ASH 2016: Multiple Myeloma

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Section of BMT and Leukemia
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Agenda

- Monoclonal Antibodies and Immunotherapy
- Novel therapies
- Stem cell transplantation

Daratumumab: CASTOR PFS
Lower risk of progression in pts who achieve MRD negativity, regardless of therapy
- DRd MRD-negative pts (n = 71); estimated 12-mo PFS > 90%
- DVd MRD-negative pts (26); estimated 12-mo PFS > 90%
- Rd MRD-negative pts (n = 16 in POLLUX and n = 6 in CASTOR); estimated 12-mo PFS > 90%
- Daratumumab + Rd or Vd shows PFS benefit in MRD-positive pts over doublets alone
- POLLUX: estimated median PFS NR vs 17 months for DRd MRD-positive (n = 215) vs Rd MRD-positive pts (n = 267)
- CASTOR: estimated median PFS NR vs 7 months for DVd MRD-positive (n = 225) vs Vd MRD-positive pts (n = 241)
PAVO: Conclusions

- SC administration of daratumumab + rHuPH20 safe and effective
- Both dose groups showed responses to SC daratumumab
  - 1800-mg group had deeper responses vs 1200-mg group
  - Preliminary efficacy similar to IV daratumumab: 38% ORR, including 1 sCR
- AEs for SC daratumumab + rHuPH20 similar to IV daratumumab
  - Low IRR incidence and intensity with SC daratumumab
- PK of SC daratumumab 1800 mg similar to 16 mg/kg IV administration
Pembrolizumab/Pomalidomide/Dexamethasone for R/R MM: Prior Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pts (N = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time from diagnosis to study, yrs (range)</td>
<td>4 (1.2-26)</td>
</tr>
<tr>
<td>Median lines of earlier therapy (range)</td>
<td>3 (2-5)</td>
</tr>
<tr>
<td>• 2 lines, %</td>
<td>35</td>
</tr>
<tr>
<td>• 3 lines, %</td>
<td>38</td>
</tr>
<tr>
<td>• &gt; 3 lines, %</td>
<td>27</td>
</tr>
<tr>
<td>Previous therapy, %</td>
<td></td>
</tr>
<tr>
<td>• ASCT</td>
<td>72</td>
</tr>
<tr>
<td>• Bortezomib</td>
<td>100</td>
</tr>
<tr>
<td>• Carfilzomib</td>
<td>50</td>
</tr>
<tr>
<td>• Lenalidomide</td>
<td>98</td>
</tr>
<tr>
<td>• Thalidomide</td>
<td>2</td>
</tr>
<tr>
<td>Refractory, %</td>
<td></td>
</tr>
<tr>
<td>• Proteasome inhibitors</td>
<td>79</td>
</tr>
<tr>
<td>• Lenalidomide</td>
<td>90</td>
</tr>
<tr>
<td>• IMiDs + proteasome inhibitors</td>
<td>73</td>
</tr>
</tbody>
</table>


Pembrolizumab/Pomalidomide/Dexamethasone for R/R MM: Efficacy

<table>
<thead>
<tr>
<th>Response, %</th>
<th>Full Efficacy Population (N = 45)</th>
<th>Refractory to 2 Classes (n = 32)</th>
<th>High-Risk Cytogenetics (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>65</td>
<td>68</td>
<td>56</td>
</tr>
<tr>
<td>Clinical benefit</td>
<td>72</td>
<td>69</td>
<td>60</td>
</tr>
<tr>
<td>Best response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• sCR</td>
<td>7</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>• CR</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>• VGPR</td>
<td>20</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>• PR</td>
<td>36</td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>• MR</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>• SD</td>
<td>23</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>• PD</td>
<td>5</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>sCR + CR + VGPR, %</td>
<td>29</td>
<td>24</td>
<td>15</td>
</tr>
</tbody>
</table>


