Praxisrelevante Fortschritte bei nicht für eine Transplantation geeigneten PatientInnen

Heinz Gisslinger
Medizinische Universität Wien
Ziele der Myelomtherapie

Erzielen von Symptomfreiheit

Erzielen von Remission:
  Unterschied ob
  hohes oder niedriges Risiko

Verlängerung des PFS

Verlängerung des Gesamtüberlebens
Fortschritte in der Therapie der Behandlung von nicht für die Transplantation geeigneten Patienten mit multiplem Myelom

**Immunmodulierende Substanzen:**
- Revlimid (Erstlinientherapie)
- Pomalidomid

**Proteasomeninhibitoren:**
- Carfilzomib
- Ixozamib

**HDAC-Inhibitoren**
- Vorinostat (Entwicklung gestoppt)
- Panabinostat

**Monoklonale Antikörper**
- Daratumumab
- Elotuzumab
FIRST (MM-020): Impact of Cytogenetics Study Design

Stratification: age, country, and ISS stage

Data cutoff: March 3, 2014
FIRST (MM-020): Frailty Analysis
Frailty Algorithm

- Pts were categorized into 3 severity groups (fit, intermediate, or frail) as described by a proxy algorithm based on the IMWG frailty scale

<table>
<thead>
<tr>
<th>IMWG Frailty Scale</th>
<th>Proxy for MM-020 Analysis</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>≤ 75 yrs</td>
<td>≤ 75 yrs</td>
<td>0</td>
</tr>
<tr>
<td>76-80 yrs</td>
<td>76-80 yrs</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 80 yrs</td>
<td>&gt; 80 yrs</td>
<td>2</td>
</tr>
<tr>
<td><strong>Activity of Daily Living score</strong></td>
<td>EQ-5D: Self Care score</td>
<td></td>
</tr>
<tr>
<td>&gt; 4</td>
<td>1 (no problem)</td>
<td>0</td>
</tr>
<tr>
<td>≤ 4</td>
<td>2-3 (moderate or severe problem)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Instrumental Activity of Daily Living score</strong></td>
<td>EQ-5D: Usual Activities score</td>
<td></td>
</tr>
<tr>
<td>&gt; 5</td>
<td>1 (no problem)</td>
<td>0</td>
</tr>
<tr>
<td>≤ 5</td>
<td>2-3 (moderate or severe problem)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Charlson Comorbidity Index score</strong></td>
<td>Charlson Comorbidity Index score</td>
<td></td>
</tr>
<tr>
<td>≤ 1</td>
<td>≤ 1</td>
<td>0</td>
</tr>
<tr>
<td>≥ 2</td>
<td>≥ 2</td>
<td>1</td>
</tr>
</tbody>
</table>

Total
- 0: Fit
- 1: Intermediate
- ≥ 2: Frail

IMWG, International Myeloma Working Group; pt, patient.
Facon T. A Frailty Scale Predicts Outcomes in Patients With Newly Diagnosed Multiple Myeloma Who Are Ineligible for Transplant Treated With Continuous Lenalidomide Plus Low-Dose Dexamethasone in the FIRST Trial. ASH 2015, abstract 4239.
FIRST (MM-020): Frailty Analysis
Breakdown of Severity Group by Treatment Arm

cont, continuous; MPT, melphalan, prednisone, and thalidomide; Rd, lenalidomide and low-dose dexamethasone; Rd18, Rd for 18 cycles.
Facon T. A Frailty Scale Predicts Outcomes in Patients With Newly Diagnosed Multiple Myeloma Who Are Ineligible for Transplant Treated With Continuous Lenalidomide Plus Low-Dose Dexamethasone in the FIRST Trial. ASH 2015, abstract 4239.

Facon T et al, ASH 2015
FIRST (MM-020): Frailty Analysis
PFS by Severity Group (Data Cutoff: March 3, 2014)

Facon T. A Frailty Scale Predicts Outcomes in Patients With Newly Diagnosed Multiple Myeloma Who Are Ineligible for Transplant Treated With Continuous Lenalidomide Plus Low-Dose Dexamethasone in the FIRST Trial. ASH 2015, abstract 4239
FIRST (MM-020): Frailty Analysis
OS by Severity Group (Data Cutoff: March 3, 2014)

HR, hazard ratio; MPT, melphalan, prednisone, and thalidomide; NR, not reached; OS, overall survival; pt, patient; Rd, lenalidomide and low-dose dexamethasone; Tx, treatment.

