Bortezomib
In Patients with Renal Failure

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Renal Impairment in Myeloma

• Severe renal failure is an important complication of myeloma

• 20-30% of patients have renal impairment at presentation

• 50% of patients at some time

• 2-5% of patients require long-term dialysis

• Increased mortality
Frequent Causes of Renal Failure in Multiple Myeloma

1. Hypercalcaemia
3. Light chain damage
4. Dehydration
5. Nephrotic drugs – particularly NSAIDS
5. Infection
6. Hyperuricaemia
7. Plasma cell infiltration
8. Amyloidosis
Mechanism of Light Chain-Induced Renal Damage

Proximal renal tubule – site of physiological resorption

10-30 g/Tag
3-5 mg FLC/Tag
κ: λ Ratio 0.63
Disrupted tubular basement membrane

Giant cell reaction
### Prospective Randomized Trials Comparing Plasmapheresis (exchange) + Hemodialysis with Hemodialysis only

<table>
<thead>
<tr>
<th>Author</th>
<th># Pts</th>
<th>Off dialysis at the end</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>With plasma exchange</td>
<td>Without plasma exchange</td>
</tr>
<tr>
<td>Zucchelli 1988</td>
<td>19/29 newly diagnosed</td>
<td>11/15</td>
<td>2/14</td>
</tr>
<tr>
<td>Johnson 1990</td>
<td>21 newly diagnosed</td>
<td>5/10</td>
<td>4/11</td>
</tr>
<tr>
<td>Clark 2005</td>
<td>97 newly diagnosed</td>
<td>36/58 *</td>
<td>27/39 *</td>
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</table>

* Primary composite end-point death, dialysis dependence or crcl <30

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Jackson, Sydney Myeloma Workshop 2005
Reversal of Renal Function by High Dose Melphalan and Autologous Transplantation

Duration of Dialysis and Pre Transplant GFR (>10ml/min) Predictors for Recovery

Lee Ck et al. BMT 2004
Rationale for Use of Bortezomib Combination Therapy in Patients with Renal Failure

1. Significant activity in patient with relapsed MM
2. Increased efficacy with addition of dexamethasone
3. Synergy with other myeloma treatments
4. Inhibition of NFκ B reduces peritubular inflammation
5. All of above
6. None of above
Proteasome Inhibition and Recovery Independent of Renal Function

A. Maximal proteasome inhibition (1 hr)

B. Proteasome inhibition (predose)

SUMMIT & CREST:
Incidence of Grade 3/4 Adverse Events was Similar Across all Creatinine Clearance (CrCL) Groups ($n = 256$)

Tolerability and Efficacy of Bortezomib in Patients with Renal Impairment
Subanalysis of SUMMIT and CREST

Comparable response rates in patients with compromised renal function

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>n</th>
<th>ORR (%)</th>
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<tbody>
<tr>
<td>&gt;80</td>
<td>105</td>
<td>45%</td>
</tr>
<tr>
<td>51–80</td>
<td>99</td>
<td>33%</td>
</tr>
<tr>
<td>≤50</td>
<td>42</td>
<td>25%</td>
</tr>
<tr>
<td>&lt;30</td>
<td>10</td>
<td>30%</td>
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</table>

Creatinine During Bortezomib Based Treatment in 10 Patients with CrCl < 30ml/min

Response rate similar to that seen in overall population
2/10 PR
1/10 MR

Results suggest that bortezomib can be administered safely to patients with renal impairment associated with MM.

Jagannath S et al, Cancer, 2005
Bortezomib in patients with renal failure requiring dialysis

- Retrospective analysis of 24 patients treated with
  - single-agent bortezomib
  - bortezomib combinations (+ dex + thal/dex + thal/doxorubicin)
- Number of therapies prior to bortezomib: median 2 (range 0–6)
  - 1 patient with no prior therapy

<table>
<thead>
<tr>
<th>Best response</th>
<th>(%)</th>
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<tbody>
<tr>
<td>ORR</td>
<td>78%</td>
</tr>
<tr>
<td>CR</td>
<td>28%</td>
</tr>
<tr>
<td>nCR</td>
<td>6%</td>
</tr>
<tr>
<td>PR</td>
<td>44%</td>
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</table>

n=24

Chanan-Khan et al. Blood 2005;106 (Abstract 2550)
Bortezomib in patients with renal failure requiring dialysis

- High response rates
- Most adverse events were mild to moderate and manageable
- Incidence and severity of adverse events comparable to those of patients with normal renal function

Chanan-Khan et al. Blood 2005;106 (Abstract 2550)
<table>
<thead>
<tr>
<th>Participating Investigators/Institutions</th>
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<tr>
<td><strong>Prof. Dr. H. Graf</strong></td>
</tr>
<tr>
<td><strong>Prof. Dr. F. Keil</strong></td>
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<tr>
<td><strong>OA Dr. A. Lang</strong></td>
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<td><strong>Prof. Dr. JG. Meran</strong></td>
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<td><strong>Prof. Dr. H. Ludwig</strong></td>
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<tr>
<td><strong>Rudolfstiftung</strong></td>
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<td><strong>KH Leoben</strong></td>
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<td><strong>KH Feldkirch</strong></td>
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<td><strong>Barmherzige Brüder Wien</strong></td>
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<td><strong>Wilhelminenspital</strong></td>
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Drugs should be administrated on Days 1, 4, 8, 11 in the following order.

1. Dexamethasone 40 mg i.v.
2. Doxorubicin 9 mg/m²/d i.v.
3. Bortezomib 1.0 or 1.3 mg/m² i.v.

Restart next cycle on Day 22.

The Bortezomib dose is planed to be 1.3 mg/m². Nevertheless for the safety reasons, the first 3 patients are going to be treated by 1.0 mg/m² Bortezomib.
Creatinine Levels During Treatment with BD±D in Acute Renal Failure in Patients with MM
Clinical Trial

BDD for Reversal of Acute Renal Failure

Primary objective:
Reversal of acute renal failure

Secondary objectives:
Tumor response (complete and partial response)
Safety of BDD in this patient population
Progression free survival
Overall survival
Participating Study Centers

Univ. Prof. Dr. Heinz Gisslinger, Vienna, Austria
Univ. Prof. Dr. Johannes Drach, Vienna, Austria
Univ. Prof. Dr. Richard Greil, Salzburg, Austria
OA Dr. Alois Lang, Feldkirch, Austria
Univ. Prof. Dr. Felix Keil, Leoben, Austria
Univ. -Prof. Dr. Werner Linkesch, Graz, Austria
Univ. Prof. Dr. Heinz Ludwig, Vienna, Austria
Dr. Miklós Egyed, Kaposvár, Hungary
Prof. MU Dr. CSc. Elena Tóthová, Košice, Slovakia
Univ. Prof. PhD. M.D. Zdenek Adam, Brno, Czech Republic
PhD M.D. Roman Hajek, Brno, Czech Republic
Univ. Prof. Dr. Boris Labar, Zagreb, Croatia
Response Criteria

Reversal of renal failure

- **Complete response**
  - Reversal of renal failure to GFR > 60ml/min

- **Partial response**
  - Improvement of GFR by > 50% but to < 60ml/min
Contact Details

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