Pembrolizumab/Pomalidomide/Dexamethasone for R/R MM: Safety

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pts (N = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median no. of cycles (range)</td>
<td>8 (3-23)</td>
</tr>
<tr>
<td>Median follow-up, mos</td>
<td>9.6</td>
</tr>
<tr>
<td>Dose reduction, n (%)</td>
<td>22 (49)</td>
</tr>
<tr>
<td>• Pembrolizumab, n*</td>
<td>2</td>
</tr>
<tr>
<td>• Pomalidomide, n*</td>
<td>13</td>
</tr>
<tr>
<td>• Dexamethasone, n‡</td>
<td>7</td>
</tr>
<tr>
<td>Discontinuation due to regimen toxicity, n (%)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>• Pneumonitis, n</td>
<td>3</td>
</tr>
<tr>
<td>• Shortness of breath, n</td>
<td>1</td>
</tr>
<tr>
<td>• Fatigue, n</td>
<td>1</td>
</tr>
<tr>
<td>Deaths, n</td>
<td>9</td>
</tr>
<tr>
<td>Disease progression, n</td>
<td>23</td>
</tr>
</tbody>
</table>

*Pneumonitis, n = 2; Fatigue, n = 5; neuropathy, n = 3; rash, n = 2; palmar erythema; n = 1; *uncontrolled hyperglycemia, n = 3; weight gain; n = 2; constipation, n = 1; lack of sleep, n = 1.

Pembrolizumab/Pomalidomide/Dexa methasone for R/R MM: Duration of Response and Survival

- PFS significantly longer in low-risk vs high-risk subgroups ($P = .0366$)

<table>
<thead>
<tr>
<th>Outcome, Mos (95% CI)</th>
<th>Full Efficacy Population (N = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of response</td>
<td>16.3 (9.9-19.1)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>17.4 (11.7-18.8)</td>
</tr>
<tr>
<td>Median OS</td>
<td>Not reached (18.8-not reached)</td>
</tr>
</tbody>
</table>


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B-cell Maturation Antigen (BCMA)-specific chimeric antigen receptor T cells (CART-BCMA) for multiple myeloma (MM): initial safety and efficacy from a phase I study


American Society of Hematology Annual Meeting
December 5, 2016

Abstract # 1147

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BCMA (TNFRSF17, CD269)

- Receptor for BAFF (Blys) and APRIL
- Expressed on plasma cells, some mature B cell subsets, and plasmacytoid DC's
  - Maintains plasma cell homeostasis
  - Not on other normal tissues
- Expressed consistently on myeloma cells
  - Varying intensity
- Promotes MM pathogenesis

BCMA-specific CAR T cells

- NCI BCMA CAR (murine scFv, CD3/CD28 domains, gamma-retroviral vector)
  - In vitro and in vivo pre-clinical activity
  - First-in-human trial (n=12)
    - Cytosine/fludarabine lymphodepletion, single infusion, 4 dose levels
    - VGPR (8/12s), sCR (1/12s), VGPR (2/12s)
    - Associated with CRS, CART expansion

- Penn/Novartis BCMA CAR (human scFv, CD3/41BB domains, lentiviral vector)
  - BCMA-binding scFv clones identified from human B cell antibody libraries
  - Lead candidate selected based on in vitro and in vivo activity

