Abstract TPS9608: Trial in progress: A First-in-Human, Phase 1b Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Anti-Tumor Activity of Neoadjuvant Use of PH-762 Administered Intratumorally in Subjects with Advanced Melanoma.

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Background

Immunotherapy with antibodies targeting immune checkpoints such as PD-1 and CTLA-4 has shown significant benefit in late-stage melanoma. However, further improvements in therapeutic options are still required. Two approaches for improving the outcome of immunotherapy with checkpoint inhibitors are neoadjuvant treatment and local intratumoral (IT) injection.

IT immunotherapy uses the tumor as its own vaccine to activate the immune system, priming an anti-tumor immune response and generating systemic tumor responses, whilst minimizing systemic exposure and off-target toxicities.

Neoadjuvant immunotherapy can induce significant pathological responses that seem to be associated with a decrease in the risk of relapse. There is currently no neoadjuvant standard of care for resectable, advanced melanoma patients.

PH-762 is a potent RNAi molecule targeting PD-1 with structural and chemical modifications conferring properties suitable for IT administration, including an optimized cell and tissue uptake profile. Pharmacology studies show potent *in vitro* silencing of PD-1 associated with T cell activation, and robust, dose-dependent *in vivo* inhibition of tumor growth in syngeneic tumor models.

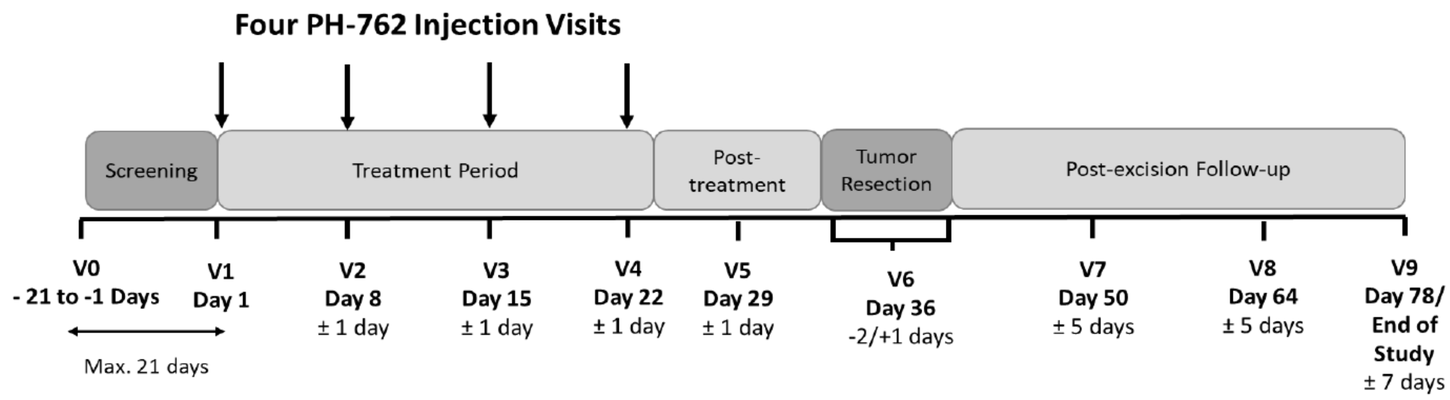
Purpose

The purpose of this study is to evaluate the safety of neoadjuvant use of PH-762 administered by IT injection in subjects with resectable stage IIIB/IIIC/IIID or IV melanoma, to determine the recommended Phase 2 dose, PK after IT injection, and potential immunologic and pathologic tumor responses.

