Abstract: 610

Immune biomarker analysis of RP1 in combination with nivolumab in patients with advanced solid tumors

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Background

- RP1 is an enhanced potency oncolytic version of herpes simplex virus 1 that expresses the human granulocyte macrophage colony stimulating factor and the fusogenic protein GALV-GP R− [1].
- IGNYTE is a phase 1/2 open label, multicenter, dose escalation and expansion trial (NCT03767348) evaluating the safety and efficacy of RP1 in combination with the anti–PD-1 inhibitor nivolumab in a range of tumor types [2].
- Here we present the biomarker data from the ongoing Phase 1/2 clinical trial of RP1 combined with nivolumab (NCT03767348) from patients enrolled in the cutaneous melanoma and anti-PD-1 naïve NMSC cohorts (n=61).

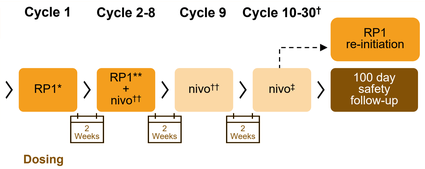
Objective

Biomarker analysis of RP1 alone and in combination with nivolumab in patients with advanced and/or refractory solid tumors

Methods

Cohorts	Target N
Melanoma[a]	30
Non-melanoma skin cancer anti–PD-1/PD-L1–failed and –naïve[b]	60
Anti–PD-1–failed cutaneous melanoma[c]	125
Non-small cell lung cancer anti–PD-1/PD-L1–failed	30
Micro Satellite Instability and deficient Mis-match Repair anti–PD-1/PD-L1–failed	30

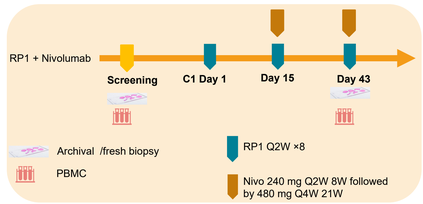
[a]Melanoma (N = 30) is fully enrolled and not recruiting.
[b]Anti–PD-1/PD-L1–naïve is fully enrolled and not recruiting; anti–PD-1/ PD-L1–failed (N = 30).
[c]Registration-directed cohort.



Dosing

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

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

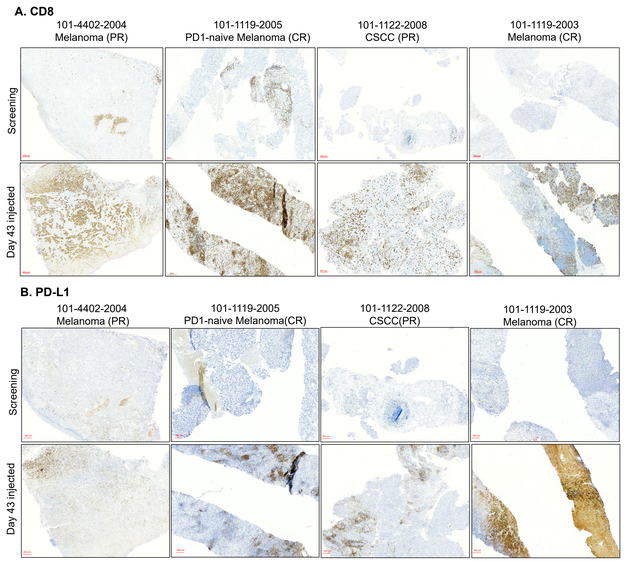


- Tumor biopsy and blood samples (PBMCs) were collected at screening and at Day 43.
- The tumor immune microenvironment (TIME) was analyzed by IHC for CD8 (SP57 clone, Ventana) and PD-L1 (PD-L1 IHC 28-8 pharmDx by Agilent).
- Gene expression analysis used the NanoString IO360 panel.
- Tumor inflammation signature score (TIS) was also calculated using the 18 gene signature previously identified as a prognostic indicator for response to pembrolizumab [3].
- Systemic anti-tumor immunity was assessed using PBMCs by sequencing the CDR3 regions of human TCRβ chains using the immunoSEQ assay.
- Correlation analysis of baseline tumor PD-L1 and CD8 status versus overall response was also performed.

Results

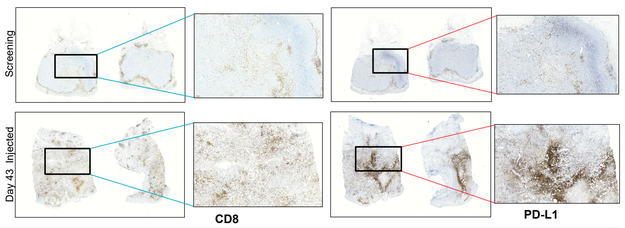
Increase in CD8+ T cell Infiltration and PD-L1 expression post treatment

