ASSOCIATION OF COMMUNITY CANCER CENTERS

Multiple Myeloma Lecture Series

Clinical Updates in Multiple Myeloma

Dr. David Vesole, MD PhD

Tuesday, August 7, 2018
1 – 2PM Eastern

Association of Community Cancer Centers
ACCC Overview

Hira Chowdhary, MPH MS
Project Manager, Provider Education
The Association of Community Cancer Centers (ACCC)

The Association of Community Cancer Centers (ACCC) promotes the entire continuum of quality cancer care for our patients and our communities. Since 1974, ACCC has been helping oncology professionals adapt to the complex changes of delivering quality cancer care.

ACCC members rely on the Association to bring them information on cancer program management, reimbursement issues, legislative and regulatory changes at the state and national levels, community cancer program standards, NCI-funded community clinical research, hospital alliances and physician relationships, and more.

More than 23,000 cancer care professionals from over 2,400 hospitals and practices nationwide are affiliated with ACCC.
Clinical Updates in Multiple Myeloma

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David H. Vesole, MD, PhD

Co-Chief, Myeloma Division
Director, Myeloma Research
John Theurer Cancer Center
Hackensack UMC
Professor of Medicine
Director, Myeloma Program
Georgetown University
BEST OF ASCO 2018: PLASMA CELL DYSRASIAS

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Multiple Choice Question:
Which of the following statements is true?

A. Pembrolizumab in combination with either lenalidomide or pomalidomide improves PFS in myeloma.

B. Preliminary results demonstrate that CAR T cells are safe, effective and potentially curative in RRMM.

C. Carfilzomib at 70 mg/m2 weekly is more efficacious and comparable toxicity to carfilzomib 27 mg/m2 given twice weekly.

D. Venetoclax plus carfilzomib only is effective in MM expressing t(11;14).
IMMUNOTHERAPY
FDA analysis of pembrolizumab trials in multiple myeloma: Immune related adverse events and response

Abstract 8008

Aviva C. Krauss, MD
OHOP/DHP
• Promising in various lymphomas

• No single agent efficacy in relapsed or refractory multiple myeloma
  – Consistent findings in pembrolizumab Phase 1b study (Ribrag et al, EHA, 6/2017)

### Table 3. Efficacy Results

<table>
<thead>
<tr>
<th>Tumor</th>
<th>OR, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell lymphoma (n = 31)</td>
<td>8 (26)</td>
</tr>
<tr>
<td>DLBCL (n = 11)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>FL (n = 10)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Other B-cell lymphoma (n = 10)</td>
<td>0</td>
</tr>
<tr>
<td>T-cell lymphoma (n = 23)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>MF (n = 13)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>PTCL (n = 5)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Other CTCL (n = 3)</td>
<td>0</td>
</tr>
<tr>
<td>Other non-CTCL (n = 2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Multiple myeloma (n = 27)</strong></td>
<td><strong>1 (4)</strong></td>
</tr>
</tbody>
</table>
2 Randomized Controlled Trials of Pembrolizumab Added to SOC in Multiple Myeloma

**Keynote 183**

- **Relapsed/refractory MM**
  - Stratified by:
    - # prior lines of tx (2 vs ≥ 3)
    - Dz status (refractory vs sensitive to len)

  1:1

  - Pembrolizumab 200 mg Q3W
  - Pomalidomide 4 mg days 1-21, 28 –day cycle
  - Dexamethasone 40 mg on days 1, 8, 15, 22

  Primary Endpoints: PFS, OS

**Keynote 185**

- **Newly diagnosed MM**
  - Stratified by:
    - Age (< vs ≥ 75y)
    - ISS* (I vs II vs III)

  1:1

  - Pembrolizumab 200 mg Q3W
  - Lenalidomide 25 mg days 1-21, 28 –day cycle
  - Dexamethasone 40 mg on days 1, 8, 15, 22

  Primary Endpoint: PFS

*ISS: International Staging System*
KN183 Results

- **N=125 (Pembro-pom-dex)**, N=124 (pom-dex)
- **Median follow-up: 8.1 months**
- **Causes of death (Pembro-pom-dex):** myocarditis, SJS, MI, pericardial hemorrhage, cardiac failure, respiratory tract infection, neutropenic sepsis, sepsis, MOD, respiratory failure, and unknown
- **SAEs: 63% vs 46%**
- **Efficacy:**
  - **ORR:** 34% Pembro-pom-dex arm vs. 40% Pom-dex arm
  - **Time-to-progression HR: 1.14 (95% CI: 0.75, 1.74)**
KN185 Results

- Median follow-up: 6.6 months
- Causes of death (pembro-len-dex): intestinal ischemia, cardiorespiratory arrest, suicide, PE, cardiac arrest, pneumonia, sudden death, myocarditis, large intestine perforation, and cardiac failure
- SAEs: 54% vs 39%
- Efficacy:
  - ORR: 64% Pembro-len-dex arm vs. 62% Len-dex arm
  - Time-to-progression HR: 0.55 (95% CI: 0.20, 1.50)
Immune Related AEs and Response

- Unique AEs not c/w IMID class effect
- Lenalidomide with or without Pembolizumab showed increased response rates in those with irAEs

