A 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 Immuno therapy with antibodies targeting PD-1 and CTLA-4 has shown significant benefit in late-stage melanoma. However, as response is limited to approximately 60%, and with emergence of resistance, further improvements in therapeutic options are still required. Two approaches for improving the outcome of immuno therapy with checkpoint inhibitors are neoadjuvant treatment and local intratumoral (IT) injection. Neoadjuvant immuno therapy can induce significant pathological responses that seem to be associated with a decrease in the risk of relapse. Currently there is no neoadjuvant standard of care for patients with resectable, advanced melanoma. IT immuno therapy uses the tumor as its own vaccine to activate the immune system, priming an anti-tumor immune response and minimizing systemic exposure and off-target toxicities. PH-762 is a potent RNAi molecule targeting PD-1 that contains structural and chemical modifications conferring rapid and efficient tissue uptake suitable for IT administration. In pharmacology studies PH-762 provided robust silencing of PD-1 associated with T cell activation, and dose-dependent inhibition of tumor growth in in vivo syngeneic tumor models with on-target PD-1 silencing-associated with immunostimulatory effects in the tumor microenvironment.

Methods The primary objective of this first-in-human study is to evaluate the safety of neoadjuvant use of PH-762 administered by IT injection. Secondary objectives include PK after IT injection, potential immunologic and pathologic tumor responses, and determination of the recommended Phase 2 dose. Subjects must have histologically confirmed stage IIIA/IIIB/IIIC/IIID or IV oligometastatic cutaneous melanoma with at least one resectable lesion that is large enough to allow IT injection, and that can undergo repeated biopsy. Subjects with brain metastases, leptomeningeal disease, uveal melanoma, and auto-immune disease are excluded. PH-762 is administered IT into one designated tumor lesion once weekly for 4 weeks prior to surgical excision at 5-6 weeks after the initial injection. The dose of PH-762 is normalized to tumor volume to ensure an equivalent local dose (tumor tissue concentration). Post tumor excision, subjects are followed-up for 6 weeks. Primary endpoint is determination of 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 with up to 5 dose levels in cohorts of 3 or more subjects. Tumor changes will be evaluated per RECIST criteria (version 1.1 and iRECIST adapted for IT therapy) and pathological response. Secondary endpoints include immunological response in tumor tissue and blood. The first cohort has been enrolled.

Trial Registration EudraCT number 2021-002859-10

Ethics Approval Approval was provided by: Comite de Protection de Personnes Sud Mediterranee III, 2021.12.04 bis _21.04174.000055