD $10^{-5}$

<table>
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<tr>
<th>Response, n (%)</th>
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<th>DL 4-6 (n = 25)</th>
<th>DL 7-9 (n = 24)</th>
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<td>4</td>
<td>8</td>
</tr>
<tr>
<td>VGPR</td>
<td>0</td>
<td>24</td>
<td>42</td>
</tr>
<tr>
<td>PR</td>
<td>7</td>
<td>0</td>
<td>17</td>
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</table>

*Includes all patients who were evaluable for response assessment at 4 wk.

- Median time to response < 1mo, 70% response within first 2 mo
- Estimated median DoR not reached
  - Probability of EFS in responders at 8 mo: 90.2% (95% CI: 72.6-96.7)
- Longest responses ongoing for >19 mo at latest data cutoff (September 30, 2021)
- MTD was not reached
- CRS: 38%; no grade ≥3 CRS or neurotoxicity; grade 2 CRS in 3 patients; grade 1 CRS within first 2 wk and resolved within a day; dose level did not correlate with CRS
FcRH5 x CD3: Cevostamab

- FcRH5 surface receptor is ubiquitously and highly expressed on myeloma cells
- Cevostamab is a novel, humanized T-cell–engaging bispecific IgG antibody
  - Targets CD3 on T-cells and FcRH5 on myeloma cells to encourage immunologic synapse formation, leading to myeloma cell death

**Cevostamab treatment schedule**
- Q3W (IV) for 17 cycles (~12 mo) or until PD or unacceptable AE
- Prophylaxis for mitigation of CRS/infusion-related reaction
  - C1 step-up dosing
  - C1-2 corticosteroid premedication*; C1-17 acetaminophen/diphenhydramine premedication
- Hospitalization (≥72 hr) after each C1 infusion

**Patients with R/R MM for which there is no available, appropriate, or tolerable tx**
- ECOG PS 0-1
- Prior CAR T-cells, ADCs, and bispecific antibodies allowed

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### Cevostamab treatment schedule

<table>
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<tr>
<th>C1 single step-up escalation†</th>
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<th>C1 double step-up escalation†</th>
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<tbody>
<tr>
<td><strong>C1D1</strong></td>
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<td>0.15-10.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C1D8</strong></td>
<td><strong>C1D1</strong></td>
<td><strong>C1D15</strong></td>
<td><strong>C1D8</strong></td>
</tr>
<tr>
<td>3.6</td>
<td>90</td>
<td>160</td>
<td>3.6</td>
</tr>
<tr>
<td>3.6</td>
<td>90</td>
<td>90</td>
<td>3.6</td>
</tr>
<tr>
<td>3.6</td>
<td>60</td>
<td>90</td>
<td>3.6</td>
</tr>
<tr>
<td>3.6</td>
<td>40</td>
<td>90</td>
<td>3.6</td>
</tr>
<tr>
<td>3.6</td>
<td>20</td>
<td>90</td>
<td>3.6</td>
</tr>
<tr>
<td>0.05-3.6</td>
<td>0.15-10.8</td>
<td>160</td>
<td>3.6</td>
</tr>
</tbody>
</table>

* Corticosteroid premedication optional from C3 onward. † All doses in mg.

---

**FcRH5 x CD3: Cevostamab**

- Responses occurred at and above 20-mg target dose level (n = 143)
- ORR increased with target dose
  - ORR in C1 single step-up expansion (3.6 mg/90 mg): 29.0%
  - ORR in C1 double step-up expansion (0.3 mg/3.6 mg/160 mg): 54.8%

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cevostamab (N = 161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to response among responders, mo (range)</td>
<td>1.0 (0.7-5.9)</td>
</tr>
<tr>
<td>Median time to best response, mo (range)</td>
<td>2.1 (0.7-11.4)</td>
</tr>
<tr>
<td>MRD negativity at &lt;10⁻⁵ in patients with ≥VGPR, n/N (%)</td>
<td>7/10 (70)</td>
</tr>
</tbody>
</table>

