Phase I Study of Pomalidomide, Bortezomib, and Dexamethasone (PVD) as First-Line Treatment of AL Amyloidosis or Light Chain Deposition Disease

Zonder JA1, Houde C1, Tuchman S2, Sukreti V3, Sanchorawala V4, Burt S1, Neveux C1, Reichel K1, Pregja S1, Matous J5

1. Karmanos Cancer Institute / Wayne State University, Detroit, MI; 2. Duke University, Durham, NC; 3. Princess Margaret Cancer Center, Toronto, ON; 4. Boston University Center, Boston, MA; 5. Colorado Blood Cancer Institute, Denver, CO;

Updated Abstract

Background

AL is a clonal plasma cell disorder in which circulating light chains form insoluble extracellular protein deposits (fibrillar and amorphous, respectively). In AL, monoclonal light chain oligomers also play a role in disease pathogenesis. Treatment of AL and LCDD aims at eliminating the abnormal plasma cell clone. Typical agents used include corticosteroids, bortezomib (BTZ), alkylators, or immunomodulatory drugs (IMiDs) such as lenalidomide (LEN) or pomalidomide (POM) which is a highly efficacious front-line regimen commonly used for multiple myeloma, a related plasma cell cancer. Despite the plethora of available regimens, the optimal therapy of AL or LCDD is lacking. Here we report our experience with POM-BTZ-DEX (PVD) for pts with AL or LCDD. Methods: This is a prospective Phase I open-label, dose-escalation study to determine the maximally tolerated dose (MTD), with assessment for dose limiting toxicity (DLT) extending through cycles 1 and 2 for each pt. Hematologic and organ responses (HR and OR) were assessed using recently updated guidelines. PVD was administered in repeating 28-day cycles until either DLT or progressive disease. Key inclusion/exclusion criteria stepped up to include patients with AL or LCDD after more than 1 cycle of anti-plasma cell therapy. Measureable disease defined as at least a 5% change from the initial FLC; and uninvolved (uFLC) serum light chains, or a serum M protein of 0.5 g/dL or greater (other not permitted without measurable uFLC before disease progression change, in percentage of difference after dual assessment). ECOG PS of 0 to 2; adequate renal, hepatic, and marrow function; no Grade 3 or higher peripheral neuropathy (PN; pts with partial grade 2 PN included). Absence of pleural or pericardial effusion or cardiac biomarkers allowed, but pts with NYHA class III/IV congestive heart failure or uncontrolled ventricular arrhythmia were excluded. Antithrombotic prophylaxis (oral anticoagulation) was recommended in pts with a recent history of deep vein thrombosis. The study was approved by the institutional review board of each institution, and adherence to the protocol and patient consent were documented. Results: Six pts have been enrolled thus far (3 each in cohorts 1 and 2, respectively). Pts are currently being screened for eligibility. The number of involved AL pts was 2 (3, 4), with both cardiac and renal, and 1 additional pt with cardiac. The median number of cycles administered was 2 (range 1-6). All pts are off therapy. The reasons for stopping therapy were as follows: 3 pts had cardiac decompensation (heart failure), 3 pts had progression of disease (2 AL, 1 LCDD). One pt had an organ response (liver), while all pts had cardiac progression (all hematologic non-responders). Conclusions: PVD dose levels 1 and 2 were well tolerated without DLTs or unexpected adverse events in pts with AL or LCDD. More resistant patients may reflect dose levels tested that for Dose escalation continued, and an expansion cohort will be enrolled using the MTD as determined.

