An Open-Label, Multicenter, Phase 1/2 Study of RP1 as a Single Agent and in Combination with PD1 Blockade in Patients with Solid Tumors

Abstract #: TPS2671

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Abstract

Background: RP1 is an attenuated oncolytic HSV-1 that expresses a fusogenic glycoprotein from gibbon ape leukemia virus (GALV-GP R-) and GM-CSF. RP1 induces potent GALV-GP R- enhanced immunogenic cell death and host anti-tumor immunity in murine tumor models and increases PD-L1 expression. This clinical trial (NCT03767348) was designed to test the hypotheses that RP1 is safe when given alone and together with nivolumab (ph 1) and has efficacy together with nivolumab in four tumor types (ph 2).

Methods: The primary goals of this clinical trial in a total of ~150 patients are to define the safety profile of RP1 alone and together with nivolumab, determine the recommended phase 2 dose (phase 1), and then in four phase 2 cohorts, to determine objective response rate in patients with melanoma, non-melanoma skin cancer, urothelial carcinoma and MSI-H solid tumors. Secondary objectives include duration of response, CR rate, PFS, viral shedding, and immune biomarker analysis. Patients with advanced cancer who failed prior therapy were eligible for the phase I component. In Phase 2 patients with histologic diagnoses of the four tumor types (N=30 for each) and who meet safety criteria for nivolumab treatment are eligible. Prior treatment with checkpoint blockade is not allowed except for the melanoma cohort. In the phase 1 portion patients are treated by intra-patient dose escalation of virus (range, 10^4 - 10^8 PFU) by intratumoral injection every two weeks for 5 total doses followed by 12 patients dosed 8 times at the RP2D in combination with nivolumab. Phase 1 patients were divided into two groups based on presence of clinically accessible lesions amenable to direct injection or those with visceral/deep lesions requiring image guidance for injection. In the phase 2 portion patients will receive the RP2D for eight injections and nivolumab will be given starting with the second RP1 injection. For the phase 1 portion, a modified 3+3 dose escalation design is used to assess safety and in the phase 2 portion, statistical analysis will be performed using a two-stage three-outcome optimum design with objective responses determined by RECIST criteria.

Background

- Oncolytic viruses (OVs) preferentially replicate in tumors as compared to normal tissue and promote immunogenic cell death and induction of host systemic anti-tumor immunity against the antigens released
- Single agent clinical activity and synergy with immune checkpoint blockade (ipilimumab and pembrolizumab) has previously been demonstrated with an oncolytic virus based on herpes simplex virus type 1 (HSV-1)[1-3]
- RP1 is a high potency oncolytic immunotherapy candidate based on a new clinical isolate of HSV-1 armed with genes encoding a fusogenic glycoprotein from gibbon ape leukemia virus (GALV-GP R-) and GM-CSF
- GALV-GP R- increases tumor cell death through cell-to-cell fusion (syncitia formation) and increases the immunogenicity of cell death (ICD)
- GM-CSF causes the proliferation and activation of antigen presenting cells
- The objective of treatment with RP1 is to maximally vaccinate patients against their own tumor, which will then synergize with immune checkpoint blockade
- RP1 is being developed for the treatment of solid tumors, in particular in combination with anti-PD1 therapy
- This poster describes an ongoing Phase 1/2 clinical trial of RP1 alone and in combination with nivolumab therapy in multiple solid tumor types

[1] JCO 2015 **33**, 2780 [2] JCO 2018 **10**, 1658 [3] Cell 2017 **170**, 1109

Phase 1 design, key inclusion criteria & objectives

Overview

- The Phase 1 portion of the clinical trial is a modified 3+3 accelerated dose titration design where multiple dose levels of RP1 are tested in each dose rising cohort by parallel assignment to cohorts for direct injection into superficial and nodal tumors and cohorts for imaging guided injection into deeper tumors including visceral tumors
- In each case, a single tumor is injected up to five times with up to 10mL of injectate depending on tumor size, and each cohort must contain at least one patient who is seronegative for HSV-1
- Following selection of the RP2D by each dosing route, patients are then enrolled into expansion cohorts in combination with nivolumab where up to 8 doses of RP1 are given into multiple tumors Q2W, up to the maximum of 10ml of injectate available. Nivolumab is given from the second RP1 dose for up to 2 years
- In the expansion cohort phase, blood samples and biopsies are taken at baseline and day 43 for biomarker analysis

Summary of key inclusion & exclusion criteria

- Advanced or metastatic non neurological solid tumors, who have progressed on standard therapy or cannot tolerate standard therapy, or for which there is no standard therapy preferred to enrollment in a clinical trial
- At least one measurable and injectable (including use of image-guided injection) tumor of ≥ 1 cm in longest diameter
- Adequate hematologic, hepatic and renal function
- ECOG performance status 0 – 1
- No prior treatment with an oncolytic therapy
- No active CNS metastases