- **Median duration of response:** 11.5 mo (95% CI: 6.0-18.4)
GPRC5D x CD3: Talquetemab (MonumenTAL-1)

- GPCR5D: orphan receptor highly expressed on MM cells relative to normal cells
- Talquetamab: first-in-class bispecific IgG4 antibody binding GPCR5D and CD3 receptors
  - Recruits CD3+ cells to GPCR5D+ myeloma cells and induces tumor cell death in preclinical cell and xenograft models

Key objectives: assess safety and tolerability of RP2D(s), antitumor activity, PK, PD

Adults with measurable MM that is R/R or intolerant to established anti-MM therapy; Hb ≥8 g/dL, platelets ≥50 x 10^9/L, ANC ≥1.0 x 10^9/L
(N_total = 102)

**Step-up Dose**
- **Wk -1**
  - **Full Dose (QW or Q2W)**
  - **Cycle 1 and Beyond**

Premedication with glucocorticoid, antihistamine, antipyretic required for step-up doses and first full dose

- **Talquetamab 405 µg/kg SC QW in 21-day cycle**
  - (n = 30)

- **Talquetamab 800 µg/kg SC Q2W in 28-day cycle**
  - (n = 25)

### GPRC5D x CD3: Talquetemab (MonumenTAL-1)

**Hematologic AEs in ≥20% of Total SC Population, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>405 μg/kg SC QW* (n = 30)</th>
<th>800 μg/kg SC Q2W* (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20 (67)</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Anemia</td>
<td>18 (60)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>12 (40)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (37)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>12 (40)</td>
<td>9 (30)</td>
</tr>
</tbody>
</table>

*With 2-3 step-up doses.

- Infections: 18/55 (33%) [ 3 (5%) with grade 3/4 ]
- Skin and nail AEs: 75% [ 7.5% with grade 3 rashes ]
- ISR: 9/55 (16%); all grade 1/2
- No toxicity-related deaths
**GPRC5D x CD3: Talquetemab (MonumenTAL-1)**

<table>
<thead>
<tr>
<th>Response, %</th>
<th>405 µg/kg SC QW*</th>
<th>800 µg/kg SC Q2W*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n/N (%)</td>
<td>21/30 (70.0)</td>
<td>14/21 (66.7)</td>
</tr>
<tr>
<td>sCR</td>
<td>10</td>
<td>9.5</td>
</tr>
<tr>
<td>CR</td>
<td>3.3</td>
<td>9.5</td>
</tr>
<tr>
<td>VGPR</td>
<td>40</td>
<td>33.3</td>
</tr>
<tr>
<td>≥VGPR (sCR + CR + VGPR)</td>
<td>53.3</td>
<td>52.4</td>
</tr>
<tr>
<td>PR</td>
<td>16.7</td>
<td>14.3</td>
</tr>
</tbody>
</table>

- Median DoR not reached in either arm
- QW arm: 11/21 (52%) responders still receiving treatment at median 10.1-mo follow-up
- Q2W arm: 12/14 (86%) responders still receiving treatment at median 7.9-mo follow-up

<table>
<thead>
<tr>
<th>Response</th>
<th>405 µg/kg SC QW* (n = 30)</th>
<th>800 µg/kg SC Q2W* (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, mo (range)</td>
<td>9.0 (0.9-17.1)</td>
<td>4.8 (0.4-11.1)</td>
</tr>
<tr>
<td>Response-evaluable patients, n</td>
<td>30</td>
<td>21</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>21 (70.0)</td>
<td>14 (66.7)</td>
</tr>
<tr>
<td>Triple-class-refractory patients, n/N (%)</td>
<td>15/23 (65.2)</td>
<td>12/18 (66.7)</td>
</tr>
<tr>
<td>Penta-drug refractory patients, n/N (%)</td>
<td>5/6 (83.3)</td>
<td>5/6 (83.3)</td>
</tr>
<tr>
<td>Median time to first confirmed response, mo (range)</td>
<td>0.9 (0.2-3.8)</td>
<td>1.2 (0.2-6.8)</td>
</tr>
</tbody>
</table>

*With 2-3 step-up doses.
Other New Treatment Mechanisms (glimpses of the future?)

