5th Annual Symposium on Current Strategies in the Management of B-cell Lymphomas, T-cell Lymphomas, Multiple Myeloma and Leukemia

Program Director

Fredrick B. Hagemeister, MD
Professor of Medicine,
Department of Lymphoma/Myeloma, Division of Cancer Medicine,
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Saturday, June 11, 2016
Hyatt Regency Houston/Galleria
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Phone (832) 802-1234

Jointly provided by

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To view full slide handouts, visit www.cancernetus.com/june11
Statement of Need/Program Overview
This symposium is intended to improve care of patients with hematological malignancies by accelerating adoption of new guidelines and evidence-based practice change. The format will include didactic lectures from known opinion leaders, question and answer sessions, and ample opportunity for participant interaction with faculty.

Target Audience
This symposium is directed primarily to hematologists/oncologists, radiation oncologists, researchers, pharmacists, registered nurses, physician assistants, nurse practitioners and fellows in training interested in new development in hematological malignancies. No specific skill or knowledge other than a basic training in hematology/oncology is required for successful participation in this activity.

Learning Objectives
After completing this activity, the participant should be better able to:
• Explain the treatment options for diffuse large B-cell lymphoma (DLBCL)
• Explain the treatment options for follicular lymphoma (FL)
• Evaluate the treatment options for chronic lymphocytic lymphoma (CLL)
• Evaluate the treatment options for mantle cell lymphoma (MCL)
• Cite the novel treatment options for peripheral T-cell lymphomas (PTCL)
• Describe the role of risk stratification and upfront therapies in multiple myeloma
• Appraise novel approaches in the treatment of relapsed and refractory multiple myeloma
• Describe the role of maintenance therapy in the management of multiple myeloma
• Describe emerging novel therapeutic pathways for multiple myeloma
• Identify updates in the treatment of chronic myelogenous leukemia (CML)
• Select appropriate treatment options for myelodysplastic syndromes (MDS)
### Agenda

**SATURDAY – June 11, 2016**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00 AM</td>
<td>Breakfast and Registrations</td>
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<tr>
<td>7:55 AM</td>
<td>Welcome and Introductions</td>
<td>Fredrick B. Hagemeister, MD</td>
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<tr>
<td>8:00 AM</td>
<td><strong>LYMPHOMA (HL, NHL, T-cell Lymphomas)</strong></td>
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<tr>
<td>8:00 AM</td>
<td>Overview of Treatment Options for Diffuse Large Cell Lymphoma (DLCL)</td>
<td>Fredrick B. Hagemeister, MD</td>
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<tr>
<td>8:30 AM</td>
<td>Overview of Treatment Options for Follicular Lymphoma (FL)</td>
<td>Nathan Fowler, MD</td>
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<tr>
<td>9:00 AM</td>
<td>Overview of Treatment Options for Chronic Lymphocytic Leukemia (CLL)</td>
<td>Frederick B. Hagemeister, MD</td>
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<tr>
<td>9:30 AM</td>
<td>Overview of Treatment Options for Mantle Cell Lymphoma (MCL)</td>
<td>Hun Ju Lee, MD</td>
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<tr>
<td>10:00 AM</td>
<td>BREAK</td>
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<tr>
<td>10:15 AM</td>
<td>Overview of Treatment Options for Peripheral and Cutaneous T-cell Lymphoma</td>
<td>Michelle Fanale, MD</td>
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<tr>
<td>10:45 AM</td>
<td>Case Report and Panel Discussion</td>
<td>Fredrick B. Hagemeister, MD/Nathan Fowler, MD/Hun Ju Lee, MD/Michelle Fanale, MD</td>
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<tr>
<td>11:00 AM</td>
<td><strong>MULTIPLE MYELOMA</strong></td>
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<tr>
<td>11:00 AM</td>
<td>Updates in the Management of Transplantation-Eligible Patients With Newly Diagnosed Myeloma</td>
<td>Robert Orlowski, MD, PhD</td>
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<tr>
<td>11:30 AM</td>
<td>Recent Approaches in the Treatment of Relapsed and Refractory Multiple Myeloma</td>
<td>Keith Stewart, MD</td>
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<tr>
<td>12:00 PM</td>
<td>Maintenance Therapy in the Management of Multiple Myeloma</td>
<td>Elisabet Manasanch, MD</td>
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<td>12:30 PM</td>
<td>LUNCH</td>
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<tr>
<td>1:30 PM</td>
<td>New Drugs and Clinical Trials in Multiple Myeloma</td>
<td>Keith Stewart, MD</td>
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<tr>
<td>2:00 PM</td>
<td>Case Report and Panel Discussion</td>
<td>Robert Orlowski, MD, PhD/Elisabet Manasanch, MD</td>
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<tr>
<td>2:15 PM</td>
<td><strong>LEUKEMIA (CML, MDS)</strong></td>
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<tr>
<td>2:15 PM</td>
<td>Overview of Therapeutic Options for Myeloproliferative Neoplasms (CML)</td>
<td>Guillermo Garcia-Manero, MD</td>
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</tr>
<tr>
<td>3:45 PM</td>
<td>Closing Remarks and Adjourn</td>
<td>Fredrick B. Hagemeister, MD</td>
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</tbody>
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Faculty

