Breaking from the paradigm of antibody-drug conjugates: Evaluation of clinical pharmacokinetics and safety of Bicycle Toxin Conjugates® (BTCs)

Abstract

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BACKGROUND

- Bicycle Toxin Conjugates® (BTCs) are chemically synthesized molecules comprising a small bicyclic peptide linked to a toxic payload (MMAE, SMANCS, or MZP).
- Zelzette® (BT8009) and BT5528 are BTCs linked to monomethyl auristatin E (MMAE), respectively, and have shown promising antitumor activity.1

METHODS

- Across trials, patients with advanced solid tumors receiving intravenous zel (BT8009) or BT5528 were monitored for safety.
- PK analysis was performed on conjugated and unconjugated MMAE, with MMAE quantified using liquid chromatography-mass spectrometry.

RESULTS

- Pharmacokinetics:
  - Both BTCs demonstrate rapid conjugate elimination in plasma, with conjugated MMAE AUC values below 1% of unconjugated MMAE AUC.
  - BTCs exhibit improved therapeutic index compared to ADCs.

- Safety:
  - No BTC-related Grade ≥3 adverse events were reported.
  - BT5528 was generally well-tolerated, with only Grade 1/2 adverse events observed.
  - Zel (BT8009)-related adverse events were primarily Grade 1/2 and included nausea, vomiting, pyrexia, and myalgia.

TABLE 1. COMPARISON OF MEAN EXPOSURES FOR ZEL (BT8009), BT5528, AND EV

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Zel (BT8009)</th>
<th>BT5528</th>
<th>EV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>16.1</td>
<td>16.8</td>
<td>5.5</td>
</tr>
<tr>
<td>AUC (ng*day/mL)</td>
<td>36.5</td>
<td>37.9</td>
<td>704</td>
</tr>
<tr>
<td>T1/2 (d)</td>
<td>1.0</td>
<td>1.0</td>
<td>2</td>
</tr>
<tr>
<td>Clearance (L/hr)</td>
<td>107</td>
<td>128</td>
<td>503</td>
</tr>
<tr>
<td>Unconjugated MMAE Cmax (ng/mL)</td>
<td>107</td>
<td>128</td>
<td>503</td>
</tr>
</tbody>
</table>

TABLE 2. SAFETY SUMMARY FOR ZEL (BT8009) AND BT5528

<table>
<thead>
<tr>
<th>Event</th>
<th>Zel (BT8009)</th>
<th>BT5528</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAEs Grade ≤2</td>
<td>137 (94)</td>
<td>41 (56)</td>
</tr>
<tr>
<td>TRAEs Grade &gt;2</td>
<td>12 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TRAEs severe</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

CONCLUSION

- BTCs offer a novel approach with a substantial difference between BTC and ADC PK profiles, with BTCs exhibiting rapid metabolism plus reduced systemic payload exposure compared to ADCs.
- BTCs also exhibit reduced biological activity in vivo compared to ADCs.

ACKNOWLEDGEMENTS

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REFERENCES

- Urol Oncol. 2023;41(6_Suppl):A498.

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FIGURE 1. ILLUSTRATION OF MMAE CONJUGATE FOR BTCs

FIGURE 2. CONCENTRATION-TIME PROFILES OF A) ZEL (BT8009) CONJUGATE (TOP) AND UNCONJUGATED MMAE (BOTTOM) AND B) EV CONJUGATE (LEFT) AND UNCONJUGATED MMAE (RIGHT)

FIGURE 3. ZEL (BT8009) AND BT5528 CONCENTRATION-TIME PROFILES OF CONJUGATE (TOP) AND UNCONJUGATED MMAE (BOTTOM)