- Gamma secretase inhibitors
- CelMoDs: small-molecule inhibitor of cereblon E3 ligase (fancy IMIDs) – Iberdomide
- Immunocytokines: TAK573
Gamma Secretase Inhibitors to increase BCMA Expression: Abstract 551

- Gamma secretase cleaves BCMA from the plasma cell surface
- Gamma secretase inhibitors can be used to increase BCMA expression on plasma cells

- GSI held at discretion of clinical team, typically in setting of CRS or neurotox
- Most patients received all preplanned doses of GSI.
Gamma Secretase Inhibitors to increase BCMA Expression: Abstract 551

Gamma Secretase Inhibition Increases BCMA Surface Density

Depth and Duration of Response

Response
- sCR
- CR
- VGPR
- PR
- SD
- PD
- Death

Prior BCMA

Months
Gamma Secretase Inhibitors to increase BCMA Expression: Abstract 551

Progression Free Survival

- Prior BCMA Tx, median PFS 2 mos, $p < 0.0001$
- No Prior BCMA Tx, median PFS not reached

Overall Survival

- No Prior BCMA Tx, median OS not reached
- Prior BCMA Tx, median OS 6 mos
CELMoDs (Iberdomide): Abstract 162

CC-220-MM-001 Iberdomide + Dexamethasone

- Iberdomide (CC-220): novel small-molecule inhibitor of cereblon E3 ligase modulator under development as a next-generation IMiD in MM\(^1,2\)
  - Binding to cereblon induces degradation of target proteins, including Ikaros and Aiolos\(^1\)
  - Shows enhanced tumoricidal and immune-stimulatory effects compared with other IMiDs and remains active in lenalidomide- and pomalidomide-resistant MM cell lines\(^1,2\)
  - In preclinical models, demonstrated synergistic activity with dexamethasone, anti-CD38 mAbs, and PIs\(^3-6\)
  - Administered as a single enantiomer (S isomer), which may mitigate sedative adverse events (sleepiness, fatigue)\(^1,7\)
- CC-220-MM-001 phase Ib/IIa study designed to identify MTD/RP2D of iberdomide alone or in combination with chemotherapy in patients with R/R MM
  - Current analysis reports results from the dose-expansion phase for patients with R/R MM treated with iberdomide + dexamethasone\(^8\)

CELMoDs (Iberdomide): Abstract 162

Phase II (at RP2D)

Cohort D
Iberdomide* 1.6 mg + Dexamethasone†

- **Primary**: efficacy (ORR)
- **Secondary**: safety, additional efficacy (DoR, PFS, OS)

Cohort I (post BCMA)
Iberdomide* 1.6 mg + Dexamethasone†

- **Primary**: preliminary efficacy and safety

≥3 prior therapies, refractory to an IMiD, PI, glucocorticoid, and anti-CD38 mAb (N = 107)

≥3 prior therapies, including BCMA-targeted therapy, LEN, POM, PI, glucocorticoid, and anti-CD38 mAb; documented disease progression within 60 days of last therapy (or PD if CAR T-cell therapy was last therapy) (N = 26)