Facon T. A Frailty Scale Predicts Outcomes in Patients With Newly Diagnosed Multiple Myeloma Who Are Ineligible for Transplant Treated With Continuous Lenalidomide Plus Low-Dose Dexamethasone in the FIRST Trial. ASH 2015, abstract 4239
Kontinuierliche Therapie mit Revlimid + Dexamethason (Fortecortin)
Unfitte vs. Fitte Patienten

Facon T et al, ASH 2015
FIRST (MM-020): Impact of Cytogenetics Response

### Odds Ratio (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>High Risk</th>
<th>Non-High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd continuous vs MPT</td>
<td>1.55 (0.61-3.95)</td>
<td>1.75 (1.10-2.77)</td>
</tr>
<tr>
<td>Rd continuous vs Rd18</td>
<td>1.60 (0.64-4.00)</td>
<td>1.07 (0.66-1.74)</td>
</tr>
</tbody>
</table>

*a Numbers may not sum due to rounding.

CR, complete response; MPT, melphalan, prednisone, and thalidomide; ORR, overall response rate; PR, partial response; Rd, lenalidomide plus low-dose dexamethasone; Rd18, Rd for 18 cycles; VGPR, very good partial response.

FIRST (MM-020): Impact of Cytogenetics on Outcomes of Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma Treated With Continuous Lenalidomide Plus Low-Dose Dexamethasone in the FIRST (MM-020) Trial. ASH 2015, abstract #730.
**FIRST (MM-020): Impact of Cytogenetics Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>3 Yr, %</th>
<th>HR (95% CI) (Rd cont vs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-High Risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd cont</td>
<td>205</td>
<td>77</td>
<td>-</td>
</tr>
<tr>
<td>Rd18</td>
<td>209</td>
<td>71</td>
<td>0.85 (0.62-1.18)</td>
</tr>
<tr>
<td>MPT</td>
<td>206</td>
<td>65</td>
<td>0.66 (0.48-0.91)</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd cont</td>
<td>43</td>
<td>41</td>
<td>-</td>
</tr>
<tr>
<td>Rd18</td>
<td>52</td>
<td>40</td>
<td>0.90 (0.55-1.47)</td>
</tr>
<tr>
<td>MPT</td>
<td>47</td>
<td>47</td>
<td>0.95 (0.57-1.59)</td>
</tr>
</tbody>
</table>

**Pts at risk:**

<table>
<thead>
<tr>
<th></th>
<th>Rd cont</th>
<th>Rd18</th>
<th>MPT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-High Risk</strong></td>
<td>205</td>
<td>209</td>
<td>206</td>
</tr>
<tr>
<td>Rd cont</td>
<td>43</td>
<td>48</td>
<td>47</td>
</tr>
</tbody>
</table>

cont, continuous; HR, hazard ratio; MPT, melphalan, prednisone, and thalidomide; pt, patient; Rd, lenalidomide plus low-dose dexamethasone; Rd18, Rd for 18 cycles.

FIRST (MM-020): Frailty Analysis
Authors’ Conclusions

• Das progressionsfreie- und Gesamtüberleben ist besser bei Patienten die mit Rev/Dex kontinuierlich behandelt werden im Vergleich zu jenen Patienten die in dieser Studie MPT bekommen haben.

• Die Bedeutung der IMWG Frailty Skala um das klinische Ansprechen vorauszusagen wurde durch diese Studie unterstrichen.

• Der Großteil der in die FIRST Studie eingebrachten Patienten bestand aus Patienten mit schlechterem Allgemeinzustand, sodass diese Studie eine für die klinische Praxis relevante Untersuchung darstellt.

• Patienten mit Niedrigrisiko – Zytogenetik profitieren durch diese Kombination mehr als Hochrisikopatienten.

• Die kontinuierliche Behandlung mit Rev/Dex kann daher als Standard zur Erstbehandlung älterer Patienten betrachtet werden.

Facon T et al, ASH 2015
First-line therapy of multiple myeloma

Lenalidomide combinations

SWOG S077 (Durie) Abstract 25 – ASH 2015
RVd vs Rd With Rd Maintenance: SWOG S0777
Study Design1,2

INDUCTION

RVd
LEN 25 mg PO d1–14
DEX 20 mg PO
D1, 2, 4, 5, 8, 9, 11, 12
BORT 1.3 mg/m² IV
D1, 4, 8, 11
8 × 21-day cycles
(n = 242)

Rd
LEN 25 mg PO d1–21
DEX 40 mg PO
D1, 8, 15, 22
6 × 28-day cycles
(n = 232)

Stratified by ISS stage and intent to SCT

ENDPOINTS
Primary: PFS
Secondary: ORR, OS, safety

MAINTENANCE

Rd
LEN 25 mg PO d1–21
DEX 40 mg PO
D1, 8, 15, 22
28-day cycles until PD, unacceptable toxicity, or withdrawal of consent

FOLLOW-UP

Follow-up for 6 years for OS

• All pts received aspirin 325 mg/day
• RVd pts received HSV prophylaxis per institutional standard

NDMM without intent for immediate SCT
(N = 474)

