# Altamira Therapeutics Announces Significant Enhancement of Immune Checkpoint Inhibition Therapy in Combination with Zbtb46 mRNA Delivered with SemaPhore Nanoparticles in Animal Tumor Models

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- Treatment with *Zbtb46* mRNA nanoparticles based on Altamira's SemaPhore™ delivery technology results in significant reduction in tumor growth ($p<0.0001$)
- Combination of nanoparticles with immune checkpoint inhibitor (anti-PD1) shows even more pronounced improvement, synergistic control of tumor growth with long-term complete remission of tumor in many cases
- Combination therapy may help to render more solid tumor patients responsive to anti-PD1 therapies (immune checkpoint inhibitors)
- Results published in Nature Immunology, one of the world's top immunology journals

Altamira Therapeutics Ltd. ("Altamira" or the "Company") (Nasdaq:CYTO), a company dedicated to developing and commercializing RNA delivery technology for targets beyond the liver, today announced the publication of a peer-reviewed article in *Nature Immunology* highlighting the important role of the *Zbtb46* gene in the control of tumor growth and demonstrating a significant reduction in tumor growth *in vivo* through treatment with *Zbtb46* mRNA delivered with Altamira's SemaPhore™ nanoparticle technology.[1] The treatment effect was potentiated when combined with anti-PD1 immune checkpoint inhibition, inducing long-term remission and promoting immunological memory. The research was conducted by a group around Professor Kyunghee Choi of the Pathology & Immunology Department of Washington University School of Medicine (St. Louis, MO).

"Immune checkpoint inhibitors such as Keytruda[2] or Opdivo[3] have shown remarkable efficacy in treating a broad range of solid tumors, but unfortunately a large number of patients are unable to benefit from them due to an immunosuppressive tumor microenvironment", observed Samuel Wickline, M.D., Altamira's Chief Scientific Adviser and a co-author of the publication. "The study from the Choi Lab shows impressive results from boosting *Zbtb46* expression with tumor vessel normalization and enhanced antitumor immunity. Administration of *Zbtb46* mRNA nanoparticles appears to provide the right conditions for anti-PD1 treatments to work in a substantially larger cancer population, helping to control tumor growth, induce long-term remission and promote immunological memory. The exciting results with *Zbtb46* mRNA nanoparticles are just another great example highlighting the potential of the SemaPhore platform for delivering mRNA therapeutics to non-hepatic tissues."

The research group studied the role of the *Zbtb46* (Zinc finger and BTB domain-containing protein 46) gene in the progression of solid tumors and in tumor angiogenesis and anti-tumor immunity. Cancers require the formation of new blood vessels (tumor angiogenesis) to grow and metastasize, supplying their cells with a supportive microenvironment rich with oxygen and nutrients. In addition, the newly formed vasculature within the tumor microenvironment may block the infiltration of T cells, thus suppressing an appropriate immune response and preventing the killing of cancer cells. The researchers found that downregulation of *Zbtb46* resulted in a pro-tumor microenvironment, including dysfunctional vasculature and immunosuppressive cell accumulation. In contrast, enforced *Zbtb46* expression mitigated the pro-tumor microenvironment features and restricted tumor growth. These findings suggest that ZBTB46 is a critical factor for angiogenesis and immunosuppressive conditions in the tumor microenvironment and could be a promising target for cancer treatment.

In a next step, the group tested the systemic delivery of *Zbtb46* mRNA with SemaPhore nanoparticles in mouse models of sarcoma and metastatic breast cancer to boost *Zbtb46* expression. The treatment resulted in sustained *Zbtb46* expression, a restored immunostimulatory tumor microenvironment and a highly significant reduction in tumor growth ($p<0.0001$). Further, the *Zbtb46* mRNA nanoparticle treatment was combined with an immune checkpoint inhibitor (anti-PD1) treatment, which resulted in even better outcomes. The authors reported: "Remarkably, *Zbtb46* nanoparticles induced dramatic anti-PD1 response in both anti-PD1-responsive [sarcoma] and anti-PD1-refractory [breast cancer] tumor models, generating long-term complete remission of tumor in many of the treated animals." Extended monotherapy with *Zbtb46* nanoparticles produced complete remission even in mice refractory to anti-PD1 treatment. Addition of a VEGF inhibitor to the combination therapy further enhanced the treatment response. Mice whose sarcoma was eliminated through treatment did not develop fresh cancers following repeated challenge, indicating the development of a protective immunological memory.