Clinical responses Median 9 prior lines of therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cytopenia status</th>
<th>Neutropenia status</th>
<th>CRS grade</th>
<th>VGPR response (0-4)</th>
<th>Best response</th>
<th>Dose level</th>
<th>Dose level</th>
<th>Dose level</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>70%</td>
<td>60%</td>
<td>2</td>
<td>2 x 10^6 (45%)</td>
<td>14 sCR</td>
<td>12</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>02</td>
<td>80%</td>
<td>50%</td>
<td>1</td>
<td>5 x 10^6 (100%)</td>
<td>14 MR</td>
<td>2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>03</td>
<td>95%</td>
<td>80%</td>
<td>3</td>
<td>2 x 10^6 (40%)</td>
<td>15 VGPR</td>
<td>5</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>04</td>
<td>15%</td>
<td>10%</td>
<td>25</td>
<td>5 x 10^6 (100%)</td>
<td>- SD</td>
<td>2</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>05</td>
<td>95%</td>
<td>1.5 x 10^6 (100%)</td>
<td>-</td>
<td>-</td>
<td>PD</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>06</td>
<td>80%</td>
<td>60%</td>
<td>225</td>
<td>5 x 10^6 (100%)</td>
<td>215 MR</td>
<td>2.5</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>07</td>
<td>15%</td>
<td>15%</td>
<td>14</td>
<td>5 x 10^6 (100%)</td>
<td>14 MR</td>
<td>1.5</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>08</td>
<td>90%</td>
<td>50%</td>
<td>2</td>
<td>5 x 10^6 (100%)</td>
<td>14 VGPR</td>
<td>2</td>
<td>0.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*No MTD by day 17
**unconfirmed; 24 hour LUPD not repeated

Safety (n=9)

- Cytokine release syndrome in 8/9 (89%)
  - Grade 1 (n=1); Grade 2 (n=4); Grade 3 (n=2); Grade 4 (n=1)
  - 4/9 received tucilizumab
  - Median hospital stay = 9 days (range 3 - 40)

- Dose-limiting toxicity (pt. 03):
  - Grade 4 PRES (posterior reversible encephalopathy syndrome)
    - Recurrent seizures, obtundation
    - MRI brain: diffuse enhancement w/ swelling and sulcal effacement
    - Rapid peripheral CART expansion
    - Solumedrol 1 giv x 3 - Cytoxan 1.5 giv qd day 17
    - Rapid improvement, resolution of MRI changes and neuro deficits

Garfall et al, ASH 2018, #5702
First in Human Study with GSK2857916, An Antibody Drug Conjugated to Microtubule-disrupting Agent Directed Against B-cell Maturation Antigen, in Patients with Relapsed/Refractory Multiple Myeloma: Results from Study BMA117159 Part 1 Dose Escalation

Adam D. Cohen1, Rakash Papad1, Suzanne Trudel1, Paul G. Richardson1, Edward N. Libby1, Nicoletta Lendvai1, Larry D. Anderson1,2, Heather J. Sutherland1, Darren Austin1, Stephen DeWitt1, Catherine E. Ellis1, Zanglong He1, Jolly Muzumdar1, Catherine Wang1, Joanna Opatrakul1, Peter M. Yavorovski1

1Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; 2University College London Hospitals NHS Foundation Trust, London, UK; Whimsical Medical Cancer Centre, Bendigo, VIC, Australia; 3Sheba Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; 4Memorial Sloan-Kettering Cancer Center, New York, NY, USA; 5Brigham and Women’s Hospital, Boston, MA, USA; 6Toronto Cancer Care {

First-in-Human Study of GSK2857916: BMA117159 Study Design

Part 1: Dose escalation: 14-day open-label single ascending dose with 14-day drug-free period (if no dose-limiting toxicity [DLT]) before each dose level.

Premedication requirements: prophylactic steroid eye drops (treat-D, 2mg/pd) and non-steroidal anti-inflammatory drugs.

Primary objectives: safety, tolerability, MTD, and recommended Phase 2 dose.

Dose (Mean ± SD mg/m²) 3.37 ± 2.3

Part 2: Expansion (randomized): patients receiving 4.0 mg/m², 4.6 mg/m², or placebo (in-dose).

Population: patients with relapsed, refractory MM, who maintenance treatment with lenalidomide, bortezomib, or irinotecan.

