Ibalizumab-uiyk

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Dr. Wood does not have any disclosures.
• **Indication**
  – In combination with other antiretroviral medications for heavily treatment-experienced adults with multidrug-resistant HIV-1 failing their current antiretroviral regimen

• **Dosing (Intravenous)**
  – Loading dose: 2,000 mg IV
  – Maintenance dose: 800 mg IV every 2 weeks

• **Contraindications and Drug-Drug Interactions**
  – No major contraindications or interactions

• **Use During Pregnancy**
  – Insufficient data

• **Common Adverse Events (≥5%)**
  – Diarrhea, dizziness, nausea, rash

Source: Ibalizumab Prescribing Information
Ibalizumab-uiyk: Mechanism of Action
HIV Cell Entry
Binding to Host Cell CD4 Receptor

Illustration: David H. Spach, MD
HIV Cell Entry
Binding to Host Cell CD4 Receptor

Illustration: David H. Spach, MD
HIV Cell Entry
Binding to Host CCR5 Co-Receptor

Illustration: David H. Spach, MD
Humanized Monoclonal Antibody
Host Cell CD4 Receptor

CD4 Receptor

- Extracellular region (370 amino acids)
  - D1-D4 Domains
- Transmembrane region (25 amino acids)
- Cytoplasmic tail (38 amino acids)

Illustration: David H. Spach, MD
Host Cell CD4 Receptor and Ibalizumab Binding
Ibalizumab: CD4 Directed Post-Attachment HIV Inhibitor

Illustration: David H. Spach, MD
Ibalizumab for Individuals with Multidrug-Resistant HIV

TMB-301 Study
Ibalizumab (IBA) for Individuals with Multidrug-Resistant HIV
TMB-301: Study Design

- **Study design**
  - Single-arm, open label study of ibalizumab (IBA) added to optimized background regimen (OBR) for individuals with virologic failure on ART
  - Primary endpoint: proportion achieving $\geq 0.5 \log_{10}$ decrease in HIV RNA 7 days after initiating IBA therapy (day 14 of study)
  - Secondary endpoints: virologic outcomes, safety, & tolerability at week 25 (after 24 weeks of IBA)

- **Inclusion Criteria**
  - Adults with HIV-1, taking ART for $\geq 6$ months, HIV RNA $>1,000$ copies/mL, and $\geq 3$ class drug resistance (but $\geq 1$ remaining active drug)

Ibalizumab (IBA) for Individuals with Multidrug-Resistant HIV
TMB-301: Study Design

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ibalizumab (n = 40)</th>
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<tbody>
<tr>
<td>Median age (range)—years</td>
<td>53 (23-65)</td>
</tr>
<tr>
<td>Male</td>
<td>34 (85%)</td>
</tr>
<tr>
<td>Non-White</td>
<td>18 (45%)</td>
</tr>
<tr>
<td>Mean duration since HIV diagnosis—years</td>
<td>20 ± 8</td>
</tr>
<tr>
<td>Mean CD4 count—cells/mm³</td>
<td>150 ± 182</td>
</tr>
<tr>
<td>Mean HIV RNA—copies/mL</td>
<td>4.5 log (31,623)</td>
</tr>
<tr>
<td>Participants with HIV RNA &gt;100,000 copies/mL</td>
<td>7 (18%)</td>
</tr>
</tbody>
</table>

Baseline Characteristics of the 40 Participants in TMB-301

Ibalizumab (IBA) for Individuals with Multidrug-Resistant HIV
TMB-301: Efficacy at Day 14

IBA monotherapy = after 7 days of IBA added to failing ART (functional monotherapy)
Control period = after 7 days of baseline failing ART prior to adding ibalizumab

Ibalizumab (IBA) for Individuals with Multidrug-Resistant HIV

TMB-301: Efficacy at Week 25

IBA added at day 7. Optimized background regimen (OBR) added at day 14. Above results are after 24 weeks of IBA.

Ibalizumab (IBA) for Individuals with Multidrug-Resistant HIV TMB-301: Efficacy at Week 25, by Baseline CD4 Cell Count

Week 25 Virologic Response (Intention-to-Treat Analysis)

Ibalizumab (IBA) for Individuals with Multidrug-Resistant HIV
TMB-301: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events (AEs)</th>
<th>Participants (n = 40)</th>
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<tbody>
<tr>
<td>Any AE, n (%)</td>
<td>32 (80)</td>
</tr>
<tr>
<td>Related to IBA</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Leading to stoppage of IBA</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Reported by ≥10% of participants</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (20)</td>
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<tr>
<td>Dizziness</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4 (10)</td>
</tr>
</tbody>
</table>

Ibalizumab (IBA)  
Resistance Testing & Cross Resistance

- IBA can be used regardless of HIV-1 tropism
- Standard genotype testing will not give IBA resistance information
- Decreased susceptibility to IBA has been observed in subjects experiencing virologic failure, and may be associated with genetic changes in the V5 loop of gp120, though the clinical significance is unclear and activity of other antiretrovirals is not affected
- IBA does not have known *in vitro* cross resistance with other antiretrovirals, including other entry inhibitors
- No CD4 polymorphisms affect IBA activity and use of IBA does not impact CD4 function

Source: *Trogarzo* Prescribing Information
Ibalizumab (IBA)
Summary

• Intravenous entry inhibitor that binds to host CD4 receptor

• Used as part of salvage antiretroviral therapy for individuals with multidrug-resistant HIV-1, typically with virologic failure on oral antiretrovirals and few antiretroviral options

• Typically combined with at least one other active antiretroviral agent and optimized background regimen

• Generally well-tolerated with no drug-drug interactions

• Resistance may develop but is rare and testing is not yet available
Acknowledgment

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