<table>
<thead>
<tr>
<th></th>
<th>KN183 (Rel/Refr)</th>
<th>KN185 (Newly diagnosed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro+</td>
<td>58%</td>
<td>68%</td>
</tr>
<tr>
<td>Pom/Dex</td>
<td>45%</td>
<td>44%</td>
</tr>
<tr>
<td>Any irAE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G≥3 irAE</td>
<td>18%</td>
<td>36%</td>
</tr>
<tr>
<td>SAE</td>
<td>63%</td>
<td>54%</td>
</tr>
<tr>
<td>ORR</td>
<td>34%</td>
<td>64%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Objective Response Rate (%)</th>
<th>None</th>
<th>Any</th>
<th>Grade≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any irAE</td>
<td>45%</td>
<td>73%</td>
<td>70%</td>
</tr>
<tr>
<td>G≥3 irAE</td>
<td>13%</td>
<td>73%</td>
<td>67%</td>
</tr>
<tr>
<td>SAE</td>
<td>46%</td>
<td>39%</td>
<td>62%</td>
</tr>
<tr>
<td>ORR</td>
<td>40%</td>
<td>62%</td>
<td>62%</td>
</tr>
</tbody>
</table>
Summary

• Decreased OS on 2 randomized trials using anti-PD-1 + SOC vs SOC in 2 populations
  – Relapsed/refractory multiple myeloma
    • ORR: no difference with or without irAE
  – Newly diagnosed multiple myeloma
    • Increased ORR in patients with irAE
    • Increased irAE rate
bb2121 Anti-BCMA CAR T Cell Therapy in Patients With Relapsed/Refractory Multiple Myeloma: Updated Results From a Multicenter Phase I Study

Abstract 8007

Noopur Raje, MD, Jesus Berdeja, MD, Yi Lin, MD, PhD, Nikhil Munshi, MD, David Siegel, MD, PhD, Michaela Liedtke, MD, Sundar Jagannath, MD, Deepu Madduri, MD, Jacalyn Rosenblatt, MD, Marcela Maus, MD, PhD, Ashley Turka, Lyh Ping Lam, PharmD, Richard A. Morgan, PhD, M. Travis Quigley, Monica Massaro, MPH, Kristen Hege, MD, Fabio Petrocca, MD, and James N. Kochenderfer, MD
bb2121 CAR-T Update

• BCMA is the latest promising target in MM
• At least 3 broad highly promising approaches directed at BCMA:
  – CAR-T cells vs. BCMA
  – BiTE (CD3 – BCMA bispecific engager)
  – Antibody Drug Conjugate vs. BCMA

  – bb2121 data presented by Raje et al. largest and most mature with CAR-T approach in MM
  – At least 18 (+) trials of BCMA directed CAR-T cells going on worldwide
bb2121 data

- bb2121 CAR-T - active and induces deep responses rapidly
- More CR/VGPR than PR; Early MRD negativity (m PFS 17.7 mo)
- Soluble BCMA – not an issue (as was feared)
- Safety comparable / better than most other CAR-T in MM and Lymphoma
- Response correlates with CAR-T cell expansion
- Cell dose matters (>150 e6 needed for bb2121)
- BCMA expression did not matter for response – early data
- Patients still relapsed (median DOR for responders ~ 12 mo)
- MRD Negativity – what does it mean in this setting?
- NOT yet a CURE!
## COMPARISON OF BCMA TARGETED CAR-T CELLS

<table>
<thead>
<tr>
<th></th>
<th>Anti-BCMA CAR (16 pts at highest dose)</th>
<th>Bb2121 (22 pts at full dose)</th>
<th>LCAR-B38M (35 pts)</th>
<th>CART-BCMA (24 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group/Company</strong></td>
<td>NCI</td>
<td>Bluebird/NCI</td>
<td>Nanjing Legend Biotech</td>
<td>Novartis/Upenn (No BCMA expression cut off)</td>
</tr>
<tr>
<td><strong>Binder/co-stimulatory signaling</strong></td>
<td>Murine/CD3 &amp; CD28</td>
<td>Murine/CD3 &amp; 4-1-BB</td>
<td>Murine/CD3 &amp; 4-1-BB</td>
<td>Fully human/CD3 &amp; 4-1BB</td>
</tr>
<tr>
<td><strong>Transfection</strong></td>
<td>Gamma-retroviral</td>
<td>Lentiviral</td>
<td>Lentiviral</td>
<td>Lentiviral</td>
</tr>
<tr>
<td><strong>Lymphodepletion</strong></td>
<td>Flu/CY d-5 to -3</td>
<td>Flu/CY d-5 to -3</td>
<td>CY</td>
<td>None / with CY</td>
</tr>
<tr>
<td><strong>Median prior lines of therapy</strong></td>
<td>9.5 (63% Refr)</td>
<td>8 (32% penta refr)</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td><strong>Reported Efficacy</strong></td>
<td>ORR- 81% VGPR -63% EFS – median 31 wks</td>
<td>ORR – 95.5% mDOR – 10.8 mo 100% MRD neg</td>
<td>15 CRs/13 PRs in 35 19 with longer f/u 100% ORR; 74% CR No CR pt relapsed at 6 mo</td>
<td>2 CRs, 3 VGPRs, 6 PRs in 24 patients Only 4 responders progressed at 40 weeks</td>
</tr>
<tr>
<td><strong>Safety Data</strong></td>
<td>Substantial but reversible</td>
<td>Manageable CRS</td>
<td>Transient CRS</td>
<td>1 death – progressive disease/candidaemia</td>
</tr>
</tbody>
</table>