Michelle A. Fanale, MD
Associate Professor, Department of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

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Associate Professor, Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX

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Keith Stewart, MD
Dean for Research, Polak Professor of Cancer Research, Mayo Clinic in Arizona, Scottsdale, AZ
Disclosure of Relevant Financial Relationships

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The faculty reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME/CE activity:

<table>
<thead>
<tr>
<th>Name</th>
<th>Conflict of Interest Disclosures</th>
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<tbody>
<tr>
<td>Michelle A. Fanale, MD</td>
<td>Speaker’s Bureau: Takeda, Celgene, Spectrum, Seattle Genetics</td>
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<td></td>
<td>Advisory Board: Celgene, Spectrum, BMS, MERCK, Seattle Genetics</td>
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<tr>
<td>Nathan H. Fowler, MD</td>
<td>Consultant: Celgene, Roche, Pharmacyclics, AbbVie</td>
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<tr>
<td>Guillermo Garcia-Manero, MD</td>
<td>No relevant financial relationships</td>
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<tr>
<td>Elisabet E. Manasanch, MD</td>
<td>No relevant financial relationships</td>
</tr>
<tr>
<td>Robert Orlowski, MD, PhD</td>
<td>Advisory Board: Array Biopharma, BMS, Celgene, FORMA Therapeutics, Janssen, MPI/Takeda, Onyx/Amgen</td>
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<td>Research Support: BMS, Celgene, MPI/Takeda, Onyx/Amgen, Spectrum Pharma</td>
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<td>Keith Stewart, MD</td>
<td>Consultant: Celgene, Novartis</td>
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<td>Advisory Board: BMS</td>
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<tr>
<td>Kamatham A. Naidu, PhD</td>
<td>No relevant financial relationships</td>
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All other individuals in a position to control content have no relevant financial relationships to disclose.
Overview of Treatment Options for Diffuse Large Cell Lymphoma (DLCL)

Fredrick B. Hagemeister, MD
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Keith Stewart, MD
Case

- 69 yo retired nurse with IgGκ multiple myeloma
- Hgb 92 and lytic lesions, Creatinine and calcium normal
- Albumin 3.8 and β2m 5.8, so ISS stage III
- FISH trisomy 9 with 1q+ amplification

Treatment

- Received RVD for 4 months with grade 1 neuropathy the only toxicity
- Autologous stem cell transplant complicated by hypotensive episode of sepsis with renal injury
- Maintenance lenalidomide (10 mg) given for 17 months – mild fatigue and daily diarrhea x 2
- On maintenance, a rising M-protein but asymptomatic, Creatinine is 1.82

Factors in Selecting Relapse Therapy

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>DISEASE</th>
<th>TREATMENT</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>Risk Status</td>
<td>Mode of Administration</td>
</tr>
<tr>
<td>Performance Status</td>
<td>Relapse Rate</td>
<td>Doublet or Triplet</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>Rate of rise</td>
<td>Cost</td>
</tr>
<tr>
<td>Poor Marrow Reserve</td>
<td>Organ damage</td>
<td>Toxicity</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Extra-medullary</td>
<td>Myelosuppression</td>
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<td></td>
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<td>Neutropenia</td>
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<td>Other comorbidities</td>
<td>Previous Therapy</td>
<td>Thrombosis</td>
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<tr>
<td>- Cardiac</td>
<td>Depth</td>
<td>Risk of SPM</td>
</tr>
<tr>
<td>- Diabetes</td>
<td>Duration</td>
<td></td>
</tr>
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</table>

Improving Survival in MM

25% of patients live less than 3 years

Follow up from diagnosis (Years)
### Factors in Selecting Relapse Therapy

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<th>TREATMENT</th>
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<td>Age</td>
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<tr>
<td>Performance Status</td>
<td>Rapidity of Relapse</td>
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<tr>
<td>Diabetes</td>
<td>Duration</td>
<td>- Risk of SPM</td>
</tr>
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</table>

### ENDOR study design

- **Randomization**: 1:1
- **N=929**
- **Stratification**:
  - Prior proteasome inhibitor therapy
  - Prior line of treatment
  - ISS stage
  - Rate of V administration

### Less Common AEs of Interest

<table>
<thead>
<tr>
<th>AE, %</th>
<th>Kd (n=462)</th>
<th>Vd (n=456)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Acute renal failure*</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Ischemic heart disease*</td>
<td>3</td>
<td>1.7</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>4</td>
<td>0.9</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>3</td>
<td>1.7</td>
</tr>
<tr>
<td>Pulmonary hypertension*</td>
<td>1.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>

