PAPER 21

TITLE: INTRA-ARTICULAR INJECTIONS OF AMB-05X, A POTENT, SELECTIVE, HUMAN MONOCLONAL ANTIBODY AGAINST COLONY STIMULATING FACTOR 1 RECEPTOR FOR THE TREATMENT OF TENOSYNOVIAL GIANT CELL TUMOR

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Background: Tenosynovial giant cell tumor (TGCT) is a rare, debilitating, but typically non-malignant neoplasm arising in the synovium of joints, bursae, and tendon sheaths. TGCT is caused by overexpression of colony-stimulating factor 1 (CSF1) leading to recruitment of CSF1 receptor (CSF1R)–expressing cells, including monocytes and macrophages, which compose the bulk of the tumor. Clinical features include significant pain with recurrent hemarthrosis, reduced range of motion, impaired quality of life, and ultimately, joint destruction. Surgical resection is the standard of care but can be associated with complications, a lengthy recovery, and high rate of recurrence, especially for the diffuse subtype (dTGCT; up to 55%). Pharmacologic therapies based CSF1R inhibition have been shown to be effective but can be associated with systemic adverse effects, including AST and ALT increases (fatal liver toxicity has been reported with pexidartinib). Given the non-life-threatening nature of TGCT, a locally administered therapeutic that enhances delivery of drug to the tumor while minimizing systemic exposure could represent a favorable pharmacologic option. We conducted a proof-of-concept study evaluating AMB-05X, a potent, selective, human mAb against CSF1R administered as an intra-articular (IA) injection to subjects with TGCT.

Methods: This was an open-label clinical study evaluating IA injections of AMB-05X Q2 weeks x 12 weeks in subjects with TGCT of the knee. Subjects were ≥18 years of age with histologically confirmed, measurable TGCT of the knee per RECIST v1.1 on MRI according to a central radiologist and tumor review committee. Subjects were excluded if they previously used pexidartinib, anti-CSF1R biologics, or oral tyrosine kinase inhibitors. Endpoints included safety and tolerability of AMB-05X and efficacy based on central radiology review of objective response (OR) per RECIST v1.1, modified RECIST, and the TGCT-specific tumor volume score (TVS), and change from baseline in pain, stiffness, range-of-motion of the affected joint, and quality-of-life (QoL).

Results: 8 subjects were enrolled and treated with IA AMB-05X at 150 mg per injection Q2 weeks. Subject characteristics were as follows: 63% female (5/8); mean (SD) age 36.6 (±19.3) years; mean (SD) body mass index 27.7 (6.2) kg/m^2. At Week 12 (end of treatment), 38% of subjects (3/8) achieved OR (all PRs) per RECIST v1.1, modified RECIST, and TVS. Onset of response was rapid with all responders (3/3) achieving OR per RECIST v1.1 by Week 6, and 2/3 achieving OR per modified RECIST and TVS by Week 6. Notable improvements across multiple clinical outcome measures were observed, including improvements in pain, stiffness, range-of-motion, and QoL (Table 1).

IA injections of AMB-05X were well-tolerated. No subjects experienced serious adverse events (SAEs). AEs were generally low-grade in severity, with most common events related to pharmacologic activity or underlying disease, including peri-orbital/facial edema, arthralgia, pruritis, and rash. Minimal-to-mild AST or ALT changes were observed with no events above Grade 1 (mild).

Table 1. Summary of Clinical Endpoint Results at Week 12

Clinical Endpoint	Baseline (Mean [SD])	Week 12 (Mean [SD])
Pain (0-10)		
Overall Severity	3.6 (2.3)	1.2 (1.4)
Overall Pain Interference	3.8 (2.6)	1.0 (1.3)
Worst Pain (last 24 hours)	5.1 (3.1)	2.3 (2.7)

Average Pain (last 24 hours)	3.8 (1.8)	1.5 (1.9)
Stiffness (0-10)	5.0 (3.3)	2.0 (2.1)
Range-of-Motion (degrees)		
Flexion	108° (54.0°)	128° (15.3°)
Extension	7.5° (32.2°)	1.7° (4.1°)
Quality-of-Life (QoL)		
PROMIS Physical Function (10-50)	36.3 (4.3)	43.0 (4.9)
EQ-5D-5L (5-25)	10.9 (2.8)	7.6 (2.6)
Visual Analogue Scale (VAS; 0-100)	73.3 (18.3)	71.4 (13.5)

Higher scores indicate improvements on the PROMIS and VAS. Lower scores indicate improvements on Pain (including all sub-scores), Stiffness, and the EQ-5D-5L. Pain and Stiffness are scored on a scale from 0-10; PROMIS ranges from 10-50; EQ-5D-5L ranges from 5-25; VAS ranges from 0-100.

Conclusions: AMB-05X is the first locally administered therapeutic evaluated in subjects with TGCT. IA administrations of AMB-05X were well tolerated and resulted in robust tumor responses and symptomatic and functional improvements after 12 weeks. These data support further development of AMB-05X into late-phase clinical trials to establish the overall clinical benefit of AMB-05X in patients with TGCT.

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