Enhanced CD8+ T-cell infiltration, PD-L1 expression, and T-cell repertoire expansion in patients with metastatic uveal melanoma responding to treatment with RP2 alone or in combination with nivolumab

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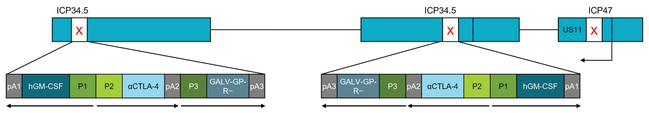
Background

- RP2 is a genetically modified herpes simplex virus type 1 that encodes granulocyte-macrophage colony-stimulating factor, the fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP-R–), and a human anti–CTLA-4 antibody-like molecule[1]
- RP2 ± nivolumab is currently being tested in clinical trials in a range of solid tumors including in patients with metastatic uveal melanoma (mUM)
- Uveal melanoma is the most common form of intraocular primary malignancy and accounts for ~90% of all cases of ocular melanoma and up to 5% of all melanomas[2-5]
- Approximately 50% of patients with uveal melanoma will develop distant metastases, with the liver representing the most frequent site of metastatic disease (~90%). Following metastasis, median overall survival is <1 year[2,3]
- As of November 20, 2023, 17 patients with uveal melanoma were enrolled (RP2 monotherapy, n = 3; RP2 + nivolumab, n = 14)
- Here, we present the biomarker data from patients with mUM treated with RP2 in combination with nivolumab

RP2 – A fusion-enhanced oncolytic HSV expressing anti–CTLA-4

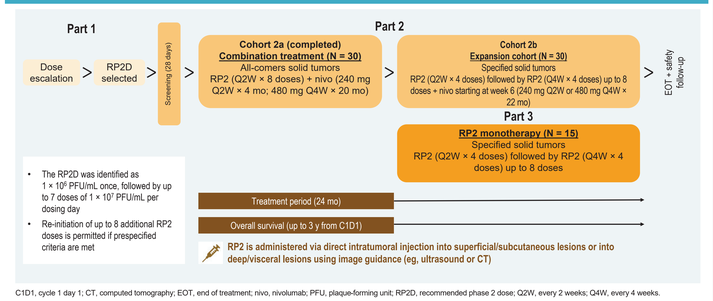


αCTLA-4, anti–cytotoxic T-lymphocyte antigen 4; GALV-GP-R–, gibbon ape leukemia virus glycoprotein with the R sequence deleted; hGM-CSF, human granulocyte-macrophage colony-stimulating factor; HSV, herpes simplex virus; ICP, infected cell protein; P, promoter; pA, polyA signal; US11, unique short 11; X, denotes inactivation of viral protein.

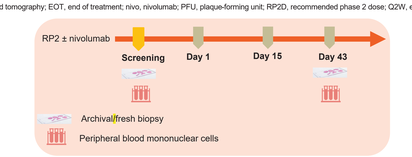
Objectives

- To evaluate the efficacy of RP2 alone and in combination with nivolumab and the impact on tumor biopsies and peripheral blood mononuclear cell (PBMC) samples collected from mUM patients enrolled in the NCT04336241 clinical trial

Methods



C1D1, cycle 1 day 1; CT, computed tomography; EOT, end of treatment; nivo, nivolumab; PFU, plaque-forming unit; RP2D, recommended phase 2 dose; Q2W, every 2 weeks; Q4W, every 4 weeks.



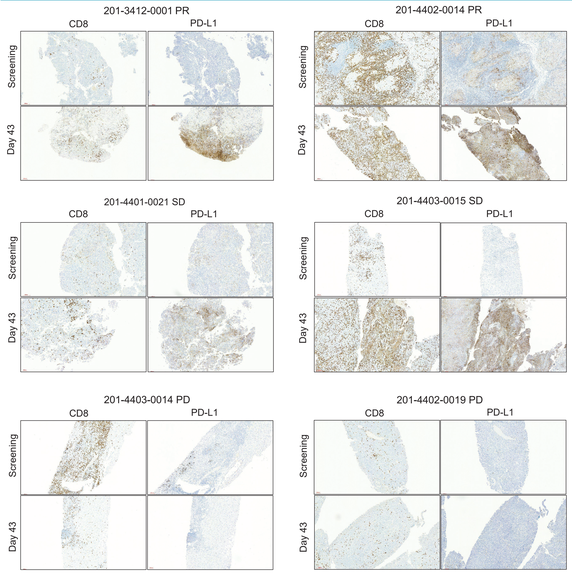
- Tumor biopsies and PBMCs were collected at screening and at day 43
- Tumor immune microenvironment was analyzed by immunohistochemistry (IHC) to detect CD8 (SP57 clone, Ventana) and PD-L1 (PD-L1 IHC 28-8 pharmDx by Agilent)
- Systemic antitumor immunity was assessed using PBMCs by sequencing the CDR3 regions of human TCRβ chains using the immunoSEQ assay.