Methods

Study treatment constitutes of once weekly injections with PH-762 into one designated tumor lesion for 4 weeks prior to surgical excision at 5-6 weeks after the initial injection. Up to 5 dose levels will be tested in a serial fashion in cohorts of 3 or more subjects. Eligible subjects will have at least one resectable melanoma deposit that is large enough to allow IT injection and that can undergo repeated biopsy. Subjects with active brain metastases, leptomeningeal disease, uveal melanoma, and auto-immune disease are excluded. The dose of PH-762 will be normalized to tumor volume to ensure an equivalent local dose (tumor tissue concentration). Post tumor excision, subjects will be followed-up for 6 weeks. Primary endpoint is to determine a safe dose of PH-762 assessed by incidence of Dose Limiting Toxicities (DLT) prior to tumor resection. Bayesian optimal interval (BOIN) design will be employed to evaluate escalating doses of PH-762 to determine the Maximum Tolerated Dose based on occurrence of DLT. Tumor changes will be evaluated per RECIST criteria (version 1.1 and iRECIST version adapted for use with IT therapy) and pathological response. Immunological response in tumor tissue and blood samples will be assessed as secondary endpoints.

Study Design



Key messages

- Neoadjuvant treatment with PH-762 RNAi provides an alternative therapeutic modality for patients with resectable, advanced melanoma
- Direct administration of PH-762 to the tumor can prime a local immune response by silencing PD-1 in the tumor microenvironment and generate a systemic immune response
- IT administration has the potential to minimize systemic exposure and off-target toxicity

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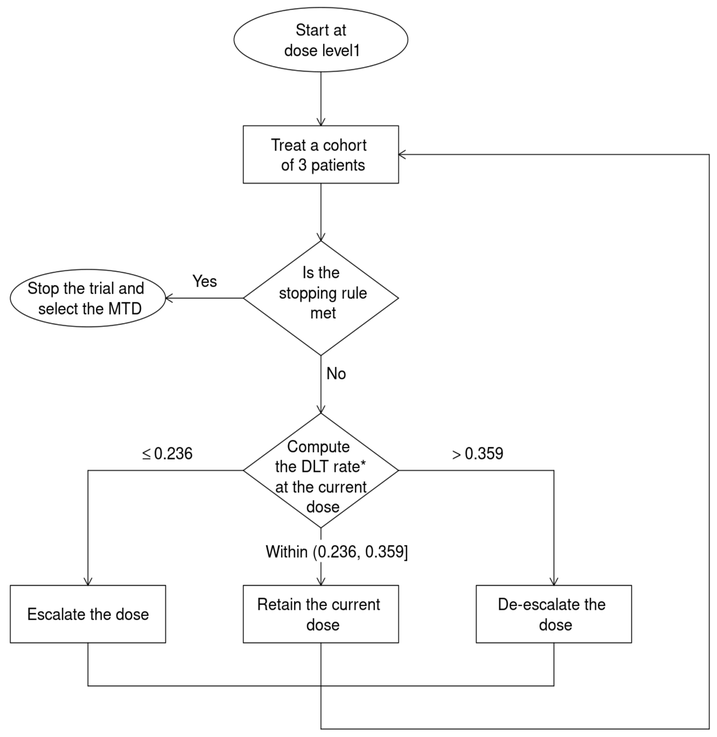
Primary Objective

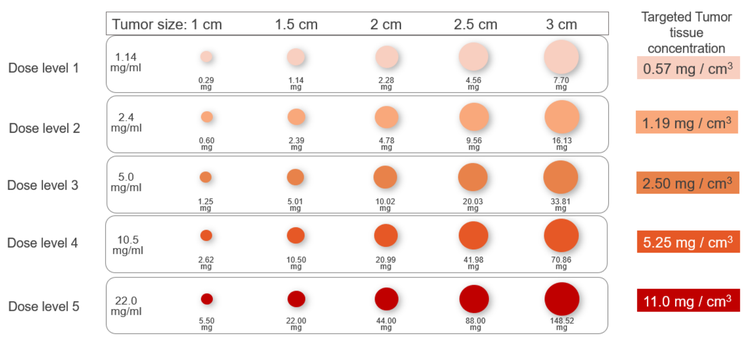
Determine a safe dose of PH-762 administered by IT injection in subjects with stage IIIB/IIIC/IIID or IV resectable melanoma

BOIN Flow Chart



$$* \text{ DLT rate} = \frac{\text{Total number of patients who experienced DLT at the current dose}}{\text{Total number of evaluable patients treated at the current dose}}$$

Dosing based on tumor volume



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