*Iberdomide (oral): Days 1-21 of each 28-day cycle.
†Dexamethasone (oral): 40 mg (20 mg if >75 yr) on Days 1, 8, 15, and 22 of each 28-day cycle.
### CC-220-MM-001 Iberdomide + Dexamethasone Dose Expansion: Baseline Characteristics and Prior Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort D (N = 107)</th>
<th>Cohort I (Post BCMA) (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yr (range)</td>
<td>64 (44-83)</td>
<td>65 (50-78)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>60 (56.1)</td>
<td>15 (57.7)</td>
</tr>
<tr>
<td>Median time since diagnosis, yr (range)</td>
<td>6.90 (1.6-24.5)</td>
<td>7.75 (0.6-24.8)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>42 (39.3)</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td>1</td>
<td>55 (51.4)</td>
<td>20 (76.9)</td>
</tr>
<tr>
<td>2</td>
<td>10 (9.3)</td>
<td>0</td>
</tr>
<tr>
<td>ISS at entry, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>46 (43.0)</td>
<td>15 (57.7)</td>
</tr>
<tr>
<td>Stage II</td>
<td>45 (42.1)</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td>Stage III</td>
<td>16 (15.0)</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>Extramedullary plasmacytoma, n (%)</td>
<td>27 (25.2)</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td>High-risk cytogenetics, n (%)</td>
<td>(n = 57)</td>
<td>(n = 18)</td>
</tr>
<tr>
<td></td>
<td>32 (29.9)</td>
<td>6 (23.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior Therapy</th>
<th>Cohort D (N = 107)</th>
<th>Cohort I (Post BCMA) (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median prior lines of therapy, n (range)</td>
<td>6 (3-23)</td>
<td>7 (4-15)</td>
</tr>
<tr>
<td>ASCT, n (%)</td>
<td>84 (78.5)</td>
<td>23 (88.5)</td>
</tr>
<tr>
<td>IMiD refractory, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>107 (100)</td>
<td>26 (100)</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>102 (95.3)</td>
<td>23 (88.5)</td>
</tr>
<tr>
<td>PI refractory, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>104 (97.2)</td>
<td>25 (96.2)</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>62 (57.9)</td>
<td>14 (53.8)</td>
</tr>
<tr>
<td>Anti-CD38 mAb refractory, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCMA exposed, n (%)</td>
<td>107 (100)</td>
<td>22 (84.6)</td>
</tr>
<tr>
<td>CAR T-cell therapy</td>
<td>1 (0.9)</td>
<td>26 (100)</td>
</tr>
<tr>
<td>ADC</td>
<td>1 (0.9)</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td>T-cell engager</td>
<td>0</td>
<td>13 (50.0)</td>
</tr>
</tbody>
</table>

Data cutoff: June 2, 2021

Slide credit: clinicaloptions.com
CC-220-MM-001 Iberdomide + Dexamethasone
Dose Expansion: TEAEs

<table>
<thead>
<tr>
<th>TEAEs of Interest, n (%)</th>
<th>Cohort D (N = 107)</th>
<th>Cohort I (Post BCMA) (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Neutropenia</td>
<td>64 (59.8)</td>
<td>27 (25.2)</td>
</tr>
<tr>
<td>▪ Febrile neutropenia</td>
<td>5 (4.7)</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>▪ Anemia</td>
<td>44 (41.1)</td>
<td>30 (28.0)</td>
</tr>
<tr>
<td>▪ Thrombocytopenia</td>
<td>38 (35.5)</td>
<td>7 (6.5)</td>
</tr>
<tr>
<td>▪ Leukopenia</td>
<td>30 (28.0)</td>
<td>11 (10.3)</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Fatigue</td>
<td>25 (23.4)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>▪ Diarrhea</td>
<td>25 (23.4)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>▪ Constipation</td>
<td>23 (21.5)</td>
<td>0</td>
</tr>
<tr>
<td>▪ Rash</td>
<td>21 (19.6)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Pneumonia</td>
<td>13 (12.1)</td>
<td>9 (8.4)</td>
</tr>
<tr>
<td>▪ COVID-19</td>
<td>10 (9.3)</td>
<td>5 (4.7)</td>
</tr>
</tbody>
</table>
CC-220-MM-001 Iberdomide + Dexamethasone
Dose Expansion: ORR