The future for CAR-T ... many more questions

• Efficacy in earlier phase of disease:
  – earlier in relapse / Post induction (in HR-MM)
• Dual targeting (CD 19 - BCMA)
• Other targets – CD 38; Kappa LC; CD138; Lewis Y Antigen, CS-1, NY1-ESO
• Mechanisms of loss of response
  – Loss BCMA expression / Shedding
• Universal CAR-T (third party; off the shelf)
• Elimination of viral transduction
Subcutaneous daratumumab in patients with relapsed or refractory multiple myeloma (RRMM): Part 2 update of the open label, multicenter, dose escalation Phase Ib study (PAVO) (abstract 8013)

Ajai Chari, Saad Z. Usmani, Maria-Victoria Mateos, Niels WCJ van de Donk, Jonathan L. Kaufman, Philippe Moreau, Albert Oriol, Torben Plesner, Lotfi Benboubker, Kevin Liu, Peter Hellemans, Tara Masterson, Pamela L. Clemens, Andrew Farnsworth, Hareth Nahi, Jesus San-Miguel

- Daratumumab (Dara) is a monoclonal antibody targeting CD38
  - Single agent activity in advanced MM (ORR ~ 30%)
  - Compelling activity in combination with PI or IMIDs: Dara Rd > Rd, Dara Vd > Vd, Dara VMP > VMP

- IV Dara is safe but
  - IRR occur in about 40-50% of patients / mostly first infusions
  - First infusion duration of about 8 hours

- Dara SC: pre-mixed co-formulation of daratumumab and recombinant human hyaluronidase with a higher daratumumab concentration, lower injection volume, and shorter injection time with manual SC injection in the abdomen
## Dara IV or SC?

<table>
<thead>
<tr>
<th></th>
<th>Dara IV ¹</th>
<th>Dara SC ²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=25</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median number of prior therapies</strong></td>
<td>5 (2-14)</td>
<td>3 (2-9)</td>
</tr>
<tr>
<td><strong>Refractoriness</strong></td>
<td>86% double refractory</td>
<td>56% double refractory</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>31%</td>
<td>52%</td>
</tr>
<tr>
<td><strong>Administration time</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First infusion</td>
<td>~ 7h</td>
<td>~ 3-5 min</td>
</tr>
<tr>
<td>Second infusion</td>
<td>~ 4.3h</td>
<td></td>
</tr>
<tr>
<td>Third infusion</td>
<td>~ 3.5h</td>
<td></td>
</tr>
<tr>
<td><strong>IRR</strong></td>
<td>40-50%</td>
<td>16%</td>
</tr>
</tbody>
</table>

2. Chari A et al, ASCO 2018 abstract 8013
Daratumumab in Combination with Carfilzomib and Dexamethasone in Lenalidomide-refractory Patients with Relapsed Multiple Myeloma: Subgroup Analysis of MMY1001
Abstract 8002

Ajai Chari,1 Joaquín Martinez-Lopez,2 Maria-Victoria Mateos,3 Joan Bladé,4 Sagar Lonial,5 Lotfi Benboubker,6 Albert Oriol,7 Bertrand Arnulf,8 Jesus San-Miguel,9 Luis Pineiro,10 Andrzej Jakubowiak,11 Carla de Boer,12 Jianping Wang,13 Jordan Schecter,13 Philippe Moreau14

1Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; 2Hospital 12 de Octubre/CNIO/Complutense University, Madrid, Spain; 3University Hospital of Salamanca/IBSAL, Salamanca, Spain; 4Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain; 5Winship Cancer Institute, Emory University, Atlanta, GA, USA; 6Hôpital Bretonneau, Centre Hospitalier Régional Universitaire (CHRU), Tours, France; 7Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Barcelona, Spain; 8Hôpital Saint Louis, Paris, France; 9Clínica Universidad de Navarra-CIMA, IDISNA, CIBERONC, Pamplona, Spain; 10Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; 11University of Chicago Medical Center, Chicago, IL, USA; 12Janssen Biologics, Leiden, The Netherlands; 13Janssen Research & Development, LLC, Raritan, NJ, USA; 14University Hospital Hôtel-Dieu, Nantes, France

*ClinicalTrials.gov Identifier: NCT01998971.
Study Design: D-Kd Arm of MMY1001

• Open-label, nonrandomized, multicenter, phase 1b study in RRMM patients
• Per protocol, DARA was administered as a **single first dose** \( (n = 10) \) or as a **split first dose** \( (n = 75) \)

### Eligibility/treatment

- Relapsed MM
  - 1-3 prior lines of therapy, including bortezomib and an IMiD
  - Len-refractory pts allowed
- Carfilzomib-naïve
- ECOG status ≤2
- LVEF ≥40%
- ANC ≥1 \( \times 10^9 \)/L
- Platelet count ≥75 \( \times 10^9 \)/L