Phase 2 Part 2 dose

Part 1: Baseline Patient and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr); median (min, max)</td>
<td>60 (18, 79)</td>
</tr>
<tr>
<td>Female, %</td>
<td>43/57</td>
</tr>
<tr>
<td>ISS stage (II/III)</td>
<td>22/27</td>
</tr>
<tr>
<td>IMWG</td>
<td>34 (19/20)</td>
</tr>
<tr>
<td>CRAD</td>
<td>28 (17/12)</td>
</tr>
<tr>
<td>Duration of MM (yr)</td>
<td>9.93 ± 5.70</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>2.89 ± 2.37</td>
</tr>
<tr>
<td>ASCT, autologous</td>
<td>2.97</td>
</tr>
<tr>
<td>CRAD</td>
<td>2.61</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>3.53 ± 2.37</td>
</tr>
<tr>
<td>High risk criteria</td>
<td>1.45 ± 1.71</td>
</tr>
</tbody>
</table>

ASCT, autologous stem cell transplant; CRAD, immunomodulatory; PI, proteasome inhibitor.
Agenda

- Monoclonal Antibodies and Immunotherapy
- Novel therapies
- Stem cell transplantation
Venetooclax Monotherapy for Relapsed/Refractory Multiple Myeloma: Safety and Efficacy Results From a Phase I Study

Shaji Kumar,1 Ravi Vij,2 Jonathan L. Kaufman,3 Joseph Mikhael,4 Thierry Facon,5 Martine Amiot,9 Philippe Moreau,9 Martin Durie,9 Tu Ju,10 Suresh Agarwal,10 John Leverson,10 Paulo Maciag,10 Maria Verdugo,10 Joel Touzeau9

1Mayo Clinic, Rochester, MN, USA; 2Washington University School of Medicine, St. Louis, MO, USA; 3Mayo Clinic Cancer Center, Scottsdale, AZ, USA; 4CHRU Lille, Hopital Huriez, France; 5CHU Grenoble, France; 6CHRU Tours, France; 7Duke University, Hematology Malignancies & Cellular Therapy, Durham, NC, USA; 8CHU de Nantes, Hôpital de la Dieu – HME, France; 9AbbVie Inc., North Chicago, IL, USA

Abstract # 488

American Society of Hematology – 58th Annual Meeting ● San Diego, California, USA ● December 4, 2016

Background

Anti-apoptotic proteins BCL-2 and MCL-1 promote multiple myeloma (MM) cell survival

Venetooclax induces cell death in multiple myeloma (MM) cell lines and primary samples, particularly those positive for the translocation t(11;14), which correlates with higher ratios of BCL2 to MCL1 and BCL2 to BCL2L1 (BCL-XL) mRNA

Dosing and Enrollment

Following a 2-week lead-in period, patients were treated on a 21-day cycle with daily venetooclax (300 to 1200 mg)

Patients who progressed while receiving monotherapy could have dexamethasone added to venetooclax and continue on study

[Diagram showing dosing and enrollment details]
Objective Response Rates in all patients and by t(11;14) Status (Median 5 prior lines of therapy)

Time to Progression and Duration of Response

Responses by BCL2:BCL2L1 Ratio Among t(11:14)-Positive Patients
Venetoclax Combined With Bortezomib and Dexamethasone for Patients With Relapsed/Refractory Multiple Myeloma

Philippe Moreau,1 Acher Chanan-Khan,1 Andrew W. Roberts,1 Amit B. Agerwala2 Thierry Facon,1 Shaj Kumar1 Cyril Tusaiez1, J. Taylor Cordon,1 Jeremy Ross,7 Wijith Murasinghe,1 Jia Jia7, Ahmed H. Salem1, Joel Leverstein,7 Paulo Macieja,7 Maria Verdugo,1 Simon J. Harrison1

1 CHU de Nantes, Hospital University of Nantes, Nantes, France; 2 Mayo Clinic, Jacksonville, FL; 3 Mayo Clinic, Rochester, MN; 4 Janssen Inc., North Chicago, IL; 5 Royal Melbourne Hospital and Walter and Eliza Hall Institute of Medical Research, Cancer and Hematology Division, Melbourne, Australia; 6 The University of Arizona Cancer Center, Tucson, AZ; 7 DFCI, Dana-Farber Cancer Institute, Boston, MA; 8 Janssen Inc., North Chicago, IL; 9 Peter MacCallum Cancer Centre, Melbourne, Australia

