AO-176, a Highly Differentiated Clinical Stage Anti-CD47 Antibody, Exerts Potent Anti-Tumor Activity in Preclinical Models of Multiple Myeloma As a Single Agent and in Combination with Approved Therapeutics

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Disclosures

• All authors are employees of Arch Oncology, Inc.
AO-176: Clearly Differentiated in the CD47 Landscape

Humanized IgG2 anti-CD47 Antibody with Multiple Mechanisms of Action

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<th>CONVENTIONAL ANTI-CD47 APPROACH</th>
<th>POTENTIAL ADVANTAGES</th>
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<tr>
<td><strong>1</strong> Blockade of CD47/SIRPα Interaction</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>2</strong> Preferential Binding to Tumor Cells vs. Normal Cells (via selective binding of CD47 co-localizing with integrin β1)</td>
<td>X</td>
<td>✓</td>
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<tr>
<td><strong>3</strong> Better Binding in Tumor Environment (Low pH)</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td><strong>4</strong> Direct Killing &amp; DAMP Induction</td>
<td>X</td>
<td>✓</td>
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Differentiated Best-in-Class Antibody | Blocking and Direct Killing | Unique Among the Anti-CD47 Field

Multiple Myeloma (MM) - A Target Indication for AO-176

AO-176 induces phagocytosis of MM cells in vitro

Human MM samples show increased CD47 expression and infiltration by phagocytes

<table>
<thead>
<tr>
<th>CD138</th>
<th>CD47</th>
<th>CD68</th>
<th>CD11c</th>
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<tr>
<td>Normal</td>
<td></td>
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<td>MM-1</td>
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<td>MM-2</td>
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AO-176 induces phagocytosis of MM cell lines

Left) Representative images from a tissue array containing MM patient samples and normal bone marrow samples, immunohistochemically stained for CD138, CD47, CD68, and CD11c. MM samples also consistently show high levels of integrin β1. All images at 16.8X magnification. Right) In vitro phagocytosis curves of human MM cell lines NCI-H929 and MM.1S treated with AO-176. The % phagocytosis of the highest concentration of IgG2 isotype control is denoted by the dotted line.
AO-176 Treatment in MM: Potent, Durable Anti-Tumor Activity

Durable Complete Responses (CRs) persist after AO-176 dosing discontinued

AO-176 increases macrophages and DCs in treated MM xenograft tumors

**Left)** Female NOD-SCID mice were subcutaneously transplanted with NCI-H929 MM cells, randomized when tumors reached approximately 100mm³ (n = 8/group), and treatment initiated. AO-176 or human IgG2 isotype control antibody was dosed at 25 mg/kg intraperitoneally every 7 days for 13 cycles. Tumors were measured weekly. Complete responses were observed in all mice in the AO-176 arm by day 60 and durability of the CRs was observed off drug for a further 120 days. **Right)** Tumors (n = 3) from mice 96 hours post-treatment with AO-176 or IgG2 isotype control antibody were harvested and analyzed by immunohistochemical staining against mouse CD68 and CD11c.
AO-176 Treatment in MM: Tumor Regression at Multiple Dose Levels
Monotherapy complete responses seen at doses as low as 3 mg/kg

Female NOD-SCID mice were subcutaneously transplanted with NCI-H929 MM cells, randomized when tumors reached approximately 100 mm³ (n = 6/group), and treatment initiated. AO-176 was dosed at 1, 3, 10, or 25 mg/kg, intraperitoneally every 7 days for 13 weeks. Human IgG2 isotype control was dosed at 25 mg/kg on the same schedule until previously established human endpoint was reached. **Left** Survival of each treatment arm. **Right** Spider plots of each AO-176 dosing group.

AO-176 increased survival at doses as low as 10 mg/kg

AO-176 led to CRs at 3 mg/kg, and inhibited tumor growth down to 1 mg/kg
AO-176 is Effective in MM Models Bearing Large Tumors

Regression observed for tumors as large as 1600 mm³

Female NOD-SCID mice were subcutaneously transplanted with NCI-H929 MM cells, randomized when tumors reached approximately 200-1600 mm³ (n = 6/group), and treatment initiated. AO-176 or human IgG2 isotype control antibody was dosed at 25 mg/kg intraperitoneally every 7 days for 7 cycles. Left) Graph of average tumor volumes from IgG2 and AO-176 treated groups. Right) Graph of individual mouse tumor volume measurements from AO-176 treatment group. Tumors were measured weekly by digital caliper.
AO-176 in Combination with Bortezomib Results in Durable CRs

Potent anti-tumor efficacy and 100% survival in MM Model

Left) Female NSG mice were subcutaneously injected with $1 \times 10^7$ RPMI-8226 cells/mouse, randomized at tumor volumes ~50-100 mm$^3$, and treatment initiated (10 mice/group). AO-176 was dosed IP at either 10 mg/kg or 25 mg/kg every 7 days, with and without co-treatment of bortezomib (1 mg/kg, dosed IV at days 1, 3, and 11). Control tumors were treated with human IgG2 isotype control antibody at 25 mg/kg. Right) Survival curves of the RPMI-8226 transplanted NSG mice. Complete CRs were observed in 9/10 mice in the 10 mg/kg AO-176 plus bortezomib group and 10/10 mice in the 25 mg/kg AO-176 plus bortezomib group.
MM.1S xenografts

MM.1S cells were subcutaneously injected (5x10⁶ per mouse) into female NOD-SCID mice (n = 9-10/group). AO-176 or human IgG2 isotype control were dosed intraperitoneally at 25 mg/kg every 7 days. Lenalidomide (25 mg/kg, left graph) or pomalidomide (10 mg/kg, right graph) were orally administered on 4 successive days, then given a 3 day break, for 5 cycles. Combination regimens were dosed on same schedule as single agents. Tumor volumes were assessed by weekly digital caliper measurement. *p<0.05

AO-176 Combines with IMiDs to Profoundly Inhibit MM Growth

Increased anti-tumor efficacy & CRs with lenalidomide or pomalidomide
Conclusions

1. CD47 is highly expressed on myeloma cells along with integrin β1, and MM patient samples show infiltration by phagocytes such as macrophages and dendritic cells.

2. AO-176 treatment results in durable complete responses in multiple MM xenograft models, including those bearing large tumors.

3. AO-176 inhibits tumor growth and achieves CRs at doses as low as 3 mg/kg in preclinical models.

4. AO-176 combines with multiple classes of MM standard of care therapies to increase efficacy in preclinical models.

AO-176 is currently being evaluated in two phase 1/2 studies for the treatment of solid tumors (NCT03834948) and multiple myeloma (NCT044445701).