### Conclusions

- **ENDEAVOR** is the first head-to-head study comparing 2 proteasome inhibitors.
- Kd resulted in a 2-fold decrease in the risk of progression or death compared with Vd.
- Median PFS of 18.7 months (Kd) vs 9.4 months (Vd).
- ORR was significantly higher with Kd than Vd (77% vs 63%).
- Median PFS of 18.7 months (Kd) vs 9.4 months (Vd).
- Rates of grade ≥3 hypertension (9% vs 3%), dyspnea (5% vs 2.2%), and cardiac failure (6% vs 1.8%) were higher in the Kd group compared with the Vd group.
- Grade ≥2 PN rates were significantly lower in the Kd group than in the Vd group (6% vs 32%).
The evidence

At least five recent randomized Phase 3 trials support triplet therapy

- IFM2005-04: VTD vs VD
- ASPIRE: KRd vs Rd
- TOURMALINE-MM1: IRd vs Rd
- ELOQUENT-2: ERd vs Rd
- PANORAMA: PanVd vs Vd
Carfilzomib, Lenalidomide, and Dexamethasone vs Lenalidomide and Dexamethasone in Patients with Relapsed Multiple Myeloma: Interim Results from ASPIRE, a Randomized, Open-Label, Multicenter Phase 3 Study


ASPIRE Study Design

Randomization
N=792

Stratification:
- β2-microglobulin
- Prior bortezomib
- Prior lenalidomide

After cycle 12, carfilzomib given on days 1, 2, 15, 16
After cycle 18, carfilzomib discontinued

28-day cycles

Primary Endpoint: Progression-Free Survival

ITT Population (N=792)

KRd vs Rd

No. at Risk:
KRd: 396 332 279 206 151 117 72 18 1
Rd: 396 287 206 151 117 72 18 1

Median PFS, mo: 26.3 vs 17.6
HR (KRd/Rd): 0.69 (0.57–0.83)
P value (one-sided): <0.0001

Secondary Endpoints: Response

<table>
<thead>
<tr>
<th>Category</th>
<th>KRd (n=392)</th>
<th>Rd (n=389)</th>
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<tr>
<td>Any AE, %</td>
<td>96.9</td>
<td>83.7</td>
</tr>
<tr>
<td>Grade ≥3 treatment-emergent AE</td>
<td>97.2</td>
<td>80.7</td>
</tr>
<tr>
<td>Deaths within 30 days of last dose, %</td>
<td>7.7</td>
<td>8.5</td>
</tr>
<tr>
<td>Deaths due to disease progression</td>
<td>1.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Deaths due to AEs</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Serious AE, %</td>
<td>59.7</td>
<td>53.7</td>
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<tr>
<td>Median treatment duration, weeks (range)</td>
<td>84.0</td>
<td>87.4</td>
</tr>
<tr>
<td>Treatment discontinuations, %</td>
<td>83.0</td>
<td>77.8</td>
</tr>
<tr>
<td>Discontinuation due to disease progression</td>
<td>17.9</td>
<td>50.1</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>15.3</td>
<td>17.7</td>
</tr>
</tbody>
</table>

Health-related Quality of Life

EORTC Global Health Status improved in the KRd group vs the Rd group over 18 cycles of treatment (P = 0.0001)

Adverse Events (AEs), Treatment Discontinuations, and Deaths
### Other AEs of Interest

<table>
<thead>
<tr>
<th>AE, %</th>
<th>All Grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>19.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Peripheral neuropathy*</td>
<td>17.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15.3</td>
<td>4.3</td>
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<tr>
<td>Acute renal failure*</td>
<td>6.4</td>
<td>3.3</td>
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<tr>
<td>Elevated creatinine</td>
<td>6.6</td>
<td>1.0</td>
</tr>
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<td>6.4</td>
<td>3.8</td>
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<td>Ischemic heart disease*</td>
<td>5.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>6.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Second primary malignancy*</td>
<td>2.8</td>
<td>2.3</td>
</tr>
</tbody>
</table>

*Grouped term.

### Conclusions

- **PFS** was significantly improved by 8.7 months with KRd (HR, 0.69; \(P<0.0001\))
- An unprecedented median PFS of 26.3 months with KRd
- **Interim OS analysis**: trend in OS favoring the KRd group; Kaplan-Meier 24-month OS rates 73.3% (KRd) versus 65.0% (Rd)
- **ORR** was higher with KRd (87.1% vs 66.7%); significantly more patients achieved ≥CR (31.8% vs 9.3%)
- **QoL Global Health Status** improved
Conclusions (continued)

- Rates of grade ≥3 hypertension (9% vs 3%), dyspnea (5% vs 2.2%), and cardiac failure (5% vs 1.8%) were higher in the Kd group compared with the Vd group.
- Grade ≥2 PN rates were significantly lower in the Kd group than in the Vd group (6% vs 32%).
- Although Kd patients remained on study treatment longer (40 weeks vs 27 weeks), treatment discontinuation due to AEs and on-study deaths due to AEs were comparable between groups.
- Kd PFS was superior to Vd regardless of age or prior bortezomib exposure.