### Dosing schedule (28-day cycles)

**DARA:**

- **Split first dose\(^a\):** 8 mg/kg Days 1-2 of Cycle 1
- Single first dose: 16 mg/kg on C1D1
- 16 mg/kg IV QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter until PD

**Carfilzomib\(^b\):**

- 20 mg/m\(^2\) IV Cycle 1 Day 1
- Escalated to 70 mg/m\(^2\) Cycle 1 Day 8+; **weekly (Days 1, 8, 15)** until PD

**Dexamethasone:** 40 mg/week (Days 1, 8, 15, 22) IV or PO until PD

### Endpoints

**Primary**
- Safety, tolerability

**Secondary**
- ORR and duration of response
- OS

**Exploratory**
- PFS
- MRD (NGS)\(^c\)
- PK

---

\(^a\)In 500-mL dilution volume.

\(^b\)Both 20 mg/m\(^2\) and 70 mg/m\(^2\) were administered as 30-min IV infusions.

\(^c\)Among patients evaluated for MRD, MRD was assessed using NGS at time of suspected CR and at 12 and 18 mo after initial dose. In cases where daratumumab is suspected of interfering with IFE and preventing clinical CR response calls, subjects with VGPR may also be evaluated for MRD.

ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; ANC, absolute neutrophil count; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; IV, intravenous; PO, oral; OS, overall survival; MRD, minimal residual disease; NGS, next generation sequencing; PK, pharmacokinetic; IFE, immunofixation; IRR, infusion-related reaction.
Overall Response and Confirmed MRD-negative Rates

- Median follow up: 12.0 months
- Among all-treated patients evaluated for MRD (n = 20), 7 patients achieved MRD negativity at $10^{-5}$
  - Post-screening MRD testing was not conducted for the remaining patients (n = 65)

Responses are anticipated to deepen over longer follow up

ORR, %

<table>
<thead>
<tr>
<th></th>
<th>PR</th>
<th>VGPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Len-refractory patients (n = 51)</td>
<td>10%</td>
<td>18%</td>
</tr>
<tr>
<td>All treated patients (n = 85)</td>
<td>10%</td>
<td>11%</td>
</tr>
</tbody>
</table>

ORR = 75%

≥CR 26%

≥VGPR 65%

ORR = 81%

≥CR 26%

≥VGPR 68%

7/20 pts

10^{-5} sensitivity threshold

35%

PR, partial response; CR, complete response; sCR, stringent complete response.
**Carfilzomib + mAbs**

**KD with Isa or Dara?**

<table>
<thead>
<tr>
<th></th>
<th>Dara KD ¹</th>
<th>Isa KD ²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>85</td>
<td>33</td>
</tr>
<tr>
<td><strong>KD dose and schedule</strong></td>
<td>20 / 70 mg/m2 D1,8,15</td>
<td>20/27 mg/m2 D1,2,8,9,15,16</td>
</tr>
<tr>
<td><strong>Median prior therapy (range)</strong></td>
<td>2 (1-3)</td>
<td>3 (2-8)</td>
</tr>
<tr>
<td><strong>Prior Carfilzomib</strong></td>
<td>No</td>
<td>Yes, 30% refractory to CFZ</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>86%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>Thrombocytopenia Gr3+</strong></td>
<td>27%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Neutropenia Gr 3+</strong></td>
<td>18%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Hypertension Gr 3+</strong></td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>IRR</strong></td>
<td>42%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Isa 10 mg/kg QW x4 then Q2W dose was selected as the optimal dose for the expansion cohort based on ORR, safety and PK modeling.
Dara 16 mg/kg QWx 8 then Q2w x 8 then Q4W

¹ Lonial S et al, ASH 2017 130:1869, Chari ASCO 2018; 8002
2- Chari, A et al. ASCO 2018 abstract 8014
CARFILZOMIB-BASED THERAPIES

• A.R.R.O.W.-once weekly-abstract 8000
• Carfilzomib + venetoclax-abstract 8004
• Car/len/dex once weekly-abstracts 8017/8022
• Is there a more convenient way of giving Carfilzomib?

• Does Carfilzomib have a dose response?

• Is toxicity comparable to conventional dosing

• What about combinations?: Abstract 8017/8022
A.R.R.O.W. Study Design

1:1 Randomization
N = 478
- Relapsed and Refractory MM
- 2-3 prior lines
- Prior exposure to IMiD & PI
- PS 0-1

Stratification:
- ISS stage
- Refractory to bortezomib
- Age (<65 vs. ≥65)

Arm A: Once-weekly carfilzomib + dex
(30 min infusion of K)
- Carfilzomib 20 mg/m² IV D1 (Cycle 1)
- Carfilzomib 70 mg/m² IV D8, 15 (Cycle 1), D1, 8, 15 (Cycle 2+)
- Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
- Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

28-day cycles

Arm B: Twice-weekly carfilzomib + dex
(10 min infusion of K)
- Carfilzomib 20 mg/m² IV D1, 2 (Cycle 1)
- Carfilzomib 27 mg/m² IV D8, 9, 15, 16 (Cycle 1), D1, 2, 8, 9, 15, 16 (Cycle 2+)
- Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
- Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

Follow-up for Disease Status until Confirmed PD
Long-term Follow-up for Survival
Primary Endpoint: Progression-Free Survival Assessed by Computational Algorithm Based on IMWG-URC

![Graph showing progression-free survival rates and median PFS months for two treatment groups.]

