**UMBRALISIB IMPROVES TOLERABILITY AND ASSOCIATED COST BURDEN OF ADVERSE EVENTS OVER PI3K INHIBITORS IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA PATIENTS; RESULTS FROM MATCHING-ADJUSTED INDIRECT COMPARISON**

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**BACKGROUND**

- Targeted therapies, such as phosphoinositide 3-kinase inhibitors (PI3Kis), provide chemotherapy free options for relapsed / refractory (R/R) follicular lymphoma (FL) patients.
- PI3Kis provide viable treatment options for R/R FL patients, but are associated with some significant toxicities1,2, creating an unmet need for improved tolerability. In addition to the burden on patients, payers are keen to be concerned about the high cost of management associated with adverse events (AEs) for their R/R FL patients.
- Ummbralisib (KRONITEC®) is an oral, once-daily, first and only multisite inhibitor of PI3K-delta (δ) and caspase 1 (CXS3)–eplorin (v) that is pharmacologically distinct from currently approved PI3Kis with high selectivity for the delta isoform of PI3K.
- Given the single-arm nature of umbralisib’s clinical trial (UNITY-NHL), the comparative effectiveness and safety of umbralisib vs. PI3Kis is not yet established.

**OBJECTIVE**

- To compare the efficacy and safety of umbralisib with PI3Kis in R/R FL through a matching-adjusted indirect comparison (MAC) and quantify the cost burden associated with AEs leading to discontinuation of treatment.

**METHODS OVERVIEW**

- MAC is a validated indirect comparison technique that uses individual patient data (IPD) from one trial and aggregate data from another to enable comparison of treatment outcomes after matching baseline characteristics.
- An MAC was conducted using IPD from the UNITY-NHL trial (NCT02793583) vs. published comparator data identified via a systematic literature review.
- After matching, differences in discontinuation rate due to AEs and median duration of response (DoR) were compared using statistical tests.
- DoR discontinuation cost burden was calculated using (i) AE rates at ED and cost of AE treatment from public databases.

**MATCHING CHARACTERISTICS**

- Patients in UNITY-NHL were matched and reweighted based on ≥1 of the following characteristics: age, sex, prior lines of therapy, ECOG status, cancer stage, FL grade, NHL trial, and ESS (UHDRS).
- To determine the economic impact of AEs, the incidence of AEs in Table 4 was multiplied by the unit cost per AE.

**RESULTS**

**Table 1. Baseline Matching Characteristics vs. Copanlisib**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline Matching Characteristics</th>
<th>Idelalisib (N=72)</th>
<th>Copanlisib (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td>Male (%)</td>
<td>Female (%)</td>
</tr>
<tr>
<td>Male</td>
<td>47%</td>
<td>53%</td>
<td>51%</td>
</tr>
<tr>
<td>Female</td>
<td>53%</td>
<td>47%</td>
<td>49%</td>
</tr>
</tbody>
</table>

**Table 2. Baseline Matching Characteristics vs. Duvelisib**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline Matching Characteristics</th>
<th>Duvelisib (N=72)</th>
<th>Duvelisib (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td>Male (%)</td>
<td>Female (%)</td>
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<tr>
<td>Male</td>
<td>47%</td>
<td>53%</td>
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<tr>
<td>Female</td>
<td>53%</td>
<td>47%</td>
<td>50%</td>
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</tbody>
</table>

**Table 3. Baseline Matching Characteristics vs. Icelalisib**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline Matching Characteristics</th>
<th>Icelalisib (N=72)</th>
<th>Icelalisib (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td>Male (%)</td>
<td>Female (%)</td>
</tr>
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<td>Male</td>
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<td>50%</td>
</tr>
<tr>
<td>Female</td>
<td>53%</td>
<td>47%</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Table 4. Baseline Event (grade ≥3) Rates and Management Cost**

<table>
<thead>
<tr>
<th>Event</th>
<th>Baseline Characteristics</th>
<th>Copanlisib (N=72)</th>
<th>Duvelisib (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea/Colitis</strong></td>
<td>27.88%</td>
<td>24.80%</td>
<td>8.00%</td>
</tr>
<tr>
<td><strong>Tumor Lysis</strong></td>
<td>9.73%</td>
<td>6.00%</td>
<td>6.00%</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>4.00%</td>
<td>4.00%</td>
<td>4.00%</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>3.00%</td>
<td>3.00%</td>
<td>3.00%</td>
</tr>
</tbody>
</table>

**DISCUSSION**

- In the absence of head-to-head trials, MAC can be a useful tool to assess comparative effectiveness of therapies.
- Patient populations across trials for umbralisib vs. PI3Kis were sufficiently matched based on key clinician characteristics making the results available across trials.
- Across comparisons against all PI3Kis, umbralisib resulted in the lowest rates of discontinuations due to AEs after adjusting for baseline patient characteristics.

**LIMITATIONS**

- Not all patient characteristics are reported across trials, and thus matching on the same characteristics was not possible across all products.
- Not all prognostic factors could be adjusted for within these analyses due to data availability and impact on ESS; notably, characteristic selection was guided by clinician recommendation.
- Not all AEs were included as part of the economic management analysis; however, all AEs consistently reported were included.

**REFERENCES**

5. Szafran PS et al., ASH 2020.

**Figures 1-5**

- **Figure 1.** Discontinuation rate due to adverse events post-matching, umbralisib vs. copanlisib.
- **Figure 2.** Duration of response post-matching, umbralisib vs. copanlisib.
- **Figure 3.** Discontinuation rate due to adverse events post-matching, umbralisib vs. duvelisib.
- **Figure 4.** Discontinuation rate due to adverse events vs. matching characteristics.
- **Figure 5.** Duration of response vs. matching characteristics.

**ECONOMIC IMPACT OF AE MANAGEMENT**

- The annual per patient cost of managing AEs was determined to be lowest for umbralisib ($2,123) compared to copanlisib ($4,880).

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**CONCLUSIONS**

- In an indirect treatment comparison accounting for differences in cross-trial characteristics, umbralisib demonstrated significantly lower AE discontinuations (~3 times lower), favorable DoR, and a lower AE management cost burden (~2 times lower) than currently approved PI3Kis for R/R FL patients.