Conclusions

- PFS was significantly improved by 8.7 months with KRd (HR, 0.69; P<0.0001).
- An unprecedented median PFS of 26.3 months with KRd.
- Interim OS analysis: trend in OS favoring the KRd group; Kaplan-Meier 24-month OS rates 73.3% (KRd) versus 65.0% (Rd).
- ORR was higher with KRd (87.1% vs 66.7%); significantly more patients achieved ≥CR (31.8% vs 9.3%).
- QoL Global Health Status improved.

TOURMALINE-MM1: Phase 3 Study of Weekly Oral Ixazomib Plus Lenalidomide-dexamethasone

Global, double-blind, randomized, placebo-controlled study design

Primary endpoint:
- PFS

Secondary endpoints:
- OS
- OS in patients with del(17p)

Response and progression (IMWG 2011 criteria) assessed by an independent review committee (IRC) blinded to both treatment and investigator assessment.

Outcomes by Cytogenetic Risk Group

Conclusions: Ixazomib, the First Oral Proteasome Inhibitor, Significantly Extends PFS in a Phase 3 Trial

- Ixazomib when combined with Rd for patients with relapsed and/or refractory MM was associated with:
  - a significant and clinically meaningful improvement in PFS
  - significantly improved TTP and response rates
  - improved PFS in high-risk patients, similar to that in the overall patient population and in standard-risk patients
- Ixazomib added limited additional toxicity to that seen with placebo-Rd
  - Low rates of PN and no cardiovascular or renal signals
  - Patient-reported quality of life was maintained
- The all-oral regimen of IRd may become a new standard of care for relapsed and/or refractory MM
- Ixazomib was approved by the US FDA on Nov 20 under the name NINLARO®
ELOQUENT Study Design

- ELOQUENT-2 is an open-label, randomized, multicenter, phase 3 trial
- Patients
  - RRMM
  - June 2011
  - Database lock: August 2015
- Statistical analysis
  - Threshold for interim OS significance was 0.014 based on 295/427 events required for final analysis

Extended Progression-Free Survival

- E-lo: Cycles 1 and 2 weekly, then every other week, 10 mg/kg IV
- Len: D1–21, 25 mg PO
- Dex: weekly, 40 mg PO
- E-Ld (Elo: Cycles 1 and 2 weekly, then every other week, 10 mg/kg IV)
- Ld: Len: D1–21, 25 mg PO
- Dex: weekly equivalent, 40 mg
- E-Ld: n=321
- Ld: n=266
- Median PFS: 14.9 mos (E-Ld); 12.1 mos (Ld)
- Relative improvement in PFS of 44% at 3 years
- OS: E-Ld 19.4 mos, vs Ld 16.6 mos
- PFS benefit with E-Ld was maintained over time (vs Ld)
- PFS benefits with E-Ld were consistent across key subgroups
- 38% fewer patients in the E-Ld vs Ld arm started a subsequent line of therapy

Summary

- Elotuzumab, a novel immunostimulatory monoclonal antibody, in combination with Ld, demonstrated a durable and clinically relevant improvement in PFS and ORR
- Extended follow-up demonstrated a 27% reduction in the risk of disease progression or death compared with Ld alone (HR 0.73; p=0.0014)
- 38% fewer patients in the E-Ld vs Ld arm started a subsequent line of therapy during the follow-up period
- PFS benefits with E-Ld were consistent across key subgroups
- Interim overall survival analysis demonstrated a strong trend in favor of E-Ld vs Ld (HR 0.77; p=0.0257)
- Updated safety and tolerability data are consistent with previous findings, confirming that there is minimal incremental toxicity associated with the addition of elotuzumab to Ld
- FDA recently granted approval for the use of elotuzumab in combination with Ld in patients with multiple myeloma who have received one to three prior therapies
Summary

• Biology supports combination therapy, continuous suppressive therapy and eradication of minor clones
• Treatment @ relapse is individualized
• Carfilzomib, Ixazomib, Elotuzumab and Pomalidomide are useful therapies following Bortezomib and Lenalidomide
• Monoclonal antibody Daratumumab as a single agent is FDA approved but likely to quickly be used in combination earlier in disease

Thank you
Maintenance Therapy in the Management of Multiple Myeloma

Elisabet Manasanch, MD
Maintenance Therapy in the Management of Multiple Myeloma

Elisabet Manasanch M.D., M.H.Sc.
Assistant Professor, Department of Lymphoma/Myeloma
Division of Cancer Medicine

5th Annual Symposium on Current Strategies in the Management of Lymphoma Myeloma and Leukemia