- **Twice-weekly Kd 20/27 mg/m\(^2\) (N=238)**
  - Median PFS: 7.6 months
  - Progression/Death, n (%): 148 (62.2%)
  - p-value (1-sided): 0.0014

- **Once-weekly Kd 20/70 mg/m\(^2\) (N=240)**
  - Median PFS: 11.2 months
  - Progression/Death, n (%): 126 (52.5%)

**Number of Subjects at Risk**:
- Kd 20/27: 238 at 0 months, 164 at 3 months, 119 at 6 months, 86 at 9 months, 41 at 12 months, 15 at 15 months, 4 at 18 months, 0 at 21 months
- Kd 20/70: 240 at 0 months, 178 at 3 months, 145 at 6 months, 114 at 9 months, 69 at 12 months, 24 at 15 months, 5 at 18 months, 0 at 21 months
## Adverse Events of Interest

<table>
<thead>
<tr>
<th>AE, % (SMQN)</th>
<th>Once-weekly Kd (n=238)</th>
<th>Twice-weekly Kd (n=235)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

- Safety findings were consistent with the known safety profile of carfilzomib, and no new risks were identified.

AE, adverse event; SMQN, standardized MedDRA Query, narrow scope
Phase 2 Study of Venetoclax Plus Carfilzomib and Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma

Abstract 8004

Luciano J. Costa,1 Edward Stadtmauer,2 Gareth Morgan,3 Gregory Monohan,4 Tibor Kovacsovics,5 Nicholas Burwick,6 Andrzej Jakubowiak,7 Mehrdad Mobasher,8 Kevin Freise,9 Jeremy A. Ross,9 John Pesko,9 Wijith Munasinghe,9 Jaclyn Cordero,9 Lura Morris,9 Paulo Maciag,9 Orlando F. Bueno,9 Shaji Kumar10

1University of Alabama at Birmingham, Birmingham, AL; 2University of Pennsylvania, Philadelphia, PA; 3University of Arkansas for Medical Sciences, Little Rock, AR; 4University of Kentucky, Lexington, KY; 5Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; 6VA Puget Sound Health Care System, University of Washington, Seattle, WA; 7The University of Chicago Medicine, Chicago, IL; 8Genentech Inc., South San Francisco, CA; 9AbbVie Inc., North Chicago, IL, 10Mayo Clinic, Rochester, MN
Background

- Anti-apoptotic proteins BCL-2 and MCL-1 promote multiple myeloma (MM) cell survival
- Venetoclax is a selective, orally available small molecule BCL-2 inhibitor\(^1\)\(^-\)\(^6\)
- Carfilzomib (K) is a proteasome inhibitor and can indirectly inhibit MCL-1\(^7\)\(^-\)\(^9\)

### Dosing

Patients received treatment in 28-day cycles

<table>
<thead>
<tr>
<th>Cohorts:</th>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
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<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Ven 400 mg/day + K 27 mg/m2 + d 40 mg</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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</tr>
<tr>
<td>2: Ven 800 mg/day + K 27 mg/m2 + d 40 mg</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3: Ven 800 mg/day + K 70 mg/m2 + d 40 mg</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>4: Ven 800 mg/day + K 56 mg/m2 + d 20 mg</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

- K (carfilzomib) dose
- d (dexamethasone) dose
Objective Responses in All Patients and Those Refractory to PIs and IMiDs

<table>
<thead>
<tr>
<th></th>
<th>sCR</th>
<th>CR</th>
<th>VGPR</th>
<th>PR</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>7%</td>
<td>14%</td>
<td>57%</td>
<td>27%</td>
<td>83%</td>
</tr>
<tr>
<td>N = 30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI Refractory</td>
<td>7%</td>
<td>17%</td>
<td>53%</td>
<td>10%</td>
<td>86%</td>
</tr>
<tr>
<td>N = 14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMiD Refractory</td>
<td>5%</td>
<td>5%</td>
<td>42%</td>
<td>26%</td>
<td>79%</td>
</tr>
<tr>
<td>N = 19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double Refractory</td>
<td>10%</td>
<td>10%</td>
<td>53%</td>
<td>60%</td>
<td>80%</td>
</tr>
<tr>
<td>N = 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ORR = Overall Response Rate
Objective Responses in Patients Based on Cytogenetic Risk Status

All Patients: N=30
- sCR: 7%
- CR: 17%
- VGPR: 33%
- PR: 27%

ORR = 83%

Cytogenetic Risk: N=7
- ORR = 100%
  - sCR: 14%
  - CR: 57%
  - VGPR: 29%
  - PR: 14%

Cytogenetic Risk: N=8
- ORR = 88%
  - sCR: 25%
  - CR: 38%
  - VGPR: 25%
  - PR: 14%

