Long-term ixazomib maintenance is tolerable and improves depth of response following ixazomib-lenalidomide-dexamethasone induction in patients with previously untreated multiple myeloma (MM): Phase 2 study results

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Ixazomib

- Ixazomib is an investigational, oral, reversible, and specific 20S proteasome inhibitor
  - The first oral proteasome inhibitor in clinical development
  - Physiochemical properties distinct from bortezomib

- Ixazomib has been evaluated in single-agent and combination studies in MM
  - Clinical activity of single-agent ixazomib seen in heavily pretreated patients
  - Data suggest a manageable toxicity profile with low rates of peripheral neuropathy (PN)
  - Phase 3 trials underway

Rationale

- Triplet regimens combining a proteasome inhibitor, an immunomodulatory drug, and a steroid shown to be active and well tolerated in previously untreated MM patients\(^1\text{-}^3\)
  - High response rates seen with the bortezomib, lenalidomide, dexamethasone (VRD/RVD) regimen\(^1\text{-}^2\)

- Increasing evidence suggests that extended treatment may add benefits to conventional induction strategies
  - Long-term maintenance therapy improves survival outcomes, including PFS and sometimes OS, in both the transplant and non-transplant settings
  - However, agents for continuous therapy need to be convenient and well tolerated
  - Oral weekly ixazomib may be an ideal maintenance drug in terms of tolerability/safety and convenience

Phase 1/2 study of weekly ixazomib plus lenalidomide-dexamethasone (NCT01217957)

- Triplet regimen investigated in an open-label, dose-escalation, phase 1/2 study, conducted in patients with previously untreated MM to:
  - Define the dose of ixazomib to be combined with lenalidomide and dexamethasone
  - Evaluate the efficacy and toxicity of the combination
  - Evaluate the feasibility, efficacy, and safety of long-term maintenance therapy with single-agent ixazomib

- The recommended phase 2 dose (RP2D) was determined to be ixazomib 4.0 mg weekly, on days 1, 8, 15, with lenalidomide 25 mg on days 1–21, and dexamethasone weekly, in 4-week cycles.\(^1\)
  - Results of induction therapy have been previously reported.\(^1\)
  - Here we report phase 2 efficacy and safety data in patients receiving ixazomib maintenance

Patient eligibility

Key inclusion criteria:
- Age ≥18 years
- ECOG performance status 0–2
- Adequate hepatic, renal, and hematologic function
- Measurable disease:
  - Serum M-protein ≥1 g/dL
  - Urine M-protein ≥200 mg/24 hours
  - Involved free light chain ≥10 mg/dL

Key exclusion criteria:
- Grade ≥2 PN
- Prior/concurrent deep vein thrombosis/pulmonary embolism
- Prior systemic MM therapy
Study design – Phase 2 dosing

- Mandatory thromboembolism prophylaxis with aspirin 81–325 mg QD or low-molecular-weight heparin while receiving lenalidomide–dexamethasone
- Stem cell collection allowed after 3 cycles; patients could proceed to ASCT after 6 cycles
- Ixazomib maintenance continued until progression or unacceptable toxicity
  - Ixazomib administered at last tolerated dose during induction
- Primary objective was CR+VGPR rate
65 patients enrolled\(^1\)
15 Phase 1, 50 Phase 2
Median no. of cycles: 7 (range 1–45)

17 patients off treatment before cycle 13 (maintenance)
- 2 Phase 1 patients
  - Both due to AEs
- 15 Phase 2 patients
  - 6 due to AEs
  - 4 patient withdrawals
  - 2 disease progression
  - 1 unsatisfactory response
  - 2 other

23 withdrew to initiate ASCT
9 Phase 1, 14 Phase 2

25 patients entered maintenance phase
- 4 Phase 1 patients (BSA-based dosing)
  - Received actual doses of 4.0, 4.0, 3.6, and 3.4 mg
- 21 Phase 2 patients (fixed dosing\(^2\))
  - 16 entered at 4.0 mg
  - 4 entered at 3.0 mg
  - 1 entered at 2.4 mg
  - Focus of the current presentation

## Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>All phase 2 patients, n=50</th>
<th>Patients receiving maintenance, n=21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>65 (34–86)</td>
<td>68 (34–77)</td>
</tr>
<tr>
<td><strong>Age ≥65 years, n (%)</strong></td>
<td>25 (50)</td>
<td>12 (57)</td>
</tr>
<tr>
<td><strong>Age ≥75 years, n (%)</strong></td>
<td>9 (18)</td>
<td>2 (10)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>30 (60)</td>
<td>13 (62)</td>
</tr>
<tr>
<td><strong>White, n (%)</strong></td>
<td>42 (84)</td>
<td>16 (76)</td>
</tr>
<tr>
<td><strong>ISS disease stage at diagnosis, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>25 (50)</td>
<td>14 (67)</td>
</tr>
<tr>
<td>II</td>
<td>19 (38)</td>
<td>7 (33)</td>
</tr>
<tr>
<td>III</td>
<td>6 (12)</td>
<td>0</td>
</tr>
<tr>
<td><strong>MM subtype, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>34 (68)</td>
<td>16 (76)</td>
</tr>
<tr>
<td>IgA</td>
<td>9 (18)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>IgD</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Light chain</td>
<td>6 (12)</td>
<td>2 (10)</td>
</tr>
<tr>
<td><strong>Median creatinine clearance, mL/min</strong></td>
<td>85.3</td>
<td>83.5</td>
</tr>
</tbody>
</table>
## Cytogenetics