Abstract # 975

American Society of Hematology - 58th Annual Meeting - San Diego, California, USA - December 5, 2016

Dosing and Enrollment

- Patients received 50–1200 mg venetoclax per designated dose escalation cohorts

<table>
<thead>
<tr>
<th>Cycles 1–8</th>
<th>Cycles 9–11</th>
<th>Cycles 12+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Designated Cohort Dose</td>
<td>Designated Cohort Dose</td>
<td>Days 1 – 30 at Monotherapy</td>
</tr>
<tr>
<td>Day 1 2 4 5 6 9 11 12</td>
<td>1 0 15 22</td>
<td></td>
</tr>
</tbody>
</table>

- Dosing cycle = 21 days for cycles 1 – 6 and 35 days for cycles 8+

| Enrollment by Dose Cohort |
| --- | --- | --- |
| Dose (mg) | Total I DE | Total SE + SE |
| 50 | 3 | 54 |
| 100 | 3 | 54 |
| 200 | 9 | 54 |
| 300 | 12 | 66 |
| 400 | 0 | 0 |
| 500 | 0 | 0 |
| 600 | 0 | 0 |
| 800 | 0 | 0 |
| 1000 | 0 | 0 |
| 1200 | 0 | 0 |

Objective Responses (Median 3 prior lines of therapy)

- ORR 38% in Non-refractory Patients
- ORR 32% in Non-refractory Patients with 1-3 Prior Therapies
- ORR 15% in Refractory Patients
- ORR 9% in Refractory Patients with 1-3 Prior Therapies
- ORR 3% in Refractory Patients with >3 Prior Therapies

Data meet at Annual Meeting.
**Time to Progression and Duration of Response by Bortezomib Status**

- **Time to Progression**
  - Bortezomib non-refractory
  - Bortezomib refractory

- **Duration of Overall Response**
  - Bortezomib non-refractory
  - Bortezomib refractory

**BCL2 Gene Expression and Clinical Response**

- **ORR**
  - BCL2 High (n=18)
  - BCL2 Low (n=27)

**Selinexor and Low Dose Dexamethasone (Sd) in Patients with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib & anti-CD38 Ab Refractory MM: STORM Study**

STORM: Study Design

- Phase II clinical trial: selinexor plus low-dose dexamethasone for heavily pretreated pts with MM refractory to most recent treatment (N = 79; median age: 68 yrs)
  - Quad: refractory to bortezomib, carfilzomib, lenalidomide, and pomalidomide
  - Penta: quad refractory and also daratumumab or isatuximab (anti-CD38 antibodies)
  - Creatinine clearance ≥ 20 mL/min, WBC count ≥ 1500/mm³, ANC ≥ 1000/mm³, platelet count ≥ 75,000/mm³ (≥ 30,000/mm³ if plasma cells ≥ 50% of marrow cellularity)
- Treatment: selinexor 80 mg plus dexamethasone 20 mg twice weekly; reductions or interruption as needed for toxicity
  - Group 1: 6 doses/28-day cycle (3 wks on/1 wk off)
  - Group 2: 8 doses/28-day cycle (4 wks continuously)
- Primary endpoints: ORR and DoR (IRC assessed)
- Secondary endpoints: PFS and OS


STORM: Treatment-Related AEs

- Selinexor dose modifications
  - Interruptions (5%)
  - Reductions (20%)
  - Discontinuation (18%)
- Manageable with supportive care measures
  - Anemia
  - Appetite stimulants
  - Hematopoietic growth factors
  - Thrombopoietin receptor agonists
  - Substitution

**STORM: Efficacy (Independent Review)**

- Median time to response: 1 mo
- Median DOR: 5 mos

**STORM: OS and PFS**

- Median OS for all pts: 5.3 mos; ≥MR: not reached
- Median PFS for all pts: 2.3 mos; ≥MR: 5.5 mos

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**Selinexor in Combination with Bortezomib and Dexamethasone (Svd) Demonstrates Significant Activity in Patients with Refractory MM: Results of Phase I STOMP Trial (MCRN02)**

**Abstract # 977**

...
Selinexor and backbone treatments of multiple myeloma patients: STOMP study design.