Cytogenetic Risk: N=22
- ORR = 82%
  - sCR: 9%
  - CR: 32%
  - VGPR: 32%
  - PR: 27%
## Summary of Safety

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>33 (79)</td>
<td>12 (29)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (57)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (38)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>13 (31)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (29)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>9 (21)</td>
<td>6 (14)</td>
</tr>
</tbody>
</table>

AEs for ≥20% of patients for any grade AE or for ≥10% with grade 3 or 4 AEs

- **1 case of laboratory TLS:**
  - patient was t(11:14+)
  - hospitalized and received hydration and allopurinol
  - TLS labs resolved and treatment resumed

<table>
<thead>
<tr>
<th>Serious adverse event, n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any serious event</strong></td>
<td>5 (12)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Influenza</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

Serious adverse events in ≥2 patients
Carfilzomib/lenalidomide/dex in RRMM

Richez et al Abstract 8017
• N = 28
• ORR 93%, with 89% ≥VGPR and 61% ≥CR. The Median TTP and OS at 12 m were 89% and 95%, respectively.
• 29% of pts dc’d, 50% due to adverse events (AEs)

Biran et al Abstract 8022
• N = 22
• ORR 90% (56 mg/m²) and 89% (70 mg/m²); 20.0% (56 mg/m²) and 30.4% (70 mg/m²) a CR or sCR
• Incidence grade ≥3 Aes was 70.0% (56 mg/m²) and 71.7% (70 mg/m²). Discontinuation due to Aes was 20.0% (56 mg/m²) and 17.4% (70 mg/m²).
Pomalidomide, Bortezomib, and Low-Dose Dexamethasone (PVd) vs Bortezomib and Low-Dose Dexamethasone (Vd) in Lenalidomide-Exposed Patients With Relapsed or Refractory Multiple Myeloma: Phase 3 OPTIMISMM Trial

Abstract 8001

Paul Richardson,1 Albert Oriol Rocafiguera,2 Meral Beksa,3 Anna Marina Liberati,4 Monica Galli,5 Fredrik Schjesvold,6 Jindriska Lindsay,7 Katja Weisel,8 Darrell White,9 Thierry Facon,10 Jesus San Miguel,11 Kazutaka Sunami,12 Peter O’Gorman,13 Pieter Sonneveld,14 Xin Yu,15 Thomas Doerr,15 Amine Bensmaine,15 Mohamed Zaki,15 Kenneth Anderson,1 Meletios Dimopoulos16 on behalf of the OPTIMISMM trial investigators

1Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; 2Institut Català d’Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Badalona, Spain; 3Ankara University, Çebeci Yerleşkesi, Dikimevi, Ankara, Turkey; 4University of Perugia, Terni, Perugia, Italy; 5A.O. Papa Giovanni XXIII, U.O. di Ematologia, Bergamo, Italy; 6Oslo University Hospital, Oslo, Norway; 7East Kent Hospitals University NHS Foundation Trust, Canterbury, United Kingdom; 8University Hospital of Tuebingen, Tuebingen, Germany; 9Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax, Canada; 10Service des Maladies du Sang, Hôpital Claude Huriez, Lille, France; 11Clinica Universidad de Navarra, CIMA, IDISNA, Pamplona, Spain; 12National Hospital Organization Okayama Medical Center, Kitaku, Okayama, Japan; 13Mater Misericordiae University Hospital, University College Dublin, Dublin, Ireland; 14Erasmus MC Cancer Institute, Rotterdam, the Netherlands; 15Celgene Corporation, Summit, NJ, USA; 16National and Kapodistrian University of Athens, Athens, Greece

Abstract 8001 : OPTIMISMM—Paul Richardson, MD
OPTIMISMM Study Design and Methods

RRMM

- 1-3 prior regimens including ≥ 2 cycles of LEN Tx
- ECOG PS ≤ 2
- Prior BORT Tx allowed (except if PD with twice weekly dose)\(^a\)

\((N = 559)\)

- Stratification
  - age (≤ 75 y vs > 75 y)
  - number of prior antimyeloma regimens (1 vs > 1)
  - β2-microglobulin levels at screening
    (< 3.5 mg/L vs ≥ 3.5 to ≤ 5.5 mg/L vs > 5.5 mg/L)

- Study endpoints
  - Primary: PFS
  - Secondary: OS, ORR by IMWG criteria, DOR, safety
  - Key exploratory: TTR, PFS2, efficacy analysis in subgroups

- Data cutoff: October 26, 2017

\(^a\) Patients with PD during therapy or within 60 days of the last dose of a BORT-containing therapy under the approved dosing schedule of 1.3 mg/m\(^2\) twice weekly were excluded.