<table>
<thead>
<tr>
<th>Patients with cytogenetic assessment, N*</th>
<th>All phase 2 patients, n=50</th>
<th>Patients receiving maintenance, n=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional/karyotype</td>
<td>7 (15)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Molecular/FISH</td>
<td>15 (32)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Both</td>
<td>25 (53)</td>
<td>10 (53)</td>
</tr>
<tr>
<td>Unfavorable cytogenetics†, n (%)</td>
<td>6 (13)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Type of cytogenetic abnormality, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>del 13 (by metaphase cytogenetics)</td>
<td>2 (4)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>del 17</td>
<td>2 (4)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>1 (2)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>1q amplification</td>
<td>1 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>

*No sample collected for 3 patients. †Unfavorable cytogenetics includes del 17, t(4;14), t(14;16), and 1q amplification abnormalities detected by FISH or metaphase cytogenetics and del 13 detected by metaphase cytogenetics.
## Treatment exposure

<table>
<thead>
<tr>
<th>At data cut-off (October 2, 2014)</th>
<th>Patients receiving maintenance, n=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median cycles of ixazomib received, n (range)</td>
<td>31 (15–35)</td>
</tr>
<tr>
<td>Total (including induction and maintenance cycles)</td>
<td>19 (3–23)</td>
</tr>
<tr>
<td>Maintenance cycles</td>
<td></td>
</tr>
<tr>
<td>Median treatment duration, months (range)</td>
<td>29.0 (16.3–33.3)</td>
</tr>
<tr>
<td>Maintenance duration, months (range)</td>
<td>19.8 (2.3–22.9)</td>
</tr>
<tr>
<td>Mean relative dose intensity* of ixazomib overall / during induction / during maintenance, %</td>
<td>92 / 95 / 89.5</td>
</tr>
<tr>
<td>Patients remaining on ixazomib maintenance, n (%)</td>
<td>11 (52%)</td>
</tr>
</tbody>
</table>

*Dose taken/dose prescribed

- Among the 29 patients in phase 2 who did not proceed to maintenance, median number of cycles of ixazomib received was 6 (1–12)
  - Median cycle of first stem cell mobilization (n=14) was cycle 4 (3–9), and patients who received ASCT received a median of 6 (3–12) cycles of ixazomib
Among the 14 patients who discontinued induction to undergo ASCT, best response to induction included 4 (29%) sCR, 4 (29%) VGPR, and 6 (43%) PR.

- Response following ASCT are not included in the above data.
10 (48%) patients improved their response during maintenance:
- 2 VGPR to nCR, 5 VGPR to CR, 1 VGPR to sCR, and 2 CR to sCR
All 21 patients who received ixazomib maintenance were alive after follow-up of 25.1–33.9 months, including a median follow-up from start of maintenance of 19.9 months (range 13.4–22.2).
Most common drug-related AEs (>20% patients overall, or with new onset in >1 patient during maintenance)

- Any AE
- Skin and SC tissue disorders
- Diarrhea
- Fatigue
- Nausea
- Peripheral neuropathies NEC
- Constipation
- Insomnia
- Vomiting
- Dysgeusia
- Abdominal distension
- Malaise
- Muscle spasms
- Anemia
- Thrombocytopenia
- Hypokalemia
- Pain in extremity
- Headache

Patients, %

Overall
- During induction
- During maintenance

NEC, not elsewhere classified
Drug-related grade 3 AEs were reported in 13 (62%) patients overall, including in 11 (52%) during induction and in 3 (14%) patients during maintenance.

There were no grade 4 drug-related AEs reported at any time during induction and maintenance among the 21 patients who received ixazomib maintenance.
Serious AEs (SAEs) and dose reductions

- Of the 21 patients who received maintenance therapy, 10 (48%) reported an SAE at any time during induction and maintenance treatment
  - Including 3 (14%) with drug-related SAEs

- SAEs were reported in 4 (19%) patients during ixazomib maintenance:
  - Grade 3 acute myocardial infarction; grade 3 pneumonia; grade 3 orthostatic hypotension; grade 2 ventricular extrasystoles
  - All were considered not related to treatment

- In total, 17 (81%) patients required any study drug dose reduction due to an AE during induction
  - Only 2 (10%) patients required ixazomib dose reduction during maintenance, due to PN and neuralgia, respectively

- There were no discontinuations due to AEs and no on-study deaths
Conclusions

- The all-oral combination of ixazomib, lenalidomide, and dexamethasone is active as induction therapy, with a manageable safety profile, at the RP2D in previously untreated MM patients
  - 90% of patients achieved PR or better, including a ≥VGPR rate of 59% and a CR rate of 22%, after up to 12 cycles of induction
  - Common AEs included skin and SC tissue disorders, diarrhea, fatigue, nausea, and peripheral neuropathy

- Data on 21 patients who received maintenance therapy indicate that single-agent ixazomib maintenance for up to 1.9 years was feasible, with a generally manageable safety profile, in patients not undergoing ASCT
  - Ixazomib maintenance improved responses following triplet induction therapy, with 48% of patients showing increased response depth during maintenance
  - Rate of CR+nCR increased from 24% after induction to 62%, with 71% ≥VGPR
  - Ixazomib maintenance contributed to durable responses
  - New-onset toxicity during single-agent ixazomib maintenance was limited

- A phase 3 trial of ixazomib plus lenalidomide–dexamethasone versus placebo plus lenalidomide–dexamethasone in patients with previously untreated MM is currently enrolling (TOURMALINE-MM2; NCT01850524)
Acknowledgments

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