

Immunology Data Shows INOVIO's INO-3107 Induced Expansion of New Clonal T Cells That Infiltrate Airway Tissue and Correspond With Reduction of Surgeries for RRP Patients Observed in Phase 1/2 Trial

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- New immunology data shows INO-3107 induced an expansion of new clonal T cells in blood that were not detectable prior to treatment
- New clonal T cells in the blood travelled to papilloma and airway tissues and generated an inflammatory and anti-viral response consistent with a reduced need for surgeries for patients with recurrent respiratory papillomatosis (RRP) caused by HPV-6 and HPV-11
- Data supporting mechanism of action for INO-3107 to be presented at 36th International Papillomavirus Conference in Edinburgh, UK

PLYMOUTH MEETING, Pa., Nov. 13, 2024 /PRNewswire/ -- INOVIO (NASDAQ:INO), a biotechnology company focused on developing and commercializing DNA medicines to help treat and protect people from HPV-related diseases, cancer, and infectious diseases, today announced new immunology data that supports the clinical activity of its lead product candidate, INO-3107, that was previously observed in a Phase 1/2 trial of RRP patients. In that prior trial, patients experienced a reduction in surgeries needed to control their RRP caused by HPV-6 and HPV-11. In the recent immunology study, INO-3107 induced the expansion of both existing and new clonal T cells that travel from the blood to the papilloma and airway tissues. The new clonal T cells accounted for the majority of T cells observed in patient papilloma or airway tissue who showed either a complete or partial response to treatment with INO-3107. These new data build upon previously reported evidence that INO-3107 elicits an antigen-specific immune response targeting HPV-6 and HPV-11, to help eliminate or control RRP by reducing the need for surgery.

"These new immunology data are consistent with the clinical effect observed in our Phase 1/2 trial of elimination or reduction in the incidence of papilloma in the airway of RRP patients," said Dr. Matthew Morrow, INOVIO's Vice President of Translational Sciences. "In a thorough immunological assessment, we observed that T cell infiltration in

airway tissues of clinical responders was predominantly comprised of a T cell population detectable only after administration of INO-3107. This evidence supports the mechanism of action of INO-3107 and its ability to induce antigen-specific cytotoxic T cells targeting HPV-6 and HPV-11. Furthermore, this data adds to the body of evidence indicating that DNA medicines are an effective CD8 T cell generating platform."

Bettie M. Steinberg, Interim Dean and Professor, Elmezzi Graduate School of Molecular Medicine, Northwell Health, said, "This is very encouraging data. Not only did most patients improve clinically with INO 3107 treatment, but the induction of a systemic inflammatory T-cell response and new T-cell clones that travel to the papilloma tissue to contribute to a cytotoxic response shows that it is possible to effectively address the immune dysregulation against HPV that is a hallmark of RRP."

Summary of Immunology Data

The new immunology data is to be presented at the 36th International Papillomavirus Conference (November 12-15). It builds on data presented at the American Association for Cancer Research (AACR) Special Conference on October 19. Collectively, these immunology data provide further support of INO-3107's ability to induce antigen-specific T cell responses against HPV-6 and HPV-11 and drive recruitment of T cells into papilloma and airway tissues of RRP patients, which could potentially slow or eliminate papilloma regrowth.

INOVIO conducted a number of immunological assessments on blood samples taken throughout the trial and tissue samples taken at the beginning and end of its 52-week Phase 1/2 trial involving 32 adult RRP patients. The immunological testing showed INO-3107 produced:

- Induction of T cell responses specific for HPV-6 and HPV-11, including cytotoxic CD8+ T cells still present at week 52, indicating an establishment of memory response
- Expansion of new clonal T cell populations in peripheral blood that travel to papilloma or airway tissues
- Induction of inflammatory responses in papilloma and airway tissue, including:
 - Interferon, cytokine and chemokine signaling
 - Adaptive and innate immune cell infiltration, with emphasis on T cells
- Cytotoxic signatures of infiltrated T cells in papilloma/airway tissue, and direct evidence of increased overall T cell infiltration compared to pre-treatment
- Clinical activity not impacted by immunosuppressive papilloma microenvironment

About RRP

RRP is a debilitating and rare disease caused primarily by HPV-6 and/or HPV-11. RRP is characterized by the development of small, wart-like growths, or papillomas, in the respiratory tract. While papillomas are generally benign, they can cause severe, life-threatening airway obstruction and respiratory complications. RRP can also

significantly affect quality of life for patients by affecting the voice box, limiting the ability to speak effectively. Surgery to remove papillomas is the standard of care for RRP; however, the papillomas often grow back. INOVIO's market research to date with patients and healthcare professionals indicates that a reduction of even one surgery matters, because every surgery poses a significant risk of causing permanent damage to the vocal cords. The most widely cited U.S. epidemiology data published in 1995 estimated that there were 14,000 active cases and about 1.8 per 100,000 new cases in adults each year.

