Dose Optimization of Duvelisib in Patients with Relapsed or Refractory T-Cell Lymphoma from the Phase 2 PRIMO Trial: Selection of Regimen for the Dose-Expansion Phase

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Background

Duvelisib is a dual PI3Kδ/1α inhibitor that was FDA approved at 150 mg orally twice daily (BID) for the treatment of: - Relapsed/refractory (RR) chronic lymphocytic leukemia or small lymphocytic lymphoma after 2 lines of prior therapy; - RR follicular lymphoma after 2 prior systemic therapies; - RR indolent lymphoma (RILT) against T-cell lymphoma cell line in vitro; - In 3 phase 1 studies (Figure 1), DUVA 25 or 75 mg BID demonstrated encouraging clinical activity in patients with RR/PTCL, a cutaneous T-cell lymphoma (CTCL), with responses observed across a spectrum of subtypes.1-3

Figure 1. Phase 1 Trials in PTCL

RESULTS

Baseline characteristics

A total of 300 patients (shared cohort: 1: DUVA, n = 30; cohort 2: DUVA, n = 15) were treated in the dose-optimization phase, and characteristics were well balanced between the groups (Table 1).

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort 1 (DUVA)</th>
<th>Cohort 2 (DUVA)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>63</td>
<td>61</td>
<td>0.63</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>46/54</td>
<td>50/50</td>
<td>0.63</td>
</tr>
<tr>
<td>Performance status</td>
<td>0.0</td>
<td>0.0</td>
<td>0.31</td>
</tr>
<tr>
<td>Number of prior therapies</td>
<td>3 (2-5)</td>
<td>4 (3-6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of prior regimens</td>
<td>18</td>
<td>21</td>
<td>0.10</td>
</tr>
<tr>
<td>IPI score</td>
<td>1 (0-3)</td>
<td>1 (0-3)</td>
<td>0.63</td>
</tr>
<tr>
<td>Number of prior regimens with documented response</td>
<td>10 (33%)</td>
<td>12 (40%)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Methods

Blood samples for pharmacokinetic assessment were collected on cycle 1, day 1 and day 7, day 10 at predose (within 0.5 hours prior to the morning dose) and 0.5, 1.2.5, 3, 4, and 8 hours postdose on cycle 1, day 1.

At each scheduled disease response assessment, a PET-CT (or CT based response was determined based on the Logan response criteria for patients without PET scans.6)

Treatment-emergent adverse events (AEs) were defined as AEs that emerged or worsened from the baseline of the first dose of study treatment to 30 days after the last dose of study treatment. The severity of AEs was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (v3.0).

The patients evaluated for efficacy in the dose-optimization cohort include patients who received ≥1 dose of study drug (n=254) and completed 1 cycle of treatment (n=150) and had ≥1 scan to assess disease response after completion of 1 cycle of treatment. The modified intent-to-treat (mITT) set included patients who received ≥1 dose of study drug.

Study design

The phase 2 PRIMO trial (NCT 02154223; NCT02733257) was designed to determine an optimal regimen of DUVA monotherapy in RILT and PTCL subtypes.4 The primary endpoint for the dose-optimization phase of the trial was a investigator-assessed ORR and for the dose-expansion phase, ORR by blinded independent review committee (BIRC).

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Figure 2. PRIMO Trial Design

Pharmacokinetics and Pharmacodynamics

Pharmacokinetic analysis demonstrated a dose-related increase in exposure, with a trended increase in the steady-state exposure of DUVA in DUVA (Figure 4). No pharmacokinetic analysis showed any correlation between drug exposure and efficacy.

In general, the number of AEs tended to higher incidences at higher exposures.

No AEs were observed in pharmacodynamic markers (sATZ in peripheral blood monocytosis and B cell ratio between DUVA and DUVA).

Low CD4 counts (≤ 500 cells/mm3) Common Terminology Criteria for Adverse Events grade 3 were associated with early discontinuation of DUVA (Figure 3B).

Figure 3. Pharmacokinetics and Pharmacodynamics

Figure 4. Response Rate: (A) DUVA by Investigator, (B) DUVA by Blinded IRC, (C) DUVA by Investigator, and (D) DUVA by Blinded IRC

CONCLUSIONS

DUVA is an oral monotherapy and chemotherapy-free regimen that is clinically active in RILT-P TCL.

An ORR of 62% (DUVA, per IRC) and 40% (DUVA, per investigator) were observed in the mITT population.

Complete responses (per investigator) were seen with DUVA and DUVA.

Early responses most frequently had occurred by first assessment at the end of cycle 1.

The DUVA safety profile was consistent with previously reported,10 with no unexpected toxicities.

DUVA demonstrated > 2-fold higher steady-state exposure than DUVA.

Higher initial exposure may be important to sustain early progression for an aggressive disease such as PTCL.

The PRIMO expansion phase (Figure 6) will investigate DUVA starting at 75 mg BID for 2 cycles to achieve higher exposure to increase the opportunity for a rapid tumor response.

Followed by 25 mg BID to maintain long-term disease control and mitigate the potential for tumor lysis.

Targeted enrollment at 100 patients

Table 2. Treatment-Emergent Adverse Events (≥ 4 patients)

Table 3. Treatment-Related Grade 3 or 4 Adverse Events (≥ 4 patients)

Safety

The most common (≥ 4 patients) TEAs are patients in either cohort are as in Table 3.

Table 3. Treatment-Related Grade 3 or 4 Adverse Events (≥ 4 patients)

REFERENCES

ACKNOWLEDGMENTS

HEAR THE STUDY

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