A Phase 1 (Ph1) Trial of Pembrolizumab (MK-3475) Combined With Lenalidomide (Len) and Low-dose Dexamethasone (Dex) in Patients (Pts) With Relapsed/Refractory Multiple Myeloma (RRMM)

David Siegel,* Philippe Moreau,2 David Avigan,3 Kenneth Anderson,4 Donna Rees,5 Jesus San Miguel,6 Maria-Victoria Mateos,7 Dianna Wu,8 Kenneth Emancipator,9 Marisa Dolled-Filhart9 Christine Gause9 Holly Brown9 Karl Heath9 Robert Iannones,9 Shelonita Rose7 Robert Orlowsky8

1John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ; 2Hematology Department, University Hospital Hotel-Dieu, Nantes, France; 3Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; 4Dana-Farber Cancer Institute, Boston, MA; 5Princess Margaret Cancer Centre, Toronto, ON, Canada; 6Clinica Universidad de Navarra, Pamplona, Spain; 7University Hospital of Salamanca, Salamanca, Spain; 8Merck & Co., Inc., Whitehouse Station, NJ; 9University of Texas M.D. Anderson Cancer Center, Houston, TX

Study Design

Open-label, Phase I, multicenter, non-randomized, dose escalation trial of MK-3475 in combination with Len and Dex in subjects with RRMM

- Modified 3+3 design for dose escalation followed by a toxicity probability interval (TPI) for dose confirmation
- Cohorts of approximately 3-6 subjects per dose level enrolled sequentially at escalating doses of 2.5, 10 and 30 mg/kg of MK-3475 in combination with Len/Dex
- After identification of preliminary MTD/IMD, additional subjects enrolled at this dose to confirm the dose based on the TPI algorithm and to further evaluate safety and preliminary efficacy of the combination
- Approximately 24 month duration
- Patients diagnosed with MM failing ≥2 lines of prior therapy, including bortezomib and thalidomide, Len, or pomalidomide
- Up to 44 subjects will be enrolled
- Treatment continues until:
  - Complete response
  - Documented disease progression
  - Unacceptable adverse event (AE)
  - Decision to withdraw the patient/consent
  - Non-compliance with trial treatment

Patient Eligibility Criteria

Significant inclusion criteria

- Patients at least 18 years old, with
- Confirmed diagnosis of MM with measurable disease
- Has relapsed/refractory (RR) MM who has failed at least two lines of prior therapy including bortezomib and an IMiD (thalidomide, lenalidomide, Len)
- An ECOG performance status of 0 or 1
- Adequate hematologic, renal and hepatic function

Significant exclusion criteria

- Myeloma and a history of repeated infections, primary amyloidosis, hyperviscosity, plasma cell leukemia, POEMS syndrome, Waldenström’s macroglobulinemia or IgM myeloma
- Diagnosis of immunoproliferation
- Prior monoclonal antibody therapy within 4 weeks prior to study Day 1
- Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1
- Active autoimmune disease requiring systemic treatment
- Evidence of interstitial lung disease
- Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody
- Antibody-mediated disease
- Autologous stem cell transplant within 12 weeks before the first infusion
- Planning for, or eligible for, allogeneic hematopoietic stem cell transplant
- Unstable or unlikely to undergo anti-thrombotic prophylactic treatment

Treatment

MK-3475 treatment (Figures 2 and 3):

- MK-3475 administered as a 30-minute IV infusion every two weeks (Days 1 and 15) of a 28-day cycle
- The starting dose of MK-3475 will be 2 mg/kg
- If tolerated, subsequent cohorts escalated to 5 mg/kg and 10 mg/kg

Len treatment (Figures 2 and 3):

- Administered orally once daily on Days 1-21 of repeated 28-day cycles
- Initial dose of 25 mg
- If ≤25 mg dose of Len is not tolerated due to toxicity, the dose may be decreased to 15 mg, 10 mg or 5 mg
- Dex (low dose) treatment (Figures 2 and 3):
  - Administered orally once weekly on Days 1, 8, 15, and 22 of each 28-day cycle
  - Initial dose of 40 mg (20 mg in subjects aged ≥75 years)

Figure 2. Trial Flow Phase I Trial of MK-3475 in combination with lenalidomide (Len) and dexamethasone (Dex)

Method

Table 1. Dose confirmation rules

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Number of patients treated at current dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>13</td>
</tr>
</tbody>
</table>

Dose confirmation (Table 1)