Patient demographics and baseline characteristics

	RP2 monotherapy (n = 3)	RP2 + nivolumab (n = 14)
Age, median (range), years	55 (48–64)	65 (38–82)
Sex, n (%)		
Female	0	5 (35.7)
Male	3 (100.0)	9 (64.3)
ECOG PS, n (%)		
0	3 (100.0)	11 (78.6)
1	0	3 (21.4)
Prior lines of treatment, n (%)		
0	0	2 (14.3)
1	1 (33.3)	5 (35.7)
2	1 (33.3)	5 (35.7)
3	0	1 (7.1)
4	1 (33.3)	1 (7.1)
Prior therapies, n (%)		
Anti–PD-1[a]	3 (100.0)	10 (71.4)
Anti–CTLA-4[b]	3 (100.0)	10 (71.4)
Anti–PD-1 and anti–CTLA-4	3 (100.0)	9 (64.3)

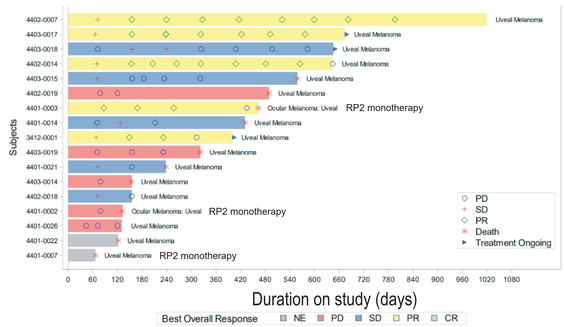
[a]Alone or combined with anti–CTLA-4.
[b]Alone or combined with anti–PD-1.
CTLA-4, cytotoxic T-lymphocyte antigen 4; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1, programmed cell death protein 1.

Increase in CD8+ T cells influx and PD-L1 expression are observed in patients treated with RP2 combined with nivolumab



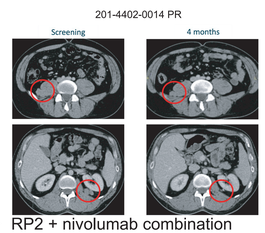
- IHC of the day 43 biopsy demonstrates an increase in intratumoral CD8 T-cell infiltration and PD-L1 expression in patients achieving partial response (PR) and stable disease (SD)

Duration of benefit; objective response rate and disease control rate

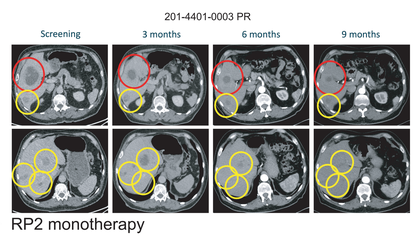


- In this pretreated population, the ORR was 29.4% (5/17; all PRs; RP2 monotherapy, 1/3; RP2 + nivolumab, 4/17)
- The disease control rate (complete response + PR + SD) was 58.8% (10/17; 5 patients with SD in RP2 + nivolumab cohort)
- The median (range) duration of response at the data cutoff was 11.47 (2.78–21.22) months

RP2 ± nivolumab in patients who progressed on prior immunotherapy



- RP2 + nivolumab combination
- More than 50% tumor reduction was observed
- Prior therapies: ipilimumab, pembrolizumab
- Patient progressed at 21.5 months after initiating treatment with RP2

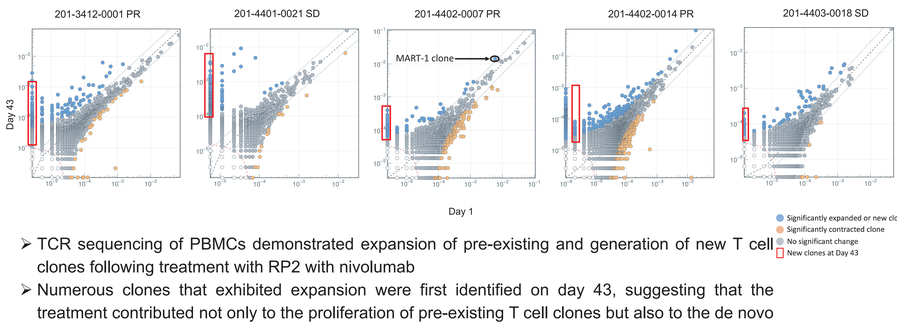


- RP2 monotherapy
- Extensive liver metastases
- Prior therapies: ipilimumab + nivolumab
- Patient progressed at 14.3 months after initiating treatment with RP2

Responses were observed in both HLA-A2*02:01–positive and HLA-A2*02:01–negative patients

HLA-A*02:01 status	Positive (n = 6)	Negative (n = 11)	Total (n = 17)
PR	1 (16.7%)	4 (36.4%)	5 (29.4%)
SD	2 (33.3%)	3 (27.3%)	5 (29.4%)
PD/NE	3 (50.0%)	4 (36.4%)	7 (41.2%)

TCR sequencing of PBMCs demonstrated expansion of existing T cell clones along with the generation of new tumor-specific T cell clones



- TCR sequencing of PBMCs demonstrated expansion of pre-existing and generation of new T cell clones following treatment with RP2 with nivolumab
- Numerous clones that exhibited expansion were first identified on day 43, suggesting that the treatment contributed not only to the proliferation of pre-existing T cell clones but also to the de novo generation of new T cell clones
- The expansion of new or pre-existing clones in the peripheral blood did not show correlation with clinical response

Summary and conclusions

- Biomarker analysis shows that RP2 treatment in combination with nivolumab leads to significant immune activation. This is evidenced by the expansion of pre-existing T cell clones and the emergence of new T cell clones in the peripheral blood, as well as increased PD-L1 expression and enhanced CD8+ T-cell infiltration in tumors form mUM patients achieving PR and SD
- RP2 monotherapy and RP2 + nivolumab demonstrate a meaningful antitumor activity with durable responses in patients with mUM, including in patients with liver metastases. These responses were observed in both HLA-A2*02:01–positive and HLA-A2*02:01–negative patients
- Based on data in this population, planning is underway for a potentially registrational clinical trial with RP2 in advanced uveal melanoma

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