**Primary Objective:** Determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D)

**Patient Populations:**
- Arm 1: selinexor + bortezomib + dexamethasone
  - MM patients relapsing after 1 prior therapy may include prior bortezomib as long as not refractory to bortezomib in their most recent line of therapy
- Arm 2: lenalidomide + bortezomib + dexamethasone
- Arm 3: lenalidomide + lenalidomide + dexamethasone

**Dosing Scheme:** Standard 3 × 3 design will be used for dose escalation.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Selinexor Dose (QW)</th>
<th>Bortezomib Dose (QW)</th>
<th>Dexamethasone (QW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>15 mg</td>
<td>1.3 mg/m² QW</td>
<td>40 mg QW</td>
</tr>
<tr>
<td>SC</td>
<td>15 mg</td>
<td>1.3 mg/m² QW</td>
<td>40 mg QW</td>
</tr>
<tr>
<td>Oral</td>
<td>20 mg</td>
<td>1.3 mg/m² QW</td>
<td>40 mg QW</td>
</tr>
<tr>
<td>SC</td>
<td>20 mg</td>
<td>1.3 mg/m² QW</td>
<td>40 mg QW</td>
</tr>
</tbody>
</table>

Expansion at RP2D + 20 patients to be enrolled.

**Svd ORR Efficacy: Sub Groups – Phase I**

- **ORR 77%**
  - ORR 85% 5%
  - ORR 90% 10%
  - ORR 95% 1%

**Treatment Related AEs at RP2D**

- Good tolerability with clear anti-MM activity with once weekly selinexor in combination with once weekly Velcade
- Considering prolonged tolerability and efficacy across all cohorts, the RP2D is:

  950 mg oral selinexor QW +
  1.3 mg/m² bortezomib QW +
  40 mg dexamethasone QW
The oral HIV protease inhibitor nelfinavir (NFV) has anti-MM activity in vivo, triggers UPR activation, sensitizes MM to proteasome inhibitors and overcomes proteasome inhibitor resistance in vitro.

N=34

Oral nelfinavir 2500 mg days 1-14 b.i.d. BTZ 1.3 mg/m² days 1, 4, 8, 11, dex 20 mg p.o. days 1, 2, 4-5, 8-9, 11-12 for a maximum of six 21-day cycles.

Median 5 prior lines of therapy

All treated patients had proteasome inhibitor refractory MM

22 patients achieved an objective response with a PR or better, resulting in an overall response rate of 65% (95% CI 49.2%-75.7%).

Driessen et al Abstract # 487
Agenda

- Monoclonal antibodies and immunotherapy
- Novel therapies
- Stem cell transplantation

STaMINA: Phase III Study Design

- Primary endpoint: PFS at 30 mos
- Secondary endpoints: OS, CR, CR conversion rate, safety, infections, hospitalization, CAI

STaMINA: PFS and OS for Overall Population
Final Results of a Phase 2 Trial of Extended Treatment With Carfilzomib, Lenalidomide, and Dexamethasone (KRd) Plus Autologous Stem Cell Transplant (ASCT) in Newly Diagnosed Multiple Myeloma


Abstract # 675

Treatment Schema

- **KRd+ASCT (5-week cycle)**
  - KRd Induction (Cycles 1-4)
  - KRd Consolidation (Cycles 5-8)
  - KRd Maintenance (Cycles 9-16)

- **KRd w/o ASCT (5-week cycle)**
  - KRd Induction (Cycles 1-4)
  - KRd Consolidation (Cycles 5-8)
  - LEN maintenance (off protocol)

*CR or suspected CR (respiratory)

