IGNYTE: An open-label, multicenter, phase 1/2 (Ph 1/2) clinical trial of RP1 ± nivolumab in patients with advanced solid tumors

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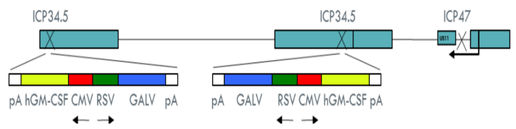
Background

- Oncolytic immunotherapies preferentially replicate in tumors and promote immunogenic cell death, intended to induce systemic anti-tumor immunity and provide an optimal means of generating a patient-specific anti-tumor immune response.
- RP1 is an enhanced potency oncolytic HSV-1 expressing a fusogenic glycoprotein (GALV-GP R-) and granulocyte macrophage colony stimulating factor (GM-CSF). Pre-clinical studies with RP1 demonstrated potent GALV-GP R-enhanced anti-tumor activity and immunogenic cell death [1].

RP1 Backbone

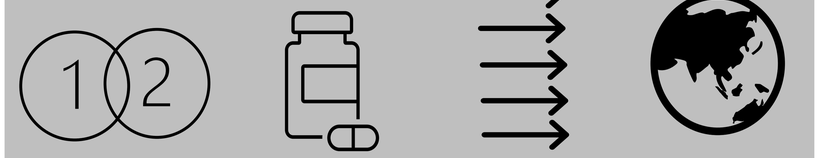


- IGNYTE is an ongoing Phase 1/2 trial that is evaluating RP1 as a single agent and in combination with the anti-PD-1 inhibitor nivolumab (nivo) in patients with solid tumors.
- The Phase 1 part of the trial is completed. The recommended phase 2 dose (RP2D) of RP1 was determined to be a first dose of 1 × 10^6 PFU/mL followed by subsequent doses of 1 × 10^7 PFU/mL [2].
- The Phase 2 part is currently ongoing and recruiting patients.
- Here we present the Phase 2 updated trial design, key eligibility criteria and endpoints (Amendment 10/Protocol version 11.0).

Objective

The objective of phase 2 part of the trial is to assess safety, tolerability and efficacy of RP1 + nivo in solid tumors including anti-PD-1/PD-L1-failed disease.

Methods

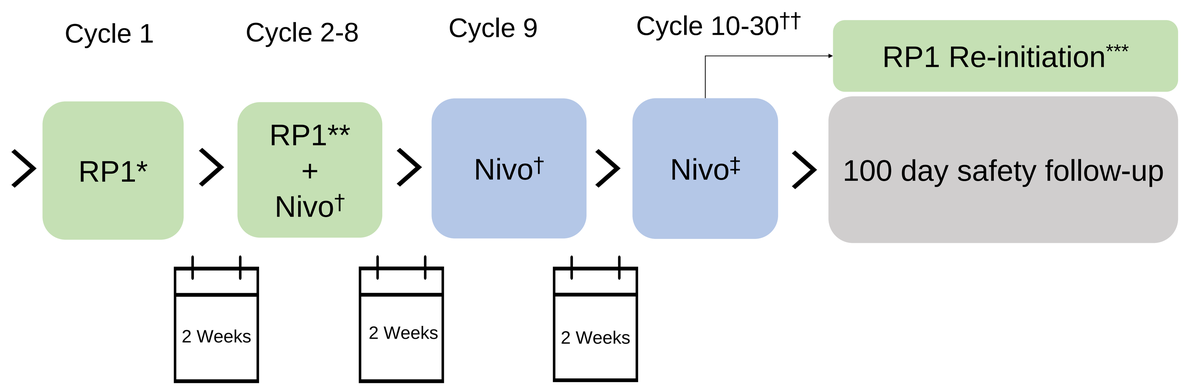


Phase 1/2 **Open-label** **Multi-cohort** **Global**

Trial Design

Actively Recruiting Cohorts[a]	Target N
Anti-PD-1-failed cutaneous melanoma	125
Non-melanoma skin cancer (NMSC) anti-PD-1/PD-L1-failed and naïve disease	60[b]
Non-small cell lung cancer (NSCLC) anti-PD-1/PD-L1-failed	30
Micro Satellite Instability and deficient Mis-match Repair (MSI-H/dMMR) anti-PD-1/PD-L1-failed disease	30