Study Design and Treatment Plans

Standard 3+3 dose escalation scale with 4 dosing levels

Individual Patient Dosing

<table>
<thead>
<tr>
<th>Pr's #</th>
<th>Best Response (B/R)</th>
<th>Time to first response (cycles)</th>
<th>Organ Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCI-01</td>
<td>SD</td>
<td>Cardiac Progression*</td>
<td></td>
</tr>
<tr>
<td>KCI-02</td>
<td>VSPR</td>
<td>4</td>
<td>Liver</td>
</tr>
<tr>
<td>KCI-03</td>
<td>SD</td>
<td>Cardiac SD</td>
<td></td>
</tr>
<tr>
<td>COL-04</td>
<td>PR</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>KCI-05</td>
<td>VSPR</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>COL-08</td>
<td>PD</td>
<td>Cardiac Progression*</td>
<td></td>
</tr>
</tbody>
</table>

Cardiac Biomarkers were measured on day 1 of each cycle of chemotherapy.

Endpoints

Maximum Tolerated Dose (MTD) of PVD for patients with AL or LCDD

Primary:

- Complete Hematologic Response rate
- Overall Hematologic Response Rate (PR + VGPR + CR)
- Organ Response Rate (heart, liver, kidney)
- Neurotoxicity Assessment (FACT-GOG/survy)
- Progression Free Survival

Secondary:

- Overall Survival
- Cardiac Biomarker analysis

Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

Baseline characteristics are presented at diagnosis (D1) and complete response (CR) at the time of DLT or progressive disease.

Cardiac Biomarkers (% change from baseline)

<table>
<thead>
<tr>
<th>Cardiac Biomarker</th>
<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT Pro-BNP</td>
<td>No change</td>
</tr>
<tr>
<td>Tropo-T</td>
<td>No change</td>
</tr>
</tbody>
</table>

Conclusions

- No DLTs were observed in the first two dosing cohorts in this Phase I trial of pomalidomide (POM), bortezomib (BTZ), and dexamethasone (DEX) as initial therapy for AL. Although the baseline DEX dose for all pts enrolled was reduced to 20 mg/d (per protocol specifications), 2 of 6 pts required subsequent DEX dose modifications. No dose reductions for POM or BTZ have been required. One toxic death (cardiovascular, unknown primary) was observed 14 months after completion of POM-BTZ-DEX therapy. The pt was treated with cyclophosphamide and dexamethasone (POM-BTZ-DEX) for 2 cycles before progression was noted.

- Three of 5 pts had a hematologic response (1 PR, 2 VGPR). One pt had a hematologic response (CR) and organ response (liver), while the three pts without a hematologic response had all had cardiac progression (NT-pro-BNP increases). No discordance between hematologic response and cardiac biomarkers was observed.

- Discontinuation continues, with patients currently being screened for dosing cohort 3.

Key Inclusion/Exclusion Criteria

- Phospho-confirmed AL or LCDD with no clinical signs/symptoms of multiple myeloma
- No more than 1 prior cycle of chemotherapy
- uFLC - 2 mg/dL, with an abnormal uFLC ratio
- Serum creatinine ≤ 2.5 mg/dL
- Adequate liver and lung function
- No Grade 2 or higher hearing loss, or peripheral sensory neuropathy
- ECOG PS 2 and NYHA class ≤ 2 (no lower limit for left ventricular ejection fraction in ECHO specified)

*Difference between included and uninvolved free light chains (mg/dL).

Key Inclusion/Exclusion Criteria

- Zonder J, et al. Plasma cell dyscrasias in which misfolded monoclonal light chains form amyloid deposits, usually affecting the kidneys. Two important prognostic factors in AL are the severity of cardiac involvement at the time of diagnosis (Ref 2), and achievement of a major reduction in the involved (i.e., amyloidogenic) free light chain (Ref 3).

References

6. Zonder J, et al. Plasma cell dyscrasias in which misfolded monoclonal light chains form amyloid deposits, usually affecting the kidneys. Two important prognostic factors in AL are the severity of cardiac involvement at the time of diagnosis (Ref 2), and achievement of a major reduction in the involved (i.e., amyloidogenic) free light chain (Ref 3).

Additional Acknowledgements: Michele Tomassini (KCI OnCore/IT); Nicole Stephens, CRN Colorado Blood Cancer Institute; Celgene Pharmaceuticals (Research Support)