BORT, bortezomib; D, day; DEX, dexamethasone; HSV, herpes simplex virus; ISS, International Staging System; LEN, lenalidomide; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, oral administration; pt, patient; Rd, lenalidomide and low-dose dexamethasone; RVd, bortezomib, lenalidomide, and low-dose dexamethasone; SCT, stem cell transplant.
Phase III Trial SWOG S0777: Results

**ORR:** RVD: 71% vs RD 64%

Durie:“…..dass in der SWOG0777 deutlich jüngere Patienten eingeschlossen waren als in der FIRST. „
Pt characteristics were similar between Tx arms, with two exceptions:

- Fewer women received RVd vs Rd (37% vs 47%; \( P = 0.033 \))
- Fewer pts ≥ 65 years received RVd vs Rd (38% vs 48%; \( P = 0.042 \))
RVd vs Rd With Rd Maintenance: SWOG S0777
Survival Analyses

<table>
<thead>
<tr>
<th></th>
<th>RVd (n = 242)</th>
<th>Rd (n = 232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos (95% Cl)</td>
<td>43 (39-51)</td>
<td>31 (26-40)</td>
</tr>
<tr>
<td>HR (96% Wald Cl)</td>
<td>0.742 (0.579-0.951)</td>
<td></td>
</tr>
<tr>
<td>1-sided stratified log-rank P-value</td>
<td>.0066(^a)</td>
<td></td>
</tr>
<tr>
<td>Median OS, mos (95% Cl)</td>
<td>NR</td>
<td>63 (55-69)</td>
</tr>
<tr>
<td>HR</td>
<td></td>
<td>0.666</td>
</tr>
<tr>
<td>2-sided log-rank P-value</td>
<td>.0114</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) This analysis reached the prespecified significance level of .02.
HR, hazard ratio; Rd, lenalidomide and low-dose dexamethasone; NR, not reached; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and low-dose dexamethasone; RVd, bortezomib, lenalidomide, and low-dose dexamethasone.

RVd vs Rd With Rd Maintenance: SWOG S0777 Authors’ Conclusions

- The addition of BORT to Rd induction therapy provides a statistically significant and clinically meaningful improvement in PFS
  - OS is also extended with the addition of BORT to Rd
- The safety and tolerability of RVd is acceptable, although neurotoxicity is increased
- RVd represents a potential new standard of care for pts with NDMM

BORT, bortezomib; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; pt, patient; Rd, lenalidomide and low-dose dexamethasone; RVd, bortezomib, lenalidomide, and low-dose dexamethasone.

Therapy of relapsed/refractory MM

Pomalidomide combinations
POM + LoDEX vs. HiDEX in Relapsed and Refractory MM
MM-010 (STRATUS): Trial Design

- Primary endpoint: Safety
- Key secondary endpoints: ORR (≥ PR by IMWG criteria), DOR, PFS, OS, and POM exposure
- Data cutoff: May 4, 2015

Thromboprophylaxis with low-dose aspirin, low-molecular-weight heparin, or equivalent was required for all pts

Registered at ClinicalTrials.gov as NCT01712789 and at EudraCT as 2012-001888-78.

AE, adverse event; DOR, duration of response; IMWG, International Myeloma Working Group; LoDEX, low-dose dexamethasone; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; POM, pomalidomide; PR, partial response; pts, patients; SPM, second primary malignancy, Tx, treatment.


Moreau P, et al. Analysis of Patient Outcomes by Prior Treatment and Depth of Response in STRATUS (MM-010), a Phase 3b Study of Pomalidomide + Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma. ASH 2015, abstract #1834.
Moreau P, et al. Analysis of Patient Outcomes by Prior Treatment and Depth of Response in STRATUS (MM-010), a Phase 3b Study of Pomalidomide + Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma. ASH 2015, abstract #1834.
MM-010 (STRATUS): PFS and OS by Depth of Response

Error bars show 95% confidence interval.
OS, overall survival; PFS, progression-free survival.
Moreau P, et al. Analysis of Patient Outcomes by Prior Treatment and Depth of Response in STRATUS (MM-010), a Phase 3b Study of Pomalidomide + Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma. ASH 2015, abstract #1834.
POM + LoDEX: Pooled Renal Analysis
Efficacy

<table>
<thead>
<tr>
<th></th>
<th>With Moderate RI</th>
<th>Without Moderate RI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MM-002 (n = 37)</td>
<td>MM-003 (n = 93)</td>
</tr>
<tr>
<td>Median PFS (95% CI), mos</td>
<td>3.8 (2.8-7.9)</td>
<td>4.0 (2.8-4.8)</td>
</tr>
<tr>
<td>Median TTP (95% CI), mos</td>
<td>4.7 (3.1-9.3)</td>
<td>4.4 (2.9-6.5)</td>
</tr>
<tr>
<td>Median DOR (95% CI), mos</td>
<td>8.3 (5.8-14.1)</td>
<td>6.6 (3.9-9.7)</td>
</tr>
<tr>
<td>Median OS (95% CI), mos</td>
<td>13.4 (8.7-23.8)</td>
<td>10.4 (6.6-12.4)</td>
</tr>
</tbody>
</table>