BORT, bortezomib; DOR, duration of response; IMWG, International Myeloma Working Group; LT, long-term; PFS2, progression-free survival after next line of therapy; TTR, time to response.
Progression-Free Survival (ITT Population)

- OPTIMISMM met its primary endpoint, demonstrating a clinically meaningful and statistically significant improvement in PFS with PVd vs Vd

<table>
<thead>
<tr>
<th></th>
<th>Events/N</th>
<th>Median PFS, mo</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVd</td>
<td>154/281</td>
<td>11.20</td>
<td>0.61 (0.49-0.77)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Vd</td>
<td>162/278</td>
<td>7.10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
|                               | PVD ¹  
(N=50) | PVD ²  
(N=34) | Elo-PVD ³  
(N=33) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bortezomib schedule</strong></td>
<td>1.3 mg/m² D1,8,15,22/28</td>
<td>1.3 mg/m² D1,4,8,11/21</td>
<td>1.3 mg/m² D1,8,15/28</td>
</tr>
<tr>
<td><strong>Pomalidomide schedule</strong></td>
<td>4 mg Po D1-21/28</td>
<td>4 mg Po D1-14/21</td>
<td>4 mg Po D1-21/28</td>
</tr>
<tr>
<td><strong>Lenalidomide refractory %</strong></td>
<td>100%</td>
<td>100%</td>
<td>NR but 100% exposed and 33% prior Pom, 24% priorCD38 mab</td>
</tr>
<tr>
<td><strong>Bortezomib exposed %</strong></td>
<td>58%</td>
<td>97%</td>
<td>PI exposed 100%</td>
</tr>
<tr>
<td><strong>Median prior lines</strong></td>
<td>2 (1-5)</td>
<td>2 (1-4)</td>
<td>3 (1-9)</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>86%</td>
<td>65%</td>
<td>52%</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>13.7 months</td>
<td>NR (DOR 7.4 months)</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>Gr3+ Neutropenia</strong></td>
<td>70%</td>
<td>44%</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Gr3+ Lung infections</strong></td>
<td>10%</td>
<td>18%</td>
<td>14%</td>
</tr>
</tbody>
</table>

**OF NOTE,** at EHA Elo-Pom/Dex superior PFS to Pom/dex (10.3 mo vs 4.7 mo, p.0078 HR 0.54; ORR 53% vs 26%, p .0029).

---

2- Richardson et al. Leukemia (2017) 31: 2695
3- Yee et al. ASCO 2018 abstract 8012
ELOQUENT-3 Study Design

An international, open-label, randomized, phase 2 trial (NCT02654132), with a 2-sided $\alpha=0.2$ and 85% power to detect a true HR of 0.57

### Patients with MM
- $\geq 2$ prior lines of therapy
- Refractory to last therapy
- Refractory or relapsed and refractory to lenalidomide and a proteasome inhibitor
- Prior pomalidomide not permitted

### Cycles 1–2
- **Elotuzumab** 10 mg/kg IV Weekly
- **Pomalidomide** 4 mg orally; Days 1–21
- **Dexamethasone** 40 mg\(^a\) equivalent\(^b\); weekly

### Cycles 3+
- **Elotuzumab** 20 mg/kg IV Every 4 weeks
- **Pomalidomide** 4 mg orally; Days 1–21
- **Dexamethasone** 40 mg\(^a\) orally; weekly

### Follow-up every 4 weeks\(^c\)

#### Endpoints
- **Primary**
  - PFS by investigator
- **Secondary**
  - Overall response rate (ORR)
  - Overall survival (OS)
- **Exploratory**
  - Safety
  - Duration of response (DOR)

#### Database lock: Feb 21, 2018
Minimum follow-up: 9.1 months

---

\(^{a}\)20 mg in patients aged $\geq$75 years

\(^{b}\)Dexamethasone was split between oral (28 or 8 mg in patients aged $\leq$75 or $>75$ years) and IV (8 mg) doses on days with elotuzumab

\(^{c}\)Follow-up continued until disease progression; follow-up for survival occurred at least every 12 weeks

HR, hazard ratio
Progression-Free Survival (ITT Definition)

- 46% reduction in the risk of progression or death with EPd
- Median PFS was more than twice as long with EPd vs Pd

HR=0.54 (95% CI 0.34, 0.86); p=0.0078

Median PFS
EPd n=60 10.3 mo
Pd n=57 4.7 mo

95% CI
EPd 5.6, NE
Pd 2.8, 7.2

ITT, intent-to-treat; NE, not estimable
ODD MAN OUT...

- Ruxolitinib + Lenalidomide in MM: abstract 8005
- Ibrutinib + rituximab in WM: abstract 8003
• IL-6 supports myeloma, activating JAK-STAT tyrosine kinases. Easier to treat myeloma depends on this microenvironment support (Oliveira MB et al).

• Constitutive NF-kB activation allows MM cells to be IL-6 independent (Yang et al).

• No JAK2 V617F mutation in myeloma (Fiorini A et al).

• High concentrations & doses of Ruxolitinib with Len/Dex in vitro and in a murine model improved killing (Chen H et al).

• Ruxolitinib 25 BID (13 pts) +/- high dose dex (7 pts combo) with no responses (NCT00639002).

Yang Y et al. Constitutive NF-κB activation confers IL-6 independence and resistance to ruxolitinib in murine plasmacytoma. JBC. 2011.
Fiorini A. Screening of JAK2 V617F mutation in multiple myeloma. Leukemia. 2006.
Chen H. Anti-myeloma activity by the combination of Ruxolitinib with Lenalidomide and steroids. ASH 2014.
Ruxolitinib + Lenalidomide + Methylprednisolone

What response rate would make this trial a clear win?

