Phio Pharmaceuticals’ INTASYL™ PH-762: Intratumoral Immunotherapy Targeting PD-1
Abstract:
Cancer’s resistance to immune surveillance and therapy poses a formidable challenge in the field of oncology. The interaction between PD-1 on T cells and PD-L1 on tumor cells plays a pivotal role in immune evasion, and, while immune checkpoint inhibitors have proven effective, their systemic administration can lead to severe adverse effects. Intratumoral immunotherapy, particularly with Phio’s INTASYL compound PH-762, represents a novel and promising strategy.

PH-762, a unique RNAi molecule targeting PD-1 mRNA, can be directly administered into the tumor, circumventing systemic side effects. Its efficient silencing of PD-1 mRNA, promotion of immune responses, and safety profile make it an attractive candidate for revolutionizing cancer treatment.

This paper explores the potential of PH-762 in intratumoral immunotherapy. By achieving localized immune stimulation and the induction of systemic anti-tumor responses, Phio’s PH-762 introduces a promising approach to enhance cancer treatment efficacy.

Introduction:
Cancer’s ability to evade the immune system and develop resistance to anti-cancer drugs presents a formidable challenge in cancer management. The interaction between PD-L1 on tumor cells and PD-1 on T cells contributes to immune system evasion. While immune checkpoint inhibitors targeting PD-1 signaling have proven effective in restoring anti-tumor immunity, their systemic administration is associated with significant adverse effects, such as grade 3-4 colitis, pneumonitis, and hepatic toxicity.1,2

Intratumoral immunotherapy is at the forefront of innovative treatment strategies. It leverages the tumor itself as a “self-vaccine” by injecting therapeutic agents directly into the tumor. This results in high local concentrations of immunostimulatory products with minimal drug requirements. The localized immune stimulation can trigger a robust anti-tumor immune response and induce systemic (abscopal) tumor responses, orchestrated by properly activated anti-tumor immune cells in the bloodstream.

Phio’s INTASYL compound PH-762 specifically targets and silences PD-1 mRNA. PH-762 can be administered via direct intratumoral injection, offering a solution to the undesirable systemic side effects associated with conventional systemic antibody treatments. PH-762’s unique structural and chemical modifications render it well-suited for intratumoral administration, ensuring an optimized cell and tissue uptake profile. In this paper, we delve into the potential of PH-762 as an asset in intratumoral immunotherapy, poised to revolutionize cancer treatment paradigms.

Although PH-762 can be injected into almost any accessible solid tumor, the three indications of most interest to Phio are cutaneous squamous cell carcinoma (cSCC), melanoma, and Merkel cell carcinoma.

INTASYL Technology:
INTASYL is a patented precision delivery technology that empowers the creation of unique compounds designed for the precise silencing of target genes. These self-delivering, chemically modified siRNA compounds can be delivered to a broad range of cell types and tissues without the need for delivery enhancements. INTASYL’s innovative approach features a simplified chemical composition, effectively reducing toxicity and enhancing tolerability and efficacy. This technology is adaptable to both intra-tumoral and adoptive cell therapy (ACT) applications, ensuring a versatile and potent therapeutic platform for gene silencing.

Market Rationale:
Phio’s primary focus indication is cutaneous squamous cell carcinoma (cSCC), which, at 1.8 million cases per year in the US alone, is second only to basal cell carcinoma in worldwide incidence.3,4,5 The majority of cSCC lesions arise on the skin of the head or neck, likely due to high sun exposure and resulting mutagenesis. Surgical resection of the lesions is typically curative, yet there remains an increased risk of disease recurrence, loss of function or disfigurement following surgical resection of advanced lesions or histologically aggressive features.6

Melanoma incidence rates have been increasing for at least 30 years. Worldwide an estimated 325,000 new cases were diagnosed in 2020.7 The disease is usually curable when detected in its early stages, however, the prognosis is not as favorable for thicker and/or ulcerated primary melanomas, melanomas with regional lymph node involvement, in transit disease, or satellite metastatic lesions.8,9