Response Rates Over the Course of Treatment

- **KRd + ASCT**
  - 4 cycles: 70%
  - 8 cycles: 87%
  - 12 cycles: 91%

- **KRd w/o ASCT**
  - 4 cycles: 58%
  - 8 cycles: 74%
  - 12 cycles: 85%

**MRD Evaluation**

- Multiparameter Flow Cytometry (MFC)
  - Sensitivity: 10^-4 – 10^-6
- Next generation sequencing (NGS)
  - Sensitivity: 10^-4

*Actual rates in subgroup of pts evaluated for MRD at the end of 8 and 18 cycles regardless of level of response*

*2700 pts (80%): MRD (-) by MFC and in eCR and 2027 (74%) MRD (-) by NGS and in eCR.
KrH vs ACT: estimated rates of MRD (-) in eCR 15% by MFC and 39% by NGS.*

---

**Treatment Outcomes**

**PFS**

- KRH vs ACT: 12% vs 24%
- Median PFS: 18 vs 26.5 months

**OS**

- KRH vs ACT: 30% vs 36%
- Median OS: 47 vs 47.5 months

*5 patients progressed (2 post transplant, 1 after consolidation, 1 after EOT, during maintenance)
Excludes 7 pts who discontinued preaur ACT or intent-to-treat (N=53), 4 year PFS 64%
At cut-off date 10/12/2016*

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**Myeloma XI: Subset Analysis**

- 132-center multicenter, open-label parallel group, randomized controlled phase II trial

- Induction 1: 4 cycles of ASCT adjuvant 6 cycles of ASCT analogs
- CRD
- CTD

- Induction 2: Bortezomib + Cyclophosphamide + Dexamethasone 1 vs 2: 209
- No further induction therapy 1 vs 2: 204

*Primary endpoint: PFS; OS
Secondary endpoints: improved response vs baseline, P/F effect in high-risk group

Jaquish Th, et al. ASH 2016, Abstract 346*
Myeloma XI: Response Rates

<table>
<thead>
<tr>
<th>Response</th>
<th>After IMiD Induction</th>
<th>After CVD Induction</th>
<th>After ASCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No CVD (n = 291)</td>
<td>CVD (n = 289)</td>
<td>No CVD (n = 133)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0.3</td>
<td>3.5</td>
</tr>
<tr>
<td>VGPR</td>
<td>4.1</td>
<td>4.2</td>
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<tr>
<td>PR</td>
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<td>84</td>
<td>39</td>
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<tr>
<td>MR</td>
<td>7.5</td>
<td>8.3</td>
<td>1.4</td>
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<tr>
<td>SD/PD</td>
<td>4.0</td>
<td>1.0</td>
<td>3.8</td>
</tr>
</tbody>
</table>


Myeloma XI: PFS and OS (Transplant Eligible)

PFS

Myeloma XI: PFS and OS (Transplant Ineligible)

PFS
Conclusions

- **Monoclonal Antibodies and Immunotherapy**
  - Daratumumab combination with Rd and Vd:
    - MRD-ve CR even in R/R MM
    - SQ daratumumab is coming
  - Pembrolizumab combination with Rd:
    - Impressive response rates but associated with some toxicity
  - BCMA CAR-T Cells and ADC:
    - Impressive responses in very heavily pretreated R/R MM

- **Novel therapies**
  - Venetoclax:
    - Impressive single agent activity in t(4,14) and in combination with bortezomib esp in BCL-2 overexpressors
  - Selinexor:
    - Impressive single agent activity even in "penta" refractory disease and in combination with btz and carfilzomib but has GI toxicity
  - Nelfinavir:
    - In combination with btz able to salvage btz refractory patients

- **Stem cell transplantation**
  - STAMINA
    - Consolidation therapy and tandem transplant no better than lenalidomide maintenance alone
  - KRd
    - Very impressive rates of MRD-ve disease when given as induction and extended consolidation post transplant
  - Risk adapted therapy
    - Additional therapy to deepen responses prior to HDCT improves long-term outcomes