About INO-3107

INO-3107 is an investigational DNA medicine designed to elicit an antigen-specific T cell response against both HPV-6 and HPV-11 proteins. These targeted T cells are designed to seek out and kill HPV-6 and HPV-11 infected cells, with the aim of potentially preventing or slowing the growth of new papillomas. In a Phase 1/2 clinical trial conducted with INO-3107, 81.3% (26/32) of patients had a decrease in surgical interventions in the year after INO-3107 administration compared to the prior year, including 28.1% (9/32) that required no surgical intervention during or after the dosing window. Patients in the trial had a median range of 4 surgeries (2-8) in the year prior to dosing. After dosing, there was a median decrease of 3 surgical interventions (95% confidence interval -3, -2). At the outset of the trial (Day 0), patients had a clinically warranted procedure to have RRP tissue surgically removed, but any surgery performed after Day 0 during the dosing window was counted against the efficacy endpoint. Treatment with INO-3107 generated a strong immune response in the trial, inducing activated CD4 T cells and activated CD8 T cells with lytic potential. T-cell responses were also observed at Week 52, indicating a persistent cellular memory response. INO-3107 was well tolerated, with trial participants experiencing mostly low-grade (Grade 1) treatment-emergent adverse effects such as injection site pain and fatigue. Like other DNA medicines, INO-3107 has shown the ability to generate antigen-specific T cells that is not affected by anti-vector immunity impacting immunogenicity, either before administration or after the first dose unlike other T-cell generating platforms such as viral vectors. This feature of DNA medicines is anticipated to allow INO-3107 to maintain T cell response and overall efficacy, which could make it an important therapeutic option for a majority of RRP patients.

The FDA previously granted INO-3107 Orphan Drug designation and Breakthrough Therapy designation and has advised INOVIO that it can submit a biologics license application under the FDA's accelerated approval program using data from INOVIO's already completed Phase 1/2 trial. The European Commission granted INO-3107 Orphan Drug designation. In addition, INOVIO has CE-marked its CELLECTRA® delivery device in the EU, which allows INOVIO to commercialize the device in the EU and other geographies that recognize CE-marking. The United Kingdom awarded INO-3107 the Innovation Passport. This designation serves as the entry point to the Innovative Licensing and Access Pathway (ILAP), which aims to accelerate time to market and facilitate patient access to medicines.

About INOVIO's DNA Medicines Platform

INOVIO's DNA medicines platform has two innovative components: precisely designed DNA plasmids, delivered by INOVIO's proprietary investigational medical device, CELLECTRA®. INOVIO uses proprietary technology to design its DNA plasmids, which are small circular DNA molecules that work like software the body's cells can download to produce specific proteins to target and fight disease. INOVIO's proprietary CELLECTRA® delivery devices are designed to optimally deliver its DNA medicines to the body's cells without requiring chemical adjuvants or lipid nanoparticles and without the risk of the anti-vector response historically seen with viral vector platforms.

About INOVIO

INOVIO is a biotechnology company focused on developing and commercializing DNA medicines to help treat and protect people from HPV-related diseases, cancer, and infectious diseases. INOVIO's technology optimizes the design and delivery of innovative DNA medicines that teach the body to manufacture its own disease-fighting tools. For more information, visit www.inovio.com.

Forward-Looking Statements

This press release contains certain forward-looking statements relating to our business, including our plans to develop and commercialize DNA medicines and expectations regarding our research and development programs, including timelines and prospects for regulatory approval, expectations regarding INO-3107's ability to maintain T cell response and overall efficacy, as well as benefits for patients. Actual events or results may differ from the expectations set forth herein as a result of a number of factors, including uncertainties inherent in pre-clinical studies, clinical trials, product development programs and commercialization activities and outcomes, the availability of funding to support continuing research and studies in an effort to prove safety and efficacy of electroporation technology as a delivery mechanism or develop viable DNA medicines, our ability to support our pipeline of DNA medicine products, the ability of our collaborators to attain development and commercial milestones for products we license and product sales that will enable us to receive future payments and royalties, the adequacy of our capital resources, the availability or potential availability of alternative therapies or treatments for the conditions targeted by us or collaborators, including alternatives that may be more efficacious or cost effective than any therapy or treatment that we and our collaborators hope to develop, issues involving product liability, issues involving patents and whether they or licenses to them will provide us with meaningful protection from others using the covered technologies, whether such proprietary rights are enforceable or defensible or infringe or allegedly infringe on rights of others or can withstand claims of invalidity and whether we can finance or devote other significant resources that may be necessary to prosecute, protect or defend them, the level of corporate expenditures, assessments of our technology by potential corporate or other partners or collaborators, capital market conditions, the impact of government healthcare proposals and other factors set forth in our Annual Report on Form 10-K for the year ended December 31, 2023, our Quarterly Report on Form 10-Q for the quarter ended June 30, 2024, and other filings we make from time to time with the Securities and Exchange Commission. There can be no assurance that any product candidate in our pipeline will be successfully developed,

manufactured, or commercialized, that the results of clinical trials will be supportive of regulatory approvals required to market products, or that any of the forward-looking information provided herein will be proven accurate. Forward-looking statements speak only as of the date of this release, and we undertake no obligation to update or revise these statements, except as may be required by law.

Contacts

Media: Jennie Willson (267) 429-8567 jennie.willson@inovio.com

Investors: Thomas Hong (267) 440-4298 thomas.hong@inovio.com

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