Conflict of Interest Disclosure

Research Funding: Signal Genetics, Merck
Consulting: Novartis

Outline

Overview
Therapy options
New agents in maintenance
Question and Answer Session

Background
Favorable results both in younger and older patients with multiple myeloma have been observed in recent years
Despite this, there is a high relapse rate after initial response to treatment
Achieving the deepest level of response and maintaining a sustained remission are important to achieve a cure in multiple myeloma
Maintenance strategies are incorporated in most phase II-III clinical trials. Sequential treatment strategy is the modern paradigm of treatment for patients with myeloma

Historical Perspective

Long term melphalan or other alkylator agent use was associated with higher risk of secondary cancers like myelodysplastic syndrome and leukemia
Interferon maintenance was first used in multiple randomized clinical trials but failed to show a benefit for overall survival
Long term steroid use associated with long term effects

Historical Perspective

Maintenance was first introduced as treatment after autologous stem cell transplantation
First drug to show a benefit for use in maintenance was thalidomide
Once lenalidomide and bortezomib where approved for treatment, these drugs have also been studied in the maintenance setting
In the future, pomalidomide, ixazomib, carfilzomib and monoclonal antibodies might also be used
Overview

Therapy Options

New agents in maintenance

Questions

Outline

**Thalidomide**

6/7 trials showed a benefit for progression free survival

Patients that were receiving thalidomide after transplant were in remission longer

2/7 trials also showed a significant increase in benefit for overall survival

**Lenalidomide**

4 clinical trials have been completed using lenalidomide in the maintenance setting

3 of these trials are after autologous transplantation

4/4 trials show that lenalidomide maintenance prolonged remission

2/4 trials show that lenalidomide maintenance also improved overall survival

**CALGB 100104 Schema**

Registration

Restaging Days 90–100

Randomization

Mel 200

ASCT

CR

PR

SD

Placebo

Lenalidomide**

10 mg/d for 6 weeks in CR

20 mg/d for 6 weeks in PR

*Reduced to Celgene Corp, Summit, NJ

**Stratification based on diagnostic β2M and thalidomide and lenalidomide use during induction

**Objectives**

- **Primary Objective:**
  - Determine the efficacy of lenalidomide in prolonging time to progression (TTP) in myeloma patients following ASCT
  - Powered to determine a TTP improvement prolongation from 24 months to 33.6 months (9.6 months)

- **Secondary Objectives:**
  - CR rate post-ASCT
  - PFS and OS
  - Feasibility of long-term lenalidomide administration
IFM 05-02 Study Design

Patients < 65 years, with non-progressive disease, < 6 months after ASCT in first line
Randomization: stratified according to Beta 2m, del13, VGPR

Consolidation:
Lenalidomide alone 25 mg/day p.o.
days 1-21 of every 28 days for 2 months

Arm A = Placebo
(N=107)
until relapse

Arm B = Lenalidomide
(N=207)
10-15 mg/day until relapse

Primary end-point: PFS.
Secondary end-points: CR rate, TTP, OS, feasibility of long-term lenalidomide.

ASCT = autologous stem cell transplant. IFM = Intergroupe Francophone du Myelome.

Follow up analysis of PFS and OS
After second relapse shows something different

MM-015: Continuous LEN in NDMM

Follow up analysis of PFS and OS
After second relapse shows something different

May be lenalidomide maintenance is associated with chemoresistance

Attal et al. ASH 2013.
Study of second line therapies was limited due to the type of analysis.

Second line time to progression was similar among all arms of the study.

Use of MPR-R did not induce resistant relapses.
**HOVON-65/GMMG-HD4**

**EVALUATION OF BORTEZOMIB AS MAINTENANCE**

Newly diagnosed multiple myeloma

Update with long term follow up

Comparison with thalidomide as maintenance option

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**Study Design**

- **NDMM, T/E: age 18-65 y**
- **Randomization**
  - 3 x VAD
  - CAD + GCST
  - MEL 200 + PRISCT
- **Thalidomide**
  - Maintenance 50 mg/day for 2 years
- **Bortezomib Maintenance**
  - 1.3 mg/m²/2 weeks for 2 years

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**HOVON-65/GMMG-HD4**

- **In this trial, bortezomib may be a superior maintenance than thalidomide**

**VMPT-VT versus VMP**

- **Newly diagnosed non-transplant eligible patients**

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**Secondary Malignancies**

Reported: small increased risk of secondary malignancies with the use of lenalidomide maintenance when compared to patients who did not receive this maintenance

---

**Secondary Malignancies**

<table>
<thead>
<tr>
<th>Trial</th>
<th>PFS (lenalidomide vs placebo)</th>
<th>3-year OS (lenalidomide vs placebo)</th>
<th>Second non-hematologic malignancy (lenalidomide vs placebo)</th>
<th>Second hematologic malignancy (lenalidomide vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG1</td>
<td>41 vs 28 months (P = 0.001)</td>
<td>80 vs 84 months (P = 0.29)</td>
<td>10 vs 8 patients</td>
<td>13 vs 5 patients</td>
</tr>
<tr>
<td>VMM015</td>
<td>26 vs 7 months (P = 0.001)</td>
<td>70 vs 82 months (P = 0.25)</td>
<td>5 vs 4 vs 3 patients2</td>
<td>7 vs 5 vs 1 patients</td>
</tr>
<tr>
<td>CALGB6</td>
<td>46 vs 27 months (P &lt; 0.001)</td>
<td>89% vs 80% (P = 0.01)</td>
<td>10 vs 5 patients</td>
<td>8 vs 1 patients</td>
</tr>
</tbody>
</table>

**Abbreviations:** OS, overall survival; PFS, progression-free survival; *Excluding non-melanoma skin cancer.* MPRH vs MPN vs MF

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Landgren et al. Leukemia. 2014
Secondary Malignancies

Risk of hematologic secondary malignancies is associated with prior use of oral melphalan.