- ORR was similar in pts with moderate RI vs without RI (30.4% vs 33.8%; P = .299)
- Median PFS (P = .070), median TTP (P = .302), and median DOR (P = .435) were similar for both pt subgroups
- Pts with moderate RI had a significantly shorter median OS vs pts without RI (P = .004)

DOR, duration of response; LoDEX, low-dose dexamethasone; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; pt, patient; RI, renal impairment; TTP, time to progression.
Overview Triplet Combination Pomalidomide rrMM new
Efficacy Results of Pomalidomide-based Triplet Therapies in Advanced rrMM

- **Response (%)**
  - PR
  - VGPR
  - CR

### Study / Author / Phase

<table>
<thead>
<tr>
<th>Study / Author / Phase</th>
<th>MM-003 / San-Miguel, 2013 / Phase III¹</th>
<th>Larocca, 2013 / Phase I/II²</th>
<th>Baz, 2014 / Phase II³</th>
<th>MM-005 / Richardson, 2015 / Phase I⁵</th>
<th>Shah, 2013 / Phase I/II⁶</th>
<th>Rosenbaum, 2014 / Phase I/II⁷</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>302</td>
<td>55⁴</td>
<td>34⁵</td>
<td>47</td>
<td>34</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>Median: 5</td>
<td>Median: 3</td>
<td>Median: 4</td>
<td>Median: 2</td>
<td>Median: 5</td>
<td>Median: 2</td>
</tr>
<tr>
<td>Inclusion criteria⁶</td>
<td>Previous LEN and BORT treatment</td>
<td>LEN-relapsed or/refractory</td>
<td>Resistant or refractory to LEN</td>
<td>LEN-refractory, prior PI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>Median 4.0 mos</td>
<td>Median 10.4 mos</td>
<td>Median 9.5 mos</td>
<td>Median 10.7 mos</td>
<td>NR</td>
<td>Median 9.7 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median 18.9 mos</td>
</tr>
</tbody>
</table>

¹ Data reported here for MTD and Phase II pts only; ² CR not reported; ³ among others

- BORT, bortezomib; CFZ, carfilzomib; CR, complete response; CYCLO, cyclophosphamide; DEX, dexamethasone; LEN, lenalidomide; ORR, overall response rate; POM, pomalidomide; PR, partial response; PRED, prednisone; VGPR, very good partial response; PFS, progression-free survival; NR, not reported.
Baz R, et al. Pomalidomide, Cyclophosphamide, and Dexamethasone Is Superior to Pomalidomide and Dexamethasone in Relapsed and Refractory Myeloma: Results of a Multicenter Randomized Phase II Study. ASH 2014, abstract #303
Cyclophosphamide; LoDEX, low-dose dexamethasone; PFS, progression free survival; POM, pomalidomide.

Baz R, et al. Pomalidomide, Cyclophosphamide, and Dexamethasone Is Superior to Pomalidomide and Dexamethasone in Relapsed and Refractory Myeloma: Results of a Multicenter Randomized Phase II Study. ASH 2014, abstract #303
# Phase III studies in relapsed and refractory MM

<table>
<thead>
<tr>
<th>Regime</th>
<th>ASPIRE</th>
<th>PANORAMA</th>
<th>ELOQUENT</th>
<th>TOURMALINE-MM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regime</td>
<td>KRd vs Rd 27 mg/m² CFZ K: max 18 cycles</td>
<td>PAN+Vd vs Vd+Plb 20 mg oral Max 12 cycles</td>
<td>Elo+Rd vs Rd 10 mg/kg Elo Until progression</td>
<td>Ixa+Rd vs Rd+Plb 4 mg Ixa Until progression</td>
</tr>
<tr>
<td>ISS III (%)</td>
<td>43</td>
<td>22</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>87.1 vs 66.7</td>
<td>60.7 vs 54.6</td>
<td>79 vs 66</td>
<td>78.3 vs 71.5</td>
</tr>
<tr>
<td>≥VGPR (%)</td>
<td>69.9 vs 40.4</td>
<td>27.6 vs 15.7</td>
<td>28 vs 21</td>
<td>48.1 vs 39</td>
</tr>
<tr>
<td>CR+sCR (%)</td>
<td>31.8 vs 9.3</td>
<td>11 vs 6</td>
<td>4 vs 7</td>
<td>11.7 vs 6.6</td>
</tr>
<tr>
<td>PFS (prim. EP)</td>
<td>26.3 vs 17.6 mo</td>
<td>12 vs 8.1 mo</td>
<td>19.4 vs 14.9 mo</td>
<td>20.6 vs 14.7 mo</td>
</tr>
<tr>
<td>OS (mo or %)</td>
<td>At 24 mo: 73.3 vs 65%</td>
<td>33.6 vs 30.4 mo</td>
<td>43.7 vs 39.6 mo</td>
<td>Not yet mature</td>
</tr>
</tbody>
</table>
Fortschritte in der Therapie der Behandlung von nicht für die Transplantation geeigneten Patienten mit multiplem Myelom