**About SemaPhore**

SemaPhore is a versatile platform designed to enable safe and effective delivery of mRNA into target cells, using systemic or local administration. It is based on a proprietary 21 amino acid peptide that can engage any type of RNA in rapid self-assembly into a polyplex. The polyplex has a size, charge, and other physical features that allow it to escape hepatic clearance and thus to reach target tissues other than the liver. SemaPhore protects the RNA payload from degradation in the circulation and allows for rapid and effective cell entrance. Efficient delivery and positive treatment outcomes have been demonstrated in multiple murine models of disease so far.

**About Altamira Therapeutics**

Altamira Therapeutics (Nasdaq: CYTO) is developing and supplying peptide-based nanoparticle technologies for efficient RNA delivery to extrahepatic tissues (OligoPhore™ / SemaPhore™ platforms). The Company currently has two flagship siRNA programs using its proprietary delivery technology AM-401 for KRAS driven cancer and AM-411 for rheumatoid arthritis, both in preclinical development beyond in vivo proof of concept. The versatile delivery platform is also suited for mRNA and other RNA modalities and made available to pharma or biotech companies through out-licensing. In

addition, Altamira holds a 49% stake (with additional economic rights) in Altamira Medica AG, which holds its commercial-stage legacy asset Bentrio®, an OTC nasal spray for allergic rhinitis. Further, the Company is in the process of partnering / divesting its inner ear legacy assets. Founded in 2003, Altamira is headquartered in Hamilton, Bermuda, with its main operations in Basel, Switzerland. For more information, visit: https://altamiratherapeutics.com/

**Forward-Looking Statements**

This press release may contain statements that constitute "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements are statements other than historical facts and may include statements that address future operating, financial or business performance or Altamira's strategies or expectations. In some cases, you can identify these statements by forward-looking words such as "may", "might", "will", "should", "expects", "plans", "anticipates", "believes", "estimates", "predicts", "projects", "potential", "outlook" or "continue", or the negative of these terms or other comparable terminology. Forward-looking statements are based on management's current expectations and beliefs and involve significant risks and uncertainties that could cause actual results, developments and business decisions to differ materially from those contemplated by these statements. These risks and uncertainties include, but are not limited to, the clinical utility of Altamira's product candidates, the timing or likelihood of regulatory filings and approvals, Altamira's intellectual property position and Altamira's financial position. These risks and uncertainties also include, but are not limited to, those described under the caption "Risk Factors" in Altamira's Annual Report on Form 20-F for the year ended December 31, 2023, and in Altamira's other filings with the Securities Exchange Commission ("SEC"), which are available free of charge on the SEC's website at: www.sec.gov. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those indicated. All forward-looking statements and all subsequent written and oral forward-looking statements attributable to Altamira or to persons acting on behalf of Altamira are expressly qualified in their entirety by reference to these risks and uncertainties. You should not place undue reliance on forward-looking statements. Forward-looking statements speak only as of the date they are made, and Altamira does not undertake any obligation to update them in light of new information, future developments or otherwise, except as may be required under applicable law.

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[1] Kabir AU et al. (2024), ZBTB46 coordinates angiogenesis and immunity to control tumor outcome, Nat Immunol https://www.nature.com/articles/s41590-024-01936-4.

[2] Keytruda (pembrolizumab) is a trademark of Merck Sharp & Dohme Corp.

[3] Opdivo (nivolumab) is a trademark of the Bristol-Myers Squibb Company.