Merkel cell carcinoma is a rare and aggressive cutaneous carcinoma that predominantly affects the elderly or those who are immunocompromised. This cancer seems to be increasingly common, and typically presents as a painless nodule on sun exposed skin, often on the head and neck. In addition to ultraviolet light, the Merkel-cell polyomavirus (MCPyV) has been implicated in the origin of these tumors.10

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Each of these tumors (i.e., cutaneous squamous cell carcinoma, melanoma, or Merkel cell carcinoma) has demonstrated response to PD-1 and PD-L1 checkpoint inhibition or blocking, including FDA-approved products for intravenous administration for the treatment of the targeted indications. Unfortunately, systemic administration of anti-PD-1 mAB carries the risk of significant adverse effects. Direct intra-tumoral injection of PH-762 provides a mechanism to circumvent those risks. PH-762 is a potent siRNA molecule targeting PD-1 mRNA. The structural and chemical modifications of the siRNA molecule used in PH-762 enable its IT administration with an optimized cell and tissue uptake profile.

**Data:**

In vitro investigations have demonstrated rapid and efficient uptake of PH-762 by human T cells that results in effective silencing of PD-1 mRNA and subsequent protein reduction. Additionally, treatment of human T cells with PH-762 resulted in an increase in interferon gamma (IFN-γ) secretion which can bolster T cell cytotoxicity towards tumor cells and attract additional T cells to the tumor; all of which directly inhibit tumor growth.

Preclinical studies have shown that intratumoral (IT) injections of murine targeted PH-762 (mPH-762) can silence the immune checkpoint PD-1 mRNA in the T cells in the tumor and increase the secretion of IFN-γ, thereby impeding tumor growth. In all models, mPH-762 was well tolerated at the maximum administered dose and treatment with mPH-762 provided robust and statistically significant inhibition of tumor growth.

Preclinical studies have also shown that IT mPH-762 increased the number of immune cells in the treated tumor with silencing of PD-1 expression across multiple immune cell populations of the tumor microenvironment (TME). Mechanistic impacts of IT mPH-762 treatment observed in TME correlated with previously described impacts of systemic anti-PD-1 antibody.

Importantly, IT mPH-762 treatment extended abscopal efficacy to untreated distal tumors in bilateral models, inducing systemic, tumor specific memory CD8+ T cells.

Toxicokinetic studies conducted in marmoset monkeys demonstrated that PH-762, when administered intravenously at doses of up to 147 mg/kg, was well-tolerated. Importantly, no detectable cytokine-release associated cytokines were found in the plasma of treated monkeys at this dose.

A first-in-human (FiH) clinical study with PH-762 administered by IT injection was performed in France, with the first patient enrolled in June 2022. Three adult patients received IT PH-762 with no reported serious adverse events (SAEs).

In addition, another 175 people have been exposed to INTASYL compounds in other trials: III by injection and 64 topically. No LDTs or SAEs were reported in the injected patients. The topical administration was well-tolerated with minimum potential for irritation.

The FDA approved Phio’s IND for PH-762 earlier this year. A Phase Ib Dose Escalation Study of Neoadjuvant Intratumoral PH-762 for Cutaneous Squamous Cell Carcinoma, Melanoma, or Merkel Cell Carcinoma is scheduled to start November 2023.

**Conclusion:**

In summary, intratumoral immunotherapy, using Phio’s INTASYL compound PH-762, offers a promising solution to the challenge of immune evasion by directly targeting PD-1 mRNA within the tumor, avoiding systemic side effects. This innovative approach has the potential to transform cancer treatment, addressing a large variety of injection accessible tumors, such as squamous cell carcinoma, melanoma, and Merkel cell carcinoma. PH-762’s localized action and ability to induce systemic responses make it a valuable tool in the fight against cancer.

**References:**