**Immunmodulierende Substanzen:**
- Revlimid (Erstlinientherapie)
- Pomalidomid

**Proteasomeninhbitorioren:**
- Carfilzomib
- Ixozamib

**HDAC-Inhibitoren**
- Vorinostat (Entwicklung gestoppt)
- Panabinostat

**Monoklonale Antikörper**
- Daratumumab
- Elotuzumab
ASPIRE Trial: Study Design

28-day cycles

Randomize 1:1

N= 792

LEN: 25 mg PO
D1-21
DEX: 40 mg PO or IV
D1, 8, 15, 22

Cycles 1-12
(28 days each)

CFZ: 20\(^a/27\) mg/m\(^2\) IV
\(^a\) D1 and 2 (cycle 1)
D8, 9, 15, 16 (cycle 1) and
D1, 2, 8, 9, 15, 16 (cycles 2-12)
LEN: 25 mg PO
D1-21
DEX: 40 mg PO or IV
D1, 8, 15, 22

Cycles 13-18
(28 days each)

CFZ: 27 mg/m\(^2\) IV
D1, 2, 15, 16
LEN: 25 mg PO
D1-21
DEX: 40 mg PO or IV
D1, 8, 15, 22

Cycles ≥ 19
(28 days each)

LEN: 25 mg PO
D1-21
DEX: 40 mg PO or IV
D1, 8, 15, 22

Tx until PD or toxicity

ASPIRE: Carfilzomib, Lenalidomide, and Dexamethasone versus Lenalidomide and Dexamethasone for the treatment of Patients with Relapsed Multiple Myeloma; CFZ: carfilzomib; D: day; DEX: dexamethasone; IV: intravenous; LEN: lenalidomide; PD: progressive disease; PO: orally; Tx: treatment.

1. Moreau P. J Clin Oncol. 2011;29 [abstract TPS227, poster presentation].

Primärer Endpunkt: Progressions-freies Überleben

ITT Population (n=792)

<table>
<thead>
<tr>
<th></th>
<th>Carfilzomib Group (N=396)</th>
<th>Control Group (N=396)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression or death — no. (%)</td>
<td>207 (52.3)</td>
<td>224 (56.6)</td>
</tr>
<tr>
<td>Median progression-free survival — mo</td>
<td>26.3</td>
<td>17.6</td>
</tr>
<tr>
<td>Hazard ratio for carfilzomib group vs. control group (95% CI)</td>
<td>0.69 (0.57–0.83)</td>
<td></td>
</tr>
</tbody>
</table>

P=0.0001

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Carfilzomib group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>396</td>
<td>396</td>
</tr>
<tr>
<td>6 months</td>
<td>332</td>
<td>287</td>
</tr>
<tr>
<td>12 months</td>
<td>279</td>
<td>206</td>
</tr>
<tr>
<td>18 months</td>
<td>222</td>
<td>151</td>
</tr>
<tr>
<td>24 months</td>
<td>179</td>
<td>117</td>
</tr>
<tr>
<td>30 months</td>
<td>112</td>
<td>72</td>
</tr>
<tr>
<td>36 months</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>42 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 months</td>
<td></td>
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</tr>
</tbody>
</table>
Sekundärer Endpunkt: Gesamtüberleben - Interims-Analyse
Medianer Follow-up 32 Monate

Medianes Gesamtüberleben wurde nicht erreicht; die Ergebnisse haben die vorher bestimmte Abbruchsgrenze (P=0.005) bei der Interims-Analyse nicht erreicht.
**PFS by Prior Line of Therapy (1 vs ≥2)**

<table>
<thead>
<tr>
<th>1 prior line of therapy</th>
<th>≥2 prior lines of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRd (n=184)</strong></td>
<td><strong>Rd (n=157)</strong></td>
</tr>
<tr>
<td><strong>PFS, median months</strong></td>
<td>29.6</td>
</tr>
<tr>
<td><strong>Hazard ratio</strong></td>
<td>0.69 (0.52–0.94)</td>
</tr>
<tr>
<td><strong>P value (one-sided)</strong></td>
<td>.008</td>
</tr>
</tbody>
</table>

CI: Confidence interval; KRd, carfilzomib, lenalidomide, and dexamethasone; PFS, progression-free survival; Rd, lenalidomide and dexamethasone.
Overall Survival by Prior Line of Therapy (1 vs ≥2)

1 prior line of therapy

≥2 prior lines of therapy

KRd, carfilzomib, lenalidomide, and dexamethasone; OS, overall survival; Rd, lenalidomide and dexamethasone.
Hematologic Grade ≥3 Adverse Events Reported in ≥3% of Patients in Any Subgroup