Duration of Maintenance

Longer might be better?

Currently, it is not clear if patients should stop maintenance after 2-3 years of therapy and more long-term follow-up data is needed, especially from conducted randomized phase III studies.

Several meta-analysis have been done on efficacy. Most meta-analysis show that overall there is a statistical improvement in PFS but not in OS*

Evaluation of level of disease (no evidence of disease vs residual disease), patient preference and tolerance to lenalidomide (quality of life, cytopenia, thrombosis) should be taken into account when making a decision of whether to stop maintenance or not.

Outline

Overview
Therapy options
New agents in maintenance
Question and Answer Session

Oral Proteasome Inhibitors/Antibodies

Reduced phase II
• Ixazomib vs placebo following ASCT and after initial therapy without ASCT

Randomized phase II
• Ixazomib/Len/Dex vs Len/Dex (2 years) post ASCT

Randomized phase II
• Ixazomib/Lenalidomide/dex consolidation following ASCT followed by lena vs no maintenance (3 years)

Randomized phase II
• Ixazomib/Lenalidomide/dex consolidation following ASCT followed by lena vs no maintenance (3 years)

Single arm phase II
• Ixazomib following ASCT (continue until progression or toxicity)

Single arm phase II
• Elotuzumab/Lenalidomide post ASCT (anti progression or toxicity)
Oral Proteasome Inhibitors

TOURMALINE MM3: Phase III randomized study of ixazomib versus placebo following ASCT


Primary endpoint: PFS

652 patients

Oral Proteasome Inhibitors

TOURMALINE MM4: Phase III randomized study of ixazomib versus placebo after initial treatment in patients who have not undergone autologous SCT as initial therapy


Primary endpoint: PFS

761 patients

Patients must have completed 6–12 months of initial standard-of-care therapy with a response of PR or better, and be randomized no later than 60 days after the last dose of initial therapy.

PATIENTS and their FAMILIES

Community (physicians/support-patient groups)

Questions

Elisabet Manasanch

eemanasanch@mdanderson.org

Robert Z. Orlowski, Donna Weber, Jatin Shah, Sheeba Thomas, Hans Lee

MDACC Myeloma Center

5th Annual Symposium on Current Strategies in the Management of Lymphoma, Myeloma and Leukemia

Thank you

Elisabet Manasanch M.D., M.H.Sc.

Assistant Professor, Department of Lymphoma/Myeloma
Division of Cancer Medicine

5th Annual Symposium on Current Strategies in the Management of Lymphoma, Myeloma and Leukemia
New Drugs and Clinical Trials in Multiple Myeloma

Keith Stewart, MD
New Agents in Multiple Myeloma

Patient Course
- The patient is treated with carfilzomib and Pomalidomide with dexamethasone
- She becomes febrile and dyspneic on day 2 of therapy, her urine output drops, she attends the ER and her creatinine is up to 274, BP is 182/102
- Carfilzomib is discontinued and she remains on Pomalidomide and dexamethasone but does not respond

Patient Course
- The patient is intolerant of both carfilzomib and bortezomib and progressed on both lenalidomide and pomalidomide
- A novel agent is sought

Patient Course
- The patient is treated with carfilzomib and Pomalidomide with dexamethasone
- She becomes febrile and dyspneic on day 2 of therapy, her urine output drops, she attends the ER and her creatinine is up to 274, BP is 182/102
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Conflict of Interest Disclosure
Consultant: Celgene, Novartis
Advisory Board: Bristol-Myers Squibb
Baseline Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DVd (n = 251)</th>
<th>Vd (n = 247)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>61 (27-88)</td>
<td>62 (28-86)</td>
</tr>
<tr>
<td>KD staging, n (%)</td>
<td>92 (37)</td>
<td>74 (31)</td>
</tr>
<tr>
<td>Cytogenetic profile, n (%)</td>
<td>28 (11)</td>
<td>19 (8)</td>
</tr>
<tr>
<td>Time from diagnosis, years</td>
<td>1.07</td>
<td>1.72</td>
</tr>
<tr>
<td>Median age</td>
<td>(0.7-3.0)</td>
<td>(0.8-16.6)</td>
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</tbody>
</table>