Summary of key objectives

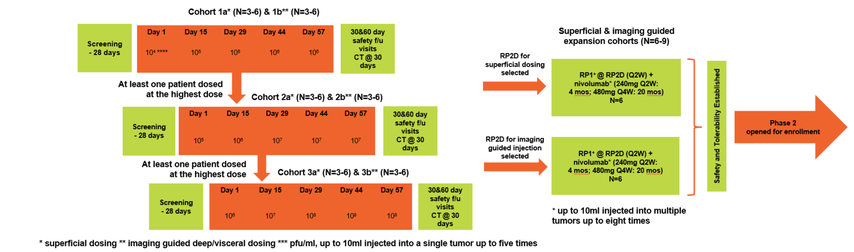
Primary:

- To determine the maximum tolerated dose (MTD) and/or the RP2D of RP1
- To assess the safety and tolerability of RP1 alone and in combination with nivolumab

Secondary:

- To assess biological activity by changes in tumor size, inflammation, necrosis and erythema
- To assess RP1 biodistribution and shedding
- To assess the changes in levels of anti-HSV-1 antibodies

Phase 1 Study Schema



Summary of biomarker analysis (Phase 1 expansion cohorts and Phase 2 only)

- Immune cell phenotyping using Isoplexis profiling of the immune cell and cytokine profile from PBMCs
- Gene expression analysis using Nanostring including an oncolytic virus and immune inflammatory gene signature panel
- CD8 T cell infiltration and PD-L1 expression by immuno-histochemistry and spatial multi-plex immuno fluorescence

Phase 2 design, key inclusion criteria & objectives

Overview

- The Phase 2 portion of the clinical trial enrolls four cohorts of 30 patients each with melanoma, non-melanoma skin cancers (NMSC), bladder cancer or MSI-H/dMMR tumors
- Other than for melanoma where prior anti-PD1 therapy is allowed, patients are naïve to anti-PD1 therapy
- Patients are dosed at the RP2D for RP1 up to eight times Q2W, combined with nivolumab from the second RP1 dose for up to two years
- RP1 is administered into injectable superficial and/or deep tumors by direct and/or imaging guided injection up to the maximum 10mL of injectate available on each injection day
- Biopsies and blood samples are taken at baseline and day 43 for biomarker analysis

Key additional inclusion criteria

- Measurable disease based upon RECIST 1.1
- Melanoma: Stage IIIb-IV melanoma (includes ocular and mucosal) for whom PD-1 directed therapy is indicated or who have previously received a PD1/L1 directed therapy
- MSI-H/dMMR tumors: Metastatic MSI-H or dMMR tumor for whom PD-1 directed therapy is indicated according to a current approved label
- NMSC: Locally advanced or metastatic unresectable NMSC; CTCL is excluded
- Bladder cancer: Locally advanced or metastatic UBC for whom PD-1/PD-L1 directed therapy is indicated according to a current approved label
- Or in each cohort patients have exhausted, become intolerant to or refuse other therapies

Summary of key objectives

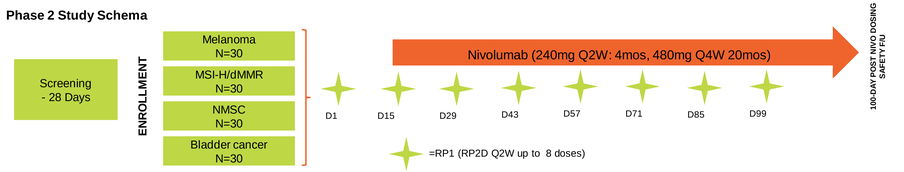
Primary:

- To assess the safety and tolerability of RP1 in combination with nivolumab
- To assess efficacy as determined by ORR using RECIST 1.1 criteria

Secondary & Exploratory:

- To assess efficacy by duration of response (DOR), complete response (CR) rate, disease control rate (DCR), progression free survival (PFS), 1-year and 2- year overall survival (OS)
- To assess immune activation through biomarker analysis

Phase 2 Study Schema



Current Trial Status

- Enrollment of the Phase 1 part of the study is complete with 22 patients enrolled in the dose rising phase and 13 patients enrolled in the expansion phase in combination with nivolumab
- Tumor types enrolled were cutaneous melanoma, uveal melanoma, mucosal melanoma, basal cell carcinoma, squamous cell carcinoma, colorectal cancer (including MSI-H/dMMR), breast cancer, bladder cancer, esophageal cancer, carcinoma of the parotid gland
- Dose rising cohort patients were enrolled in the UK, and expansion cohort patients enrolled in both the UK and the US
- Following selection of the RP2D, the phase 2 portion of the study is currently open for enrollment in the US and the UK
- Initial data from the Phase 1 part of the study (dose rising, RP1 in combination with nivolumab, and biomarker data) is expected to be presented in Q4 2019