<table>
<thead>
<tr>
<th>Hematologic grade ≥3 AEs (preferred terms), n (%)</th>
<th>1 prior line of therapy</th>
<th>≥2 prior lines of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KRd (n=182)</td>
<td>Rd (n=154)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>48 (26.4)</td>
<td>34 (22.1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>31 (17.0)</td>
<td>30 (19.5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>28 (15.4)</td>
<td>18 (11.7)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>6 (3.3)</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>6 (3.3)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>6 (3.3)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Decreased neutrophil count</td>
<td>4 (2.2)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

|                                                  | KRd (n=210)             | Rd (n=235)               |
| Neutropenia                                       | 68 (32.4)               | 69 (29.4)                |
| Anemia                                            | 39 (18.6)               | 37 (15.7)                |
| Thrombocytopenia                                  | 37 (17.6)               | 30 (12.8)                |
| Leukopenia                                        | 6 (2.9)                 | 11 (4.7)                 |
| Lymphopenia                                       | 5 (2.4)                 | 5 (2.1)                  |
| Decreased platelet count                          | 6 (2.9)                 | 6 (2.6)                  |
| Decreased neutrophil count                        | 8 (3.8)                 | 10 (4.3)                 |

AE, adverse event; KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.
Median PFS


*Descriptive P-value.
ENDEAVOR Study Design

Randomization 1:1
N=929
Stratification:
• Prior proteasome inhibitor therapy
• Prior lines of treatment
• ISS stage
• Route of V administration

Kd
Carfilzomib 56 mg/m² IV
Days 1, 2, 8, 9, 15, 16 (20 mg/m² days 1, 2, cycle 1 only)
Infusion duration: 30 minutes for all doses
Dexamethasone 20 mg
Days 1, 2, 8, 9, 15, 16, 22, 23
28-day cycles until PD or unacceptable toxicity

Vd
Bortezomib 1.3 mg/m² (IV bolus or subcutaneous injection)
Days 1, 4, 8, 11
Dexamethasone 20 mg
Days 1, 2, 4, 5, 8, 9, 11, 12
21-day cycles until PD or unacceptable toxicity

International Staging System; IV, intravenous; Kd, carfilzomib and dexamethasone; PD, progressive disease; Vd, bortezomib and dexamethasone; V, bortezomib.
Primary End Point: Progression-Free Survival

*Intent-to-Treat Population (N=929)*

- **Disease progression or death – n (%):**
  - Kd (n=464): 171 (37)
  - Vd (n=465): 243 (52)

- **Median PFS – months:**
  - Kd: 18.7
  - Vd: 9.4

- **HR for Kd vs Vd (95% CI):**
  - 0.53 (0.44–0.65)
  - 1-sided P < 0.0001

- **Median follow-up:** 11.2 months

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Kd, carfilzomib and dexamethasone; PFS, progression-free survival; Vd, bortezomib and dexamethasone.

Carfilzomib is not approved in EU.
Secondary End Point: Response Rates

- **Median DOR:** 21.3 months (95% CI, 21.3–NE) for Kd vs 10.4 months (95% CI, 9.3–13.8) for Vd

CI, confidence interval; CR, complete response; DOR, duration of response; ORR, overall response rate; Kd, carfilzomib and dexamethasone; NE, not estimable; PR, partial response; Vd, bortezomib and dexamethasone; VGPR, very good partial response.

Carfilzomib is not approved in EU.
Secondary End Point: Overall Survival

*Intent-to-Treat Population (N=929)*

OS data were immature; the study will continue until the final OS analysis is performed.

<table>
<thead>
<tr>
<th>Months Since Randomization</th>
<th>Kd (n=464)</th>
<th>Vd (n=465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>75 (16)</td>
<td>88 (19)</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
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<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Death – n (%)

Median OS – months

HR for Kd vs. Vd (95% CI)

0.79 (0.58–1.08)

1-sided $P=0.066$

CI, confidence interval; HR, hazard ratio; ITT, intent to treat; Kd, carfilzomib and dexamethasone; NE, not estimable; OS, overall survival; Vd, bortezomib and dexamethasone.