**DVd administration:** Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/min permitted.

**Key eligibility:**
- RRMM
- Prior bortezomib
- Refractory to IMiD (IMO/2 cycles)
- Prior PI + IMiD, n (%) 112 (45) 129 (52)
- Prior IMiD, n (%) 179 (71) 198 (80)
- Prior PI, n (%) 169 (67) 172 (70)
- Prior ASCT, n (%) 156 (62) 149 (60)
- Time to response: 7.4 (range, 0.4-16.9) months

**Primary Endpoint:**
- OS
- TTP
- MRD
- ORR, VGPR, CR

**Secondary Endpoints:**
- Safety

**Rationale:**
- 70% reduction in the risk of disease progression for DVd vs Vd

**Patient Disposition**

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<th>Patients</th>
<th>DVd (n = 251)</th>
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<tr>
<td>Randomized, n</td>
<td>251</td>
<td>247</td>
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<tr>
<td>Treated, n (%)</td>
<td>243 (97)</td>
<td>237 (96)</td>
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<tr>
<td>Discontinued treatment, n (%)</td>
<td>74 (31)</td>
<td>104 (44)</td>
</tr>
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<td>Reasons for discontinuation</td>
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<td></td>
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<td>Progressive disease</td>
<td>47 (19)</td>
<td>60 (25)</td>
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<td>Non-compliance with study drug Withdrawal by patient</td>
<td>3 (1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.4)</td>
<td>2 (0)</td>
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**Primary Endpoints:**

- Median OS: Not reached
- Median TTP: Not reached

**Secondary Endpoints:**

- OS
- TTP
- MRD
- ORR, VGPR, CR

**Rationale:**
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**Primary Endpoints:**

- Median OS: Not reached
- Median TTP: Not reached

**Secondary Endpoints:**

- OS
- TTP
- MRD
- ORR, VGPR, CR

**Rationale:**
- 70% reduction in the risk of disease progression for DVd vs Vd
**PFS: Subgroup Analysis**

<table>
<thead>
<tr>
<th>Age</th>
<th>HR (95% CI)</th>
<th>Favor DVd</th>
<th>Favor Vd</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 years</td>
<td>0.44 (0.28, 0.68)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>≥65 years</td>
<td>0.55 (0.31, 0.98)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Prior ASCT

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>Favor DVd</th>
<th>Favor Vd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>0.31 (0.18, 0.52)</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>0.66 (0.31, 1.41)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Overall Response Rate**

<table>
<thead>
<tr>
<th>Grade 3-4 TEAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory Peripheral Neuropathy</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Lymphopenia</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>

**Infusion-related Reactions (IRRs)**

<table>
<thead>
<tr>
<th>Safety Analysis Set (n = 243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
</tr>
<tr>
<td>Patients with IRRs, %</td>
</tr>
<tr>
<td>Most common (&gt;5%) IRRs</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Bronchospasm</td>
</tr>
<tr>
<td>Cough</td>
</tr>
</tbody>
</table>

Preinfusion: dexamethasone 20 mg, paracetamol 650-1000 mg, diphenhydramine 25-50 mg
Stop infusion immediately for mild symptoms; cease immediately if any grade 3-4 symptoms
PI-based Studies

<table>
<thead>
<tr>
<th>Daratumumab &amp; Dv vs Dv</th>
<th>Carfilzomib &amp; Kd vs Vd1</th>
<th>Panobinostat &amp; PVd vs Vd2,3</th>
<th>Elotuzumab &amp; EVd vs Vd4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS HR (95% CI)</td>
<td>0.39 (0.28-0.53)</td>
<td>0.53 (0.46-0.63)</td>
<td>0.72 (0.59-0.88)</td>
</tr>
<tr>
<td>PFS Median mo</td>
<td>NE</td>
<td>18.7, 12.0, 9.7</td>
<td>21.3, 13.1, 11.4</td>
</tr>
<tr>
<td>V/CR</td>
<td>59%</td>
<td>54%</td>
<td>94% (0.70-1.14)</td>
</tr>
<tr>
<td>Duration of response, mo</td>
<td>NE</td>
<td>13%</td>
<td>0.79 (0.56-1.08)</td>
</tr>
<tr>
<td>OS HR (95% CI)</td>
<td>0.77 (0.47-1.26)</td>
<td>0.72 (0.59-0.88)</td>
<td>0.61 (0.32-1.15)</td>
</tr>
</tbody>
</table>

Conclusions

- Daratumumab-Vd significantly improved PFS, TTP, and ORR in comparison with Vd alone
  - DVD was associated with a 61% reduction in the risk of progression/death

- Treatment benefit of DVD vs Vd was consistent across subgroups
  - Earlier treatment with DVD may be the most beneficial

- Daratumumab-Vd doubled VGPR and CR rates

- Daratumumab-Vd was not associated with any cumulative toxicities

Daratumumab Phase III Pollux DaraRd versus Rd

- 569 patients with relapsed or refractory multiple myeloma were enrolled in the study.

