<table>
<thead>
<tr>
<th>Company</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson &amp; Johnson</td>
<td>Disease Monitoring Committee</td>
</tr>
<tr>
<td>Celgene</td>
<td>Disease Monitoring Committees</td>
</tr>
<tr>
<td>Novartis</td>
<td>Disease Monitoring Boards</td>
</tr>
<tr>
<td>Merck</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>Independent Monitoring Committee</td>
</tr>
<tr>
<td>Aeterna Zentaris (Keryx)</td>
<td>Data &amp; Safety Monitoring Board</td>
</tr>
<tr>
<td>Onyx</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>Binding Site</td>
<td>Honoraria</td>
</tr>
</tbody>
</table>
URETHANE AND STILBAMIDINE IN MULTIPLE MYELOMA *
REPORT ON TWO CASES
NILS ALWALL
M.D. Lund
From the Medical Clinic, Lund University, Sweden

Lancet 2:388, 1947
Survival from Onset of Treatment of Multiple Myeloma

Surviving (%)

Placebo

Urethane

Blood 27(3):335, March 1966
Treatment of Multiple Myeloma

L-sarcolysin (L-phenylalanine mustard) (Melphalan) (Alkeran)

Blokhin et al, 1958
Bergsagel et al, 1962
# Multiple Myeloma

## Single (M/P) vs Combination Chemotherapy (CCT)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/P</td>
<td>53</td>
</tr>
<tr>
<td>CCT</td>
<td>60</td>
</tr>
</tbody>
</table>

\[ P < 0.00001 \]

- No difference in survival
- No subsets with benefit

\[ n = 4,930 \text{ (20 trials)} \]
Autologous Stem Cell Transplant

- Plasma cell leukemia
- Melphalan 140 mg/m² IV with good response
- Collected stem cells
- Relapsed and given Melphalan 140 mg/m² IV plus stem cells
- Treated 8 myeloma patients

Novel Agents

- Thalidomide
- Bortezomib (Velcade)
- Lenalidomide (Revlimid)
Multiple Myeloma
Novel Agents

Pomalidomide (Pomalyst)  CC-4047
Carfilzomib (Kyprolis)  PR-171
Multiple Myeloma
Novel Agents

- Proteosome inhibitor (oral/IV)  MLN-9708
- Proteosome inhibitor (oral)  NPI-0052
- Elotuzumab
- Bendamustine
- Histone deacetylase inhibitor  Vorinostat (SAHA)
- Histone deacetylase inhibitor  Panobinostat
Multiple Myeloma 1971-2006
n=2,981

Survival, med
29.9 mo

Survival, med
44.8 mo

Diagnosis after 1996

Diagnosis during/before 1996

P<0.001

Multiple Myeloma
Mayo Patients

2001-2005
2006-2010

47%
66%

P < 0.0001

S. Kumar, 2012
Phase 1/2 study of weekly MLN9708, an investigational oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma

Shaji K. Kumar,1 Jesus G. Berdeja,2 Ruben Niesvizky,3 Sagar Lonial,4 Mehdi Hamadani,5 A. Keith Stewart,6 Vivek Roy,7 Parameswaran Hari,8 Robert Vescio,9 Deborah Berg,10 Jianchang Lin,10 Alessandra Di Bacco,10 Jose Estevam,10 Neeraj Gupta,10 Ai-Min Hui,10 Paul G. Richardson11

1Division of Hematology, Mayo Clinic, Rochester, MN; 2Sarah Cannon Research Institute, Nashville, TN; 3Center of Excellence for Lymphoma and Myeloma, Weill Medical College of Cornell University, New York Presbyterian Hospital, New York, NY; 4Winship Cancer Institute of Emory University, Atlanta, GA; 5West Virginia University, Mary Babb Randolph Cancer Center, Morgantown, WV; 6Mayo Clinic College of Medicine, Scottsdale, AZ; 7Mayo Clinic, Jacksonville, FL; 8Division of Hematology Oncology, Medical College of Wisconsin, Milwaukee, WI; 9Cedars-Sinai Outpatient Cancer Center at the Samuel Oschin Comprehensive Cancer Institute, Los Angeles, CA; 10Millennium Pharmaceuticals, Inc., Cambridge, MA; 11Dana-Farber Cancer Institute, Boston, MA
Study design

- **Phase 1**: oral MLN9708 dose-escalation
  - Standard 3+3 schema, 33% dose increments, based on cycle 1 dose-limiting toxicities (DLTs)
- **Phase 2**: oral MLN9708 at the RP2D from phase 1
- Stem cell collection allowed after 3 cycles, with autologous stem cell transplantation (ASCT) deferred until after 6 cycles
- MLN9708 maintenance continued until progression or unacceptable toxicity
- Mandatory thromboprophylaxis with aspirin or low-molecular-weight heparin
Grade 3 (≥5%) and all grade 4 AEs (N=65)

**Hematologic**
- Neutropenia
- Anemia
- Thrombocytopenia

**Non-Hematologic**
- Rash
- Vomiting
- Fatigue
- Diarrhea
- Hyponatremia
- Nausea
- Back pain
- Dehydration
- Hypokalemia
- Hypophosphatemia
- Sepsis
- Dyspnea
- Renal failure chronic

*Occurred in same patient
‘Rash’ includes pruritic, papular, maculo-papular, erythematous, rash, palmar-plantar erythrodysesthesia

*Occurred in same patient
Peripheral neuropathy (PN)

- A total of 21 patients (32%) reported treatment-emergent PN
  - Includes the preferred terms of ‘peripheral neuropathy’ and ‘peripheral sensory neuropathy’
  - 2 had PN at baseline

- PN was grade 1 in the majority (n=13) of patients
- Grade 2 reported in 6 patients
- Grade 3 reported in 2 patients (3%)
  - Both patients off study; PN has resolved in one, and has reduced to grade 1 (mild, without impact on activities of daily living) in the other
Preliminary response data over course of treatment – patients treated at RP2D (2.23 mg/m\(^2\) / 4.0 mg)

- After 4 cycles (n=47):
  - ORR 94%
  - 19 CR
  - ≥VGPR 49%
  - 30 VGPR
  - 45 PR

- After 8 cycles (n=19):
  - ORR 95%
  - 32 CR
  - ≥VGPR 58%
  - 26 VGPR
  - 37 PR

- Overall (n=52):
  - ORR 90%
  - 23 CR
  - ≥VGPR 58%
  - 35 VGPR
  - 32 PR

- Of 3 response-evaluable patients who completed 12 cycles, 2 achieved CR and 1 VGPR
Conclusions

- The all-oral combination of weekly MLN9708, lenalidomide, and dexamethasone appears to be generally well tolerated
  - To date, the incidence of PN has been limited with this triplet regimen

- The primary endpoint of the study was met, suggesting antitumor activity at the RP2D
  - At data cut-off, with a median drug exposure of 6 months, 92% of patients overall had achieved PR or better, including a ≥VGPR rate of 55% and a CR rate of 23%
  - Responses increased with number of cycles and deepened over time
  - 88% of patients achieving CR who were evaluable for MRD status were confirmed as MRD-negative

- A phase 3 trial of MLN9708 plus lenalidomide–dexamethasone versus placebo plus lenalidomide–dexamethasone in patients with relapsed and/or refractory MM is currently enrolling (NCT01564537)
  - A phase 3 trial of MLN9708 plus lenalidomide–dexamethasone in previously untreated MM is in the planning stages