Carfilzomib is not approved in EU.
**Ixazomib in transplant-ineligible patients**

Best confirmed response

<table>
<thead>
<tr>
<th>Confirmed response, * n (%)</th>
<th>ICd-300 (N=32)</th>
<th>ICd-400 (N=34)</th>
<th>All (N=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + VGPR</td>
<td>10 (28)</td>
<td>7 (21)</td>
<td>17 (26)</td>
</tr>
<tr>
<td>ORR (CR + VGPR + PR)</td>
<td>25 (78)</td>
<td>22 (65)</td>
<td>47 (71)</td>
</tr>
<tr>
<td>CR</td>
<td>3 (10)</td>
<td>3 (9)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>sCR</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>PR</td>
<td>22 (69)</td>
<td>19 (56)</td>
<td>41 (62)</td>
</tr>
<tr>
<td>VGPR</td>
<td>7 (22)</td>
<td>4 (12)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>SD</td>
<td>6 (16)</td>
<td>9 (26)</td>
<td>15 (23)</td>
</tr>
</tbody>
</table>

*response-evaluable patients

Dimopoulos, M et al. Presented at ASH 2015 (Abstract 26), oral presentation
Ixazomib in transplant ineligible patients
Accumulated response rate over time*

*first confirmed or unconfirmed response

Data cut-off 2 Sept 2015

Median time to
≥PR: 1.3 cycles

≥PR

≥VGPR

Median follow-up
Ixazomib in transplant ineligible patients
Progression-free survival

- Median follow-up of 9.2 months

Dimopoulos, M et al. Presented at ASH 2015 (Abstract 26), oral presentation
Fortschritte in der Therapie der Behandlung von nicht für die Transplantation geeigneten Patienten mit multiples Myelom

**Immunmodulierende Substanzen:**
- Revlimid (Erstlinientherapie)
- Pomalidomid

**Proteasomeninhibitoren:**
- Carfilzomib
- Ixozamib

**HDAC-Inhibitoren**
- Vorinostat (Entwicklung gestoppt)
- Panabinostat

**Monoklonale Antikörper**
- Daratumumab
- Elotuzumab
PANORAMA 1 Studiendesign

Ptn (N=768)
- Rel oder Rel/Ref MM (BTZ-ref exkludiert)
- 1-3 vorheriger Therapielinien
- Stratifizierungsfaktoren
  - Vorherige Therapielinien
  - Vorheriges BTZ

Behandlungsphase I
Acht 21-Tage Zyklen (24 Wochen)
- Panobinostat + Bortezomib + Dexamethasone
- Plazebo + Bortezomib + Dexamethasone

Behandlungsphase II
Vier 42-Tage Zyklen (24 Wochen)
- Panobinostat + Bortezomib + Dexamethasone
- Plazebo + Bortezomib + Dexamethasone

Ptn mit klinischem Benefit\(^a\) in Phase I können in Phase II übertreten

Follow-up

- Primärer Endpunkt: Progressions-freies Überleben
- Sekundärer Endpunkt: Gesamtüberleben
- Andere sekundäre Endpunkte: ORR, nCR/CR Rate,, DOR, TTR, TTP, QoL und Sicherheit

\(^a\) Erreichen von ≥ keine Veränderung nach den modifizierten EBMT Kriterien (SD oder besser)

Studie wurde in 215 Zentren in 34 Ländern durchgeführt
Primary Endpoint (PFS) – overall study population

Primary endpoint met ($P < .0001$), with clinically relevant increase in median PFS of 3.9 months for PAN-BTZ-Dex arm

- Updated IRC analysis demonstrated greater concordance with PFS by investigator per protocol assessment
- The data cutoff date for the final analysis of PFS was September 10, 2013

Richardson PG. 2014. ASCO. Oral present. 8510
**Detailed Subgroup Analysis of PFS By Prior Treatment**

**Longer median PFS Linked With Longer “Treatment-free Interval”**

<table>
<thead>
<tr>
<th>Time (months)</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>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of exposure</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TFI ... Treatment-free interval</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>= PFS – med. exposure time</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Overall study population (n=768)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo arm</th>
<th>PANO arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>TFI</td>
<td>Gray</td>
<td>Purple</td>
</tr>
<tr>
<td>(\Delta) PFS</td>
<td>3.9 mo</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment Free Interval = \(~7\) mo**
Alternative Therapiemöglichkeiten für Zweit- und Mehrlinientherapien

Immunmodulierende Substanzen:
- Pomalidomid

Proteasomeninhibitoren:
- Carfilzomib
- Ixozamib

HDAC-Inhibitoren
- Vorinostat (Entwicklung gestoppt)
- Panabinostat

Monoklonale Antikörper
- Daratumumab
- Elotuzumab
- Monoklonaler Antikörper von Morphosys
# Myeloma targets and antibodies in development