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Cohort D (N = 107)</th>
<th>Cohort I (Post BCMA) (N = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• sCR</td>
<td>28 (26.2)</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>• CR</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>• VGPR</td>
<td>8 (7.5)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>• PR</td>
<td>19 (17.8)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td><strong>MR</strong></td>
<td>11 (10.3)</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>46 (43.0)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>15 (14.0)</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td><strong>NE</strong></td>
<td>7 (6.5)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>CBR (sCR + CR + VGPR + PR + MR)</td>
<td>39 (36.4)</td>
<td>10 (41.7)</td>
</tr>
<tr>
<td>DCR (sCR + CR + VGPR + PR + MR + SD)</td>
<td>85 (79.4)</td>
<td>18 (75.0)</td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
Modakafusp alfa is a novel first-in-class immunocytokine designed to deliver IFNa2b to CD38+ cells

Modakafusp alfa
Binds with high affinity to unique epitope of CD38
Signals through IFNAR2 to:
- activate innate and adaptive immune cells
- direct anti-proliferative/apoptotic signals to tumor cells

CD38 is widely expressed on innate and adaptive immune cells, multiple myeloma cells, and subsets of tumor cells of other hematologic malignancies
Modakafusp Alfa (TAK573): Abstract 898

Overall response rate

- Among 29 patients who received modakafusp alfa 1.5 mg/kg Q4W (5 in dose escalation and 24 in ongoing dose expansion):
  - 11 patients had ≥PR (ORR 38%), including 6 with VGPR and 2 with CR (28% ≥VGPR)
- Among 26 anti-CD38 mAb-refractory patients, ORR was also 38% (31% ≥VGPR):
  - Among the 4 patients who received an anti-CD38 mAb in their most recent line of therapy, 1 achieved a CR, and 2 achieved a VGPR (ORR 75%)
- Of the 15 patients with prior anti-BCMA therapy, 3 (20%) had a VGPR

Among patients with > PR
- Median time to response was 1m, median time to best response was 2 m

Among all patients in the 1.5mg/kg cohort, median PFS was 5.7 mo
Updates in AL Amyloidosis

- ANDROMEDA
- CAEL-101
ANDROMEDA: Subcutaneous Daratumumab + VCd vs VCd Alone in Newly Diagnosed AL Amyloidosis

- Randomized, open-label phase III trial of Dara-VCd vs VCd alone in patients with newly diagnosed AL amyloidosis

  **Stratified by cardiac stage (I vs II vs III), transplant (yes vs no), CrCl (≥60 mL/min vs <60 mL/min)**

  Adults with AL amyloidosis with ≥1 organ affected; no prior tx for MM or AL amyloidosis; cardiac stage I-IIIa; eGFR ≥20 mL/min (N = 388)

  **Primary endpoint:** hematologic CR in ITT population

  **Secondary endpoints:** MOD-PFS, organ response rate, time to hematologic response, OS, safety

**Screening at Day 28**

- **Dara SC 1800 mg QW cycles 1-2; Q2W cycles 3-6 + VCd**
  - QW for 6 cycles (n = 195)

- **VCd**
  - QW for 6 cycles (n = 193)

  *SC bortezomib (1.3 mg/m²), cyclophosphamide (300 mg/m² orally), or IV (500 mg max weekly) and dexamethasone (40 mg orally or IV) once/wk for six 28-day cycles.

- **Dara SC 1800 mg Q4W until MOD-PFS* or max 24 cycles (n = 195)**

  *MOD-PFS composite endpoint including end-stage cardiac disease, end-stage renal disease, hematologic progression per consensus guidelines, and death.

- **Observed until MOD-PFS† (if Dara SC d/c before MOD-PFS)**

- **Observed until MOD-PFS†**


Slide credit: clinicaloptions.com
Over 2 Yr of Follow-up, Hematologic Response Rates Deepened Over Time With Dara-VCd vs VCd

- Longer follow-up confirmed the increasingly higher rate of CR with Dara-VCd vs VCd (60% vs 19%)
  - Within the Dara-VCd arm the CR rate deepened over time (53% vs 60% with 14.4 mo longer follow-up)
  - \(\geq\)VGPR* within the Dara-VCd arm increased from 77% to 79%

CR defined as normalization of FLC levels and FLCr and negative serum and urine immunofixation

*Among \(\geq\)VGPR responders (D-VCd, n = 154; VCd, n = 97).