- Confirmation of the preliminary MTD identified in the dose escalation with additional patients will continue until ≥4 of 13 subjects (combined from dose escalation and dose confirmation) experience a DLT
- As subjects become evaluable for DLT assessment, the number of subjects who are evaluable for DLT versus the number of subjects who developed a DLT will be continuously assessed and de-escalation and re-escalation to eligible doses will occur as necessary
- If enrollment expands to 13 subjects for a dose level ≤54 of the 13 subjects develop a DLT, then the dose confirmation will stop

Planned Statistical Analysis

- After dose confirmation, the dose-response relationship (percentage of subjects experiencing at least one DLT in Cycle 1) for each dose level selected for dose confirmation will be estimated by a Bayesian pooling of adjacent violators analysis using all DLT data from the trial
- The dose-response relationship, along with other tolerability data, will be used to determine the recommended Phase 2 dose for the combination regimen
- Efficacy endpoints will be summarized for each dose level using descriptive statistics
- Primary efficacy analysis population:
  - Receive at least one dose of study treatment
  - Have a baseline and post-baseline data as needed
- Summary statistics will be provided for key efficacy endpoints:
  - Objective Response Rate
  - Complete Response Rate and stringent complete response rate
  - Duration of response
  - Progression-free survival
  - Time to progression
  - Overall survival
  - Change from baseline PD-L1 expression

Sample Size

- The sample size of the study depends primarily on clinical considerations
- A maximum of 32 subjects available for safety and tolerability will be enrolled in dose escalation and dose confirmation
- If Len toxicity is observed, then 6-12 additional subjects may be enrolled to further evaluate the triplet with a lower dose of Len

Safety Analyses

- The safety analysis population will include all patients who received at least 1 dose of study therapy
- Safety monitoring will occur continuously in the study
- Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, laboratory tests, vital signs, and ECG measurements
- Dose limiting toxicities will be listed
- At the end of the trial, a dose-response curve for the rate of subjects experiencing a DLT in Cycle 1 will be estimated using the pooling-of-adjacent-violators algorithm
- The dose-response curve will be used to determine the MTD
- The MTD is defined as the dose at which the percentage of subjects experiencing a DLT is the closest to 25%
- The 80% Bayes credible intervals (characterizing the uncertainty in the estimates of the rates of interest) for the DLT rate in Cycle 1 for the identified MTD level will be provided
- Summary statistics (median and range) for time to onset of first drug-related toxicity in each dose level will be provided
- AEs will be summarized as counts, frequencies and grade by NC1 CTCAE version 4.0 for each dose level of each combination regimen
- Laboratory values will be graded by NC1 CTCAE version 4.0
- The percentage of subjects with laboratory abnormalities by grades will be tabulated
- Summary statistics for baseline, on-treatment, and change from baseline values of continuous measures such as changes from baseline in ECOG, laboratory, vital signs, and ECOG parameters will be provided by dose-level in table format

No formal interim analyses are planned for this trial.

This study (Clinicaltrials.gov: NCT02036502) is being conducted in concert with Good Clinical Practices.

Table 1. Dose confirmation rules

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Number of patient treated at current dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>E</td>
</tr>
<tr>
<td>5</td>
<td>E</td>
</tr>
<tr>
<td>6</td>
<td>E</td>
</tr>
<tr>
<td>7</td>
<td>E</td>
</tr>
<tr>
<td>8</td>
<td>E</td>
</tr>
<tr>
<td>9</td>
<td>E</td>
</tr>
<tr>
<td>10</td>
<td>E</td>
</tr>
<tr>
<td>11</td>
<td>E</td>
</tr>
<tr>
<td>12</td>
<td>E</td>
</tr>
</tbody>
</table>

Dose escalation

- DLT:
  - Grade 4 hematologic toxicity lasting ≥7 days
  - Grade 4 non-hematologic toxicity (not laboratory)
  - Grade 3 non-hematologic toxicity (not laboratory), except inadequately treated nausea, hypersensitivity reactions, or fatigue lasting ≥3 days
  - Any Grade 3 non-hematologic laboratory value if:
    - Renal or liver function abnormality
    - Medical intervention is required to treat the subject, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for ≥1 week
  - Febrile neutropenia Grade 3 or 4
  - Thrombocytopenia <20,000/μl if associated with bleeding and requires platelet transfusion
  - Grade 5 toxicity (i.e., death)
  - A delay of ≥1 week due to drug-related toxicity in initiating Cycle 2
  - Unable to complete at least 80% of any of the three treatments during the first course of therapy due to treatment-related toxicity (even if not meeting other DLT criteria)

References


Copyright © 2014 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. All Rights Reserved.