<table>
<thead>
<tr>
<th>Myeloma Target</th>
<th>mAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD30</td>
<td>Brentuximab vedotin</td>
</tr>
<tr>
<td>CD38</td>
<td>SAR650984, <strong>Daratumumab, MOR-202</strong></td>
</tr>
<tr>
<td>CD40</td>
<td>Lucatumumab, Dacetuzumab</td>
</tr>
<tr>
<td>CD54 (ICAM-1)</td>
<td>BI-505</td>
</tr>
<tr>
<td>CD56</td>
<td>Lorvotuzumab</td>
</tr>
<tr>
<td>CD70</td>
<td>SGN-70</td>
</tr>
<tr>
<td>CD74</td>
<td>Miltatuzumab (-doxorubicin)</td>
</tr>
<tr>
<td>CD138</td>
<td>BT062</td>
</tr>
<tr>
<td>CD200</td>
<td>Samalizumab</td>
</tr>
<tr>
<td>BCMA</td>
<td>GSK2857916</td>
</tr>
<tr>
<td>CXCR4</td>
<td>Ulocuplumab</td>
</tr>
<tr>
<td>FcRL5</td>
<td>Anti-FcRL5(hu10A8)-SPDB-DM4</td>
</tr>
<tr>
<td>SLamF7</td>
<td><strong>Elotuzumab</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune Targets</th>
<th>mAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIR</td>
<td>IPH2101</td>
</tr>
<tr>
<td>CD47</td>
<td>CC-90002</td>
</tr>
<tr>
<td>CD137</td>
<td>BMS-663513</td>
</tr>
<tr>
<td>PD-1</td>
<td>Pembrolizumab, nivolumab, pidilizumab</td>
</tr>
<tr>
<td>PD-L1</td>
<td>BMS-936559, MPDL3280A</td>
</tr>
</tbody>
</table>

*IMW 2015*
Phase I/II Daratumumab Monotherapy Study: IMWG Response and PFS

IMWG Response

- All Patients: n = 32
- ≤ 2 mg/kg: n = 20
- ≥ 4 mg/kg: n = 12

Response Rate (%)

PFS

- 4-24 mg/kg (n = 12)
  - median follow up time: 18.4 wks (0-53)
- 0.005-2 mg/kg (n = 20)
  - median follow up time: 8.6 wks (0-29)

Log-rank test $P = .007$

Lenalidomide on Effector and Target Cells: Enhanced ADCC Via NK Cell Activation & CD38 Upregulation

**NCI-H929**
(CD38 high, lenalidomide cytotoxicity sensitive)
- Lenalidomide added to effector cells and MM cell line
- MOR202 added to effector cells and MM cell line

**AMO-1**
(CD38 low, lenalidomide cytotoxicity insensitive)

![Graphs showing specific killing activity vs. MOR202 concentration for NCI-H929 and AMO-1 cell lines.](image)

- LEN-induced effector cell activation
- LEN-induced CD38 upregulation
- LEN-induced cytotoxic effect on target cells
MOR 202: Clinical Benefit Rate (CBR)

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Cohort 1 ibr 420 mg* (n = 13)</th>
<th>Cohort 2 ibr 560 mg + dex (n = 18)</th>
<th>Cohort 3 ibr 840 mg* (n = 18)</th>
<th>Cohort 4 ibr 840 mg + dex (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBR (MR or better)</td>
<td>1 (8)</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>10 (23)</td>
</tr>
<tr>
<td>PR</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>MR</td>
<td>1 (8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>8 (19)</td>
</tr>
<tr>
<td>SD ≥ 4 cycles</td>
<td>1 (8)</td>
<td>4 (22)</td>
<td>6 (33)</td>
<td>12 (28)</td>
</tr>
</tbody>
</table>

*International Myeloma Workshop, 2015*
ELOQUENT-2 Study Design

- Open-label, international, randomized, multicenter, phase 3 trial (168 global sites)

Key inclusion criteria
- RRMM
- 1–3 prior lines of therapy
- Prior Len exposure permitted in 10% of study population (patients not refractory to Len)

Elo plus Len/Dex (E-Ld) schedule (n=321)
- Elo (10 mg/kg IV): Cycle 1 and 2: weekly; Cycles 3+: every other week
- Len (25 mg PO): Days 1–21
- Dex: weekly equivalent, 40 mg

Len/Dex (Ld) schedule (n=325)
- Len (25 mg PO): Days 1–21;
- Dex: 40 mg PO Days 1, 8, 15, 22

Assessment
- Tumor response: every 4 weeks until progressive disease
- Survival: every 12 weeks after disease progression

Endpoints:
- Co-primary: PFS and ORR
- Other: overall survival (data not yet mature), duration of response, quality of life, safety

- All patients received premedication to mitigate infusion reactions prior to elotuzumab administration
- Elotuzumab IV infusion administered ~ 2–3 hours

Lonial et al, NEJM 2015
Co-primary Endpoint: Progression-Free Survival

E-Ld–treated patients had a 30% reduction in the risk of disease progression or death; treatment difference at 1 and 2 years was 11% and 14%, respectively.

PFS analysis used the primary definition of PFS

Lonial et al, NEJM 2015
Co-primary Endpoint: Overall Response Rate

*Defined as partial response or better. †Complete response rates in the E-Ld group may be underestimated due to interference from therapeutic antibody in immunofixation and serum protein electrophoresis assay.

Lonial et al, NEJM 2015
Danke für die Aufmerksamkeit