- The study met the primary endpoint of improving progression free survival (PFS); Hazard Ratio (HR) = 0.34, p<0.0001.

- ORR 93 versus 76%, CR 43 versus 19%

- The median PFS for patients treated with daratumumab has not been reached, compared to median PFS of 18.4 months for patients who did not receive daratumumab.

A Dose Finding Phase 1/2 Trial of Isatuximab (SAR650984, Anti-CD38 mAb) as a Single Agent in Relapsed/Refractory Multiple Myeloma

Response Summary (IMWG criteria): All Treated Patients
What Else is New in MM Therapeutics?

- Oral Proteasome Inhibitors: Oprozomib
- Monoclonal Antibodies: Isatuximab, Durvalumab
- Kinase Inhibitors: Afuresertib, Dinaciclib, PIM (LGH447), Trametinib
- HDACs: Ricolinostat
- Novel mechanisms: Venetoclax, Selinexor, Bromodomain
- Immunotherapies: BCMA CAR-T, BITE

Selinexor, Novel Anticancer Agent: Restores Tumor Suppressors

- Genome-wide studies in multiple myeloma identify XPO1/CRM1 as a critical target validated using the selective nuclear export inhibitor KPT-276

Best Responses in Evaluable Patients: Single-Agent Selinexor vs Selinexor + Low Dex

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>CBR</th>
<th>ORR</th>
<th>sCR</th>
<th>PR</th>
<th>MR</th>
<th>PD</th>
<th>Study Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selinexor high dose: ≥35 mg/m²</td>
<td>14</td>
<td>3 (21%)</td>
<td>1 (7%)</td>
<td>2 (14%)</td>
<td>8 (57%)</td>
<td>3 (21%)</td>
<td>301+</td>
<td></td>
</tr>
<tr>
<td>Selinexor (45 mg/m²) + Low Dose Dex (20 mg)</td>
<td>9</td>
<td>8 (89%)</td>
<td>6 (67%)</td>
<td>1 (11%)</td>
<td>5 (55%)</td>
<td>2 (22%)</td>
<td>1 (11%)</td>
<td></td>
</tr>
</tbody>
</table>

Durable Responses After Multiple Prior Therapies in Relapsed/Refractory MM Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Maximal Δ Best Response</th>
<th># Prior Tx</th>
<th>Study Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selinexor 45 mg/m² + Dexamethasone 20 mg</td>
<td>-77% PR 7</td>
<td>301+</td>
<td></td>
</tr>
<tr>
<td>Selinexor 45 mg/m² + Dexamethasone 20 mg</td>
<td>-99% sCR 5</td>
<td>288</td>
<td></td>
</tr>
<tr>
<td>Selinexor 45 mg/m² + Dexamethasone 20 mg</td>
<td>-54% PD 5</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Selinexor 45 mg/m² + Dexamethasone 20 mg</td>
<td>-58% PR 10</td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>Selinexor 45 mg/m² + Dexamethasone 20 mg</td>
<td>-61% MR 9</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>Selinexor 45 mg/m² + Dexamethasone 20 mg</td>
<td>-82% MR 16</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Selinexor 45 mg/m² + Dexamethasone 20 mg</td>
<td>-60% PD 8</td>
<td>241+</td>
<td></td>
</tr>
</tbody>
</table>

Venetoclax an Inhibitor of Bcl-2 Critical for Apoptosis

- Signals of cellular damage
- Targets Bcl-2 and Bcl-XL
- Survives in Bcl-2-overexpressing cells
- Signals of death
- Multidomain proteins
- Mitochondria
- Pro-apoptotic proteins
- Anti-apoptotic proteins
- Cell death (apoptosis)
Venetoclax in t(11;14) MM

Rationale for Targeting Programmed Cell Death Protein 1 (PD-1) and its Ligand PD-L1 in MM

Best Response to Treatment (IMWG Criteria)

Max. % Change From Baseline M Protein or FLC

Chimeric Antigen Receptor (CAR) T Cells Against CD19 for Multiple Myeloma
B-Cell Maturation Antigen (BCMA) CAR-T

Remissions of Multiple Myeloma during a First-in-Humans Clinical Trial of T Cells Expressing an Anti-BCMA Chimeric Antigen Receptor

- BCMA targeted CAR-T cells infused after 3 days of cyclophosphamide and fludarabine
- Highest dose level in 2 patients—severe cytokine release syndrome
- 90-100% clearance of bone marrow plasma cells


Summary

- Monoclonal antibodies here to stay – Rituxan for Myeloma
- Venetoclax for t(11;14) excellent choice (off label for now)
- Selinexor promising
- Checkpoint inhibitors ?
- CAR-T cells ?
- Kinase Inhibitors ?

Thank you
Overview of Therapeutic Options for Myeloproliferative Neoplasms (CML)

Guillermo Garcia-Manero, MD
Overview of Therapeutic Options for Myelodysplastic Syndromes (MDS)

Guillermo Garcia-Manero, MD