Higher Organ Response Rates With D-VCd vs VCd

**Cardiac Response Rates**

- **6 Mo**
  - Odds ratio: 2.4
  - 95% CI: 1.4-4.4; \( P = 0.0029 \)
- **18 Mo**
  - Odds ratio: 3.7
  - 95% CI: 2.1-6.6; \( P < 0.0001 \)

**Renal Response Rates**

- **6 Mo**
  - Odds ratio: 3.3
  - 95% CI: 1.9-5.9; \( P < 0.0001 \)
- **18 Mo**
  - Odds ratio: 4.4
  - 95% CI: 2.4-7.9; \( P < 0.0001 \)

Monoclonal Antibody CAEL-101 in Patients With R/R AL Amyloidosis

- CAEL101 is a monoclonal antibody that binds to a neoepitope on κ and λ light chain fibrils, resulting in the clearance of amyloid from tissues and organs

- An open-label phase Ia/b study enrolling patients (N = 27) with established the safety of CAEL-101 up to 500 mg/m² in patients with R/R AL amyloidosis

4 patients with cardiac involvement were not evaluable due to BL proteinuria being too low (≤560 pg/mL) for a meaningful evaluation.

4 patients with renal involvement were not evaluable due to BL proteinuria being too low (≤500 mg/24 hr) for a meaningful evaluation.

Caelum CARES Program

- Evaluating the safety of CAEL-101 in patients with Mayo Stage IIIA/B AL amyloidosis in 2 parallel phase III trials (Study 301: NCT04504825 and Study 302: NCT04512235)

- **Primary endpoint:** OS

- **Secondary endpoints:** change from BL to wk 50 (6MWT distance, QoL per KCCQ-OS and SF-36 v2 PCS, GLS %), safety

**Screening up to Day 28**

- **CAEL-101 + SoC* anti-PCD treatment**
  - Study 301 (Stage IIIB): n = 74
  - Study 302 (Stage IIIA): n = 178

- **Placebo† + SoC anti-PCD treatment**
  - Study 301 (Stage IIIB): n = 37
  - Study 302 (Stage IIIA): n = 89

*CyBorD. †CAEL-101/matching placebo 1000 mg/m² Q1 wk x 4, then every other wk until required number of deaths observed.

Adults with Mayo stage IIIB (Study 301) or Mayo stage IIIA (Study 302) AL amyloidosis with cardiac involvement and adequate bone marrow reserve and hepatic function.


Slide credit: clinicaloptions.com
MM / AL Amyloid Trials at OHSU

ODU Myeloma Clinical Research Team: myelomaRT@ohsu.edu

Smoldering
• ECOG EAA173: Daratumumab / Len / Dex vs Len / Dex

Newly Diagnosed
• ECOG EAA181 (Transplant ineligible): Daratumumab / Len / Dex x9, then Dara / Len / Dex vs Dara / Len / Dex + Velcade consolidation

Relapsed / Refractory
• OHSU IIT: Isatuximab / Carfilzomib / Pomalidomide (1st relapse)
• HPN217 (Harpoon): T-cell activating construct (BCMA target)
• CC-99712 (Celgene): IV CC-99712 (BCMA ADC)
• DREAMM 12: Belantamab in renal failure

Maintenance
• MMY3021 (Janssen): MRD+ patients only: SC Dara + Len vs Len
• SWOG S1803: MRD+ or MRD- patients: SC Dara + Len vs Len

AL Amyloidosis
• CAEL 101-301/302: Newly dx AL amyloid, Mayo Stage IIIa and IIIb cardiac disease
Thank You