[a]Melanoma cohort (N=30) is fully enrolled and not recruiting.
[b]Anti-PD-1/PD-L1-naïve (N) = 30; anti-PD-1/PD-L1-failed (N) = 30.



Dosing

RP1
*First dose = 1 X 10^6 PFU/mL
**Subsequent doses = 1 X 10^7 PFU/mL

Nivo
†240 mg (Q2W)
‡480 mg (Q4W)
†† Dosing with nivo begins at Dose 2 of RP1; therefore a maximum of 29 cycles of nivo will be given

RP1 Re-initiation***
- Re-initiation with up to 8 additional doses of RP1 Q2W in combination with nivo 480mg Q4W if the following protocol criteria are met:
  - (i) injectable disease and lesions that are safe to inject, (ii) stable performance status, (iii) patient did not experience either of the following during the first course of RP1 treatment: a Grade 4 AE, a Grade 3 injection site reaction (e.g. injection site necrosis) lasting > 14 days, a suspected imAE Grade 3 event or Grade 3 infections lasting more > 14 days, unless the AE was deemed not related to RP1.
- The additional course of RP1 may be given for persistent or progressive lesions if persistence or progression is confirmed after at least 4 weeks, or for new lesion(s), at any time within 24 months from treatment initiation with RP1.

Follow-up

- 3 follow-up visits will be completed:
  - 30 day post last RP1 dose
  - 60 days post last RP1 dose
  - 100 days past last nivo dose
- Patients will be followed for long-term response and survival for 3 years from the first dose of RP1.

Key Eligibility Criteria

Inclusion

- Stage IIIb-IV cutaneous melanoma who have progressed on anti-PD-1 ± anti-CTLA.
- Metastatic MSI-H or dMMR disease who have progressed on prior anti-PD-1 therapy.
- Locally advanced or metastatic NMSC that have progressed on prior PD-1/PD-L1 therapy.
- Anti-PD-1/PD-L1 failed NSCLC.
- Patients with at least one measurable tumor of ≥1cm in longest diameter and ECOG ≤1.

Exclusion

- Prior treatment with an oncolytic virus.
- Active significant herpetic infections or prior complications of HSV-1.
- Conditions requiring treatment with immunosuppressive doses (>10 mg daily prednisone or equivalent) of systemic corticosteroids other than for corticosteroid replacement therapy within 14 days of enrollment.
- Systemic anticancer therapies within 4 weeks prior to enrollment (excluding PD-1/PD-L1) and systemic infection requiring IV antibiotics or other serious infection within 14 days prior to dosing.
- Patients with uncontrolled, untreated brain or CNS metastasis.

Key Endpoints

- **Primary**
  - Objective response rate (ORR).
  - For anti-PD-1-failed cutaneous melanoma cohort, ORR will be assessed by independent review.
  - Safety and tolerability.
- **Secondary**
  - Duration of response (DOR), complete response rate (CRR), disease control rate (DCR), overall survival (OS) and progression-free survival (PFS).
- **Exploratory**
  - Biomarker analysis using tumor biopsies and peripheral blood, including the assessment of RP1 biodistribution and shedding.

IGNYTE is now recruiting patients. To learn more about enrolling your patient contact: clinicaltrials@replimune.com or +1 (781)-222-9570.

Additional information could be obtained by visiting ClinicalTrials.Gov (NCT03767348).

References:
1. Thomas S, et al. *J Immunother Cancer*. 2019;7(1):214.
2. Aroldi F, et al. *J Immunother Cancer*. 2020;8.

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