• ASPIRE: ORR 66%, ≥ VGPR 40%
  (20% Len exposed, ≈15% refractory to Thal, ≈7% refractory Len)

• TOURMALINE: ORR 72%, ≥ VGPR 39%
  (12% Len exposed, 47% Thal exposed, 25% Thal refractory)

• POLLUX: ORR 76%, ≥ VGPR 49%
  (17% Len exposed, 44% Thal exposed, 4-9% IMiD refractory)

• This trial: ORR 40%, ≥ VGPR 8%
  (100% IMiD exposed, 50% Len refractory)
Randomized Phase 3 Trial of Ibrutinib/Rituximab vs Placebo/Rituximab in Waldenström’s Macroglobulinemia

Abstract 8003

Meletios A. Dimopoulos, MD1; Alessandra Tedeschi, MD2; Judith Trotman, FRACP3; Ramón García-Sanz, MD, PhD4; David MacDonald, MD5; Veronique Leblond, MD, PhD6; Beatrice Mahe, MD7; Charles Herbaux, MD8; Constantine Tam, MBBS9; M. Lia Palomba, MD10; Jeffrey V. Matous, MD11; Chaim Shustik, MD12; Efstathios Kastritis, MD1; Steven P. Treon, MD, PhD13; Jianling Li, MS14; Zeena Salman, BS14; Thorsten Graef, MD, PhD14; Christian Buske, MD15 on behalf of the iNNOVATE Study Group and the European Consortium for Waldenström’s Macroglobulinemia

1National and Kapodistrian University of Athens School of Medicine, Athens, Greece; 2ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; 3Concord Hospital, University of Sydney, Concord, Australia; 4Hospital Universitario de Salamanca, Salamanca, Spain; 5The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada; 6Département d’ Hématologie Hôpital Pitié-Salpêtrière APHP, UPMC Université Paris, Paris, France; 7Centre Hospitalier Universitaire de Nantes, Nantes, France; 8Centre Hospitalier Régional Universitaire de Lille, Institute of Hematolog-Tranfusion, Lille, France; 9Peter MacCallum Cancer Centre & St. Vincent’s Hospital and the University of Melbourne, Melbourne, Australia; 10Memorial Sloan Kettering Cancer Center, New York City, NY, USA; 11Colorado Blood Cancer Institute, Denver, CO, USA; 12Royal Victoria Hospital at McGill University Health Centre, Montreal, Canada; 13Dana-Farber Cancer Institute, Boston, MA, USA; 14Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA, USA; 15Comprehensive Cancer Center Ulm, Institute of Experimental Cancer Research, University Hospital of Ulm, Ulm, Germany.
Ibrutinib + Rituximab vs Rituximab alone [iNNOVATE]

| Eligibility                  | • Hb<10g/dL, Plt < 100K, bulky adenopathy, organomegaly, B symptoms, hyperviscosity, symptomatic neuropathy, cryoglobulinemia  
|                             | • Rituximab sensitive |
| Treatment                   | Rituximab weeks 1-4 and 17-20 +/- Ibrutinib 420 mg daily |
| Priors                      | 45% newly diagnosed |
| Responses                   | ≥PR 72% Ibrutinib+R vs 32% R alone (p<0.0001)  
|                             | 30-month PFS at 26.5 month f/u: 82% vs 28% (p<0.0001).  
|                             | No OS benefit |
| Adverse events              | 8% couldn’t tolerate I / 4% couldn’t tolerate R alone  
|                             | No ‘unexpected’ toxicities |
Ibrutinib + Rituximab vs Rituximab alone [iNNOVATE]

- Infusion-related reactions: 1% vs 16% R alone
- Grade ³⁄₄ atrial fibrillation – 12% vs 1% R alone
- Pneumonia/upper respiratory tract – 12% vs 3% R alone
Multiple Choice Question:
Which of the following statements is true?

A. Pembrolizumab in combination with either lenalidomide or pomalidomide improves PFS in myeloma.
B. Preliminary results demonstrate that CAR T cells are safe, effective and potentially curative in RRMM.
C. Carfilzomib at 70 mg/m2 weekly is more efficacious and comparable toxicity to carfilzomib 27 mg/m2 given twice weekly.
D. Venetoclax plus carfilzomib only is effective in MM expressing t(11;14).
SUMMARY

• PD-1 inhibitors in myeloma appear dead on arrival
• Once weekly carfilzomib 70 mg/m2 is superior to twice weekly carfilzomib at 27 mg/m2
• Once weekly carfilzomib/lenalidomide/dexamethasone is active but with moderate toxicities
• Carfilzomib + monoclonal antibodies or venetoclax looks very promising
• CAR T cell data is encouraging but the data sets are small with short follow up; CRS in MM is less than ALL and NHL
• Subcutaneous daratumumab in myeloma (and amyloidosis) should be FDA approved in the not too distant future
• Pomalidomide/bortezomib/dex is superior to pomalidomide/dex
• Ruxolitinib+Lenalidomide+Methylprednisolone is promising even in len-refractory MM
• Ibrutinib + rituximab is superior to rituximab alone in WM
DISCUSSION

Question & Answer

Joe Kim, MD, MPH, MBA
Submit questions for the speaker using the chat box.
Thank you!