Figure 1. Change in CD8+ T cells and PD-L1 expression



Reversal of T cell exclusion

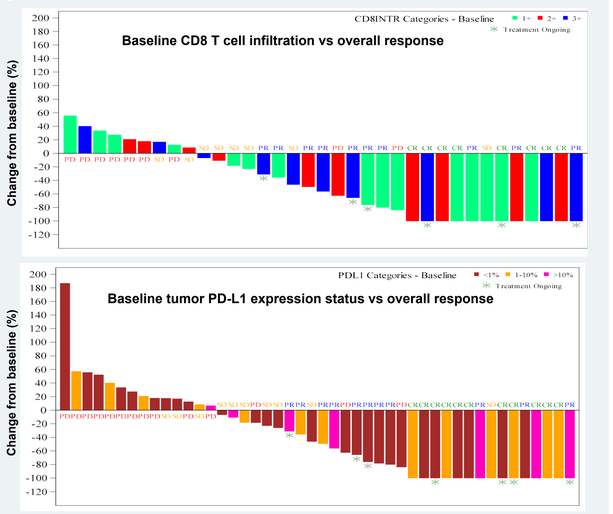
Figure 2. Reversal of T cell exclusion and corresponding increase in PD-L1 expression in an ipi/nivo failed melanoma patient



- CD8+ T cells presence and PD-L1 expression are restricted to tumor margins at baseline.
- Following RP1 treatment, IHC results from biopsy samples collected on Day-43 demonstrate a striking influx of intratumoral CD8+ T cells, indicative of a reversal of baseline T cell exclusion.
- Also an increase in PD-L1 expression was observed following RP1 treatment.

Baseline CD8+ T cell and PD-L1 expression vs. overall response

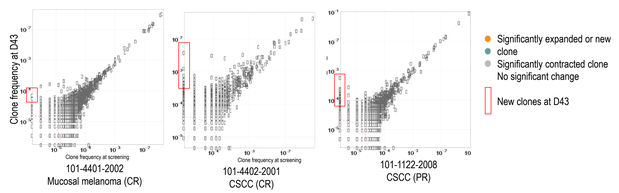
Figure 3.



- Waterfall plots indicate no association between baseline tumor PD-L1 status or CD8+ T cell infiltration status with % change in tumor volume.
- Responses were observed irrespective of baseline CD8+ T cell infiltration and PD-L1 expression status.

Expansion & generation of T-cell clones with RP1 + nivolumab

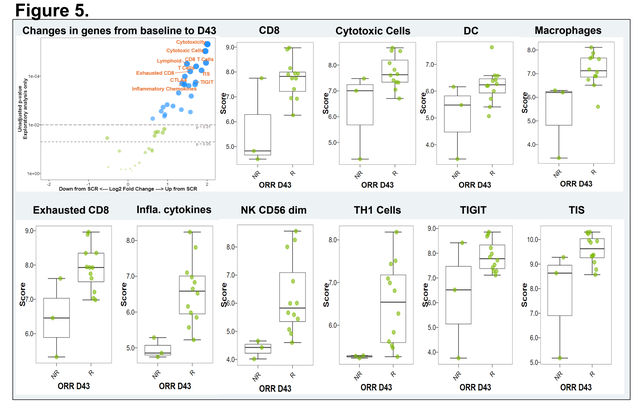
Figure 4.



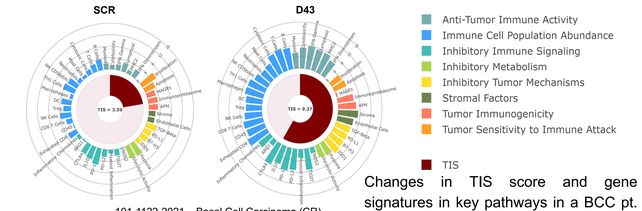
- TCR sequencing of PBMCs revealed expansion of T cell clones following treatment with RP1 in combination with nivolumab.
- Many of the clones (range 20-80%) were newly detected at Day 43 when compared with baseline.
- Generation of new T cell clones and expansion of existing T cell clones was observed.

Increased expression of genes associated with immune activation

Figure 5.



Examples of changes in relative gene expression signatures at baseline and post treatment



101-1122-2021 – Basal Cell Carcinoma (CR)

Changes in TIS score and gene signatures in key pathways in a BCC pt. who achieved a CR

Conclusions

- Immunohistochemistry for CD8 and PD-L1 from paired tumor biopsies demonstrated a robust increase in infiltration of CD8+ T cells and PD-L1 expression and reversal of T cell exclusion, in patients treated with RP1+nivolumab treatment, including in patients who failed prior anti-PD-1 therapy (Fig 1 A-B & Fig 2).
- T cell receptor sequencing demonstrated the expansion of existing T cell clones and generation of new T cell clones (Fig 4).
- Gene expression analysis demonstrated a significant increase in the expression levels of genes associated with innate and adaptive immune activation and genes previously reported to be associated with responsiveness to anti-PD-1 therapy (Fig 5).
- Tumor inflammation signature (TIS) scores increased following treatment.
- Overall the biomarker data demonstrate that treatment with RP1 combined with nivolumab increases immune activation in patients with skin cancer.
- This is consistent with the intended mechanism of action of RP1 and consistent with the clinical efficacy data generated to date.

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

Additional information can be obtained by visiting Clinicaltrials.gov (NCT03767348)

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