Abstract: 9527

Preliminary safety and efficacy results from an open-label, multicenter, phase 1 study of RP2 as a single agent and in combination with nivolumab in a cohort of patients with uveal melanoma

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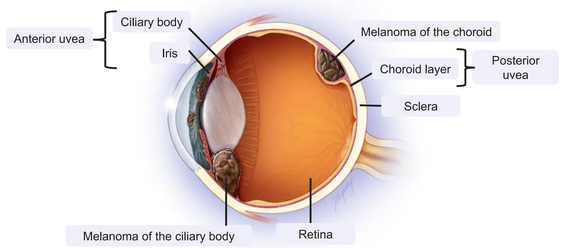
Background

- 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[1-4]
- Uveal melanoma can arise from melanocytes of the iris, ciliary body, or choroid (**Figure 1**)[1,2]

Figure 1. Anatomical diagram of uveal melanoma



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- Approximately half of patients with uveal melanoma will develop distant metastases, with the liver representing the most frequent site of metastatic disease (~90%)[1,2]
  - Following metastasis, median overall survival is <1 year[1,5]
- Uveal melanoma is clinically challenging, as it is an immunologically "cold" tumor type that does not respond well to immunotherapy[1]
  - Single-agent immune checkpoint inhibitor therapies (eg, anti–programmed cell death protein 1 [PD-1] antibodies) typically exhibit low response rates in patients with metastatic uveal melanoma (~5%–10%)[6,7]
  - Combination therapies of anti–PD-1 and anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) agents have shown higher response rates (12%–18%), but at the expense of significant immune-related systemic toxicities[8,9]
- Tebentafusp is the first US Food and Drug Administration–approved agent for the treatment of unresectable or metastatic uveal melanoma in human leukocyte antigen (HLA)-A*02:01–positive adults[10-12]
  - Tebentafusp demonstrated 1-year overall survival of 73% vs 59% with investigator's choice of monotherapy (hazard ratio, 0.51; *P* <0.001) in a phase 3 trial of patients with treatment-naïve metastatic uveal melanoma; objective response rate (ORR) was 9% vs 5%, respectively[11]
  - One-year survival on second-line tebentafusp (62%) compared favorably with historical data[12]
- Thus, there remains a significant unmet need for treatments with higher efficacy and tolerability for patients with uveal melanoma, especially for those who are HLA-A*02:01–negative or have failed to respond to or progressed on tebentafusp or anti–PD-1 monotherapy

Figure 2. RP2 backbone

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; ICP, infected cell protein; P, promoter; pA, polyA signal; US11, unique short 11; X, denotes inactivation of viral protein.

- 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 (**Figure 2**)[13]
- GALV-GP-R– expression is intended to increase immunogenic cell death via cell-to-cell fusion, and local expression of anti–CTLA-4 is intended to augment systemic tumor-specific immune response without systemic immune-related toxicities
- RP2 is being evaluated in an open-label, multicenter, phase 1 clinical trial as a monotherapy and in combination with nivolumab (anti–PD-1; NCT04336241). Here, we present updated safety and efficacy data of RP2 ± nivolumab in a cohort of patients with uveal melanoma

Methods

Patients and study design

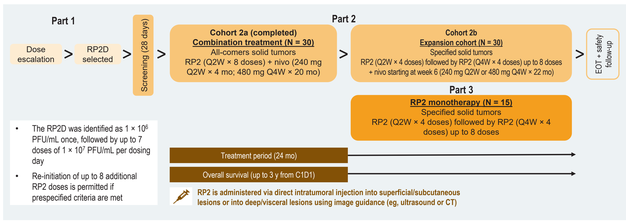
- Key eligibility criteria are shown in **Table 1**
- This is a 3-part, multicenter, open-label phase 1 dose-escalation and expansion monotherapy and combination-treatment study (**Figure 3**)
- **Primary objective**: Assess the safety, tolerability, and ORR of RP2 alone and in combination with nivolumab

Table 1. Key eligibility criteria

Inclusion	Exclusion
• Age ≥18 years	• Prior treatment with OI
• Histologically or cytologically confirmed advanced or metastatic non-neurological solid tumors (including uveal melanoma)	• Known history of hepatitis B (hepatitis B surface antigen reactive), hepatitis C virus (hepatitis C RNA detected), or HIV infection
• Progressed on or cannot tolerate standard therapy	• Active significant herpetic infections or prior complications of HSV-1 infection
• Must have ≥1 measurable and injectable tumor ≥1 cm in longest diameter (or shortest diameter of lymph nodes)	• Known active CNS metastases and/or carcinomatous meningitis
• ECOG PS 0–1	• Major surgery ≤2 weeks prior to starting study drug[a]

[a]If a patient underwent major surgery, they must have recovered adequately from all complications of the intervention prior to starting study treatment.
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HSV-1, herpes simplex virus type 1; OI, oncolytic immunotherapy.

Figure 3. Study design



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.

Results

Patients

- As of December 2022, 17 patients with uveal melanoma were enrolled (RP2 monotherapy, n = 3; RP2 + nivolumab, n = 14)
- The majority of patients received both prior anti–PD-1 and anti–CTLA-4 therapy (12/17; 70.6%), and 17.6% (3/17) received ≥3 prior lines of therapy (**Table 2**)

Table 2. 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.

Results

Efficacy

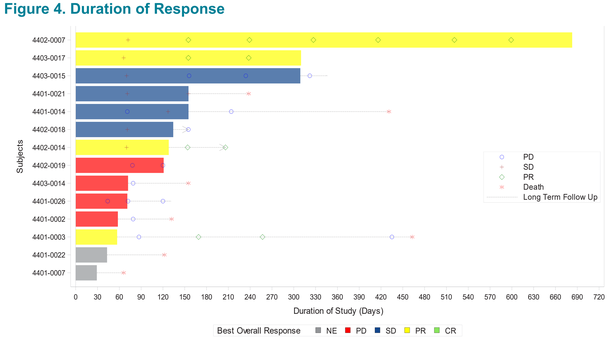
- In this pretreated population, the ORR for the 14 patients with sufficient follow-up for analysis was 28.6% (4/14; all partial responses [PRs]; RP2 monotherapy, 1/3; RP2 + nivolumab, 3/11; **Table 3**)
- The disease control rate (complete response + PR + stable disease [SD]) was 57.1% (8/14; 4 patients with SD in RP2 + nivolumab cohort)
- The median (range) duration of response at the data cutoff was 5.8 (1.7–14.7) months (**Figure 4**)

Table 3. Patients with uveal melanoma treated with RP2

Patient #	RP2 monotherapy or combination w/ nivolumab	Prior therapies	Sites of disease	Best response
4401-0002	Monotherapy	Ipilimumab + nivolumab, temozolomide, selumetinib + vistusertib, carboplatin	Lung, liver, abdomen, chest, lymph nodes, subcutaneous, bone	PD
4401-0003	Monotherapy	Ipilimumab + nivolumab	Liver	PR
4401-0007	Monotherapy	Ipilimumab + nivolumab, intratumoral AGI-134	Liver, kidney, head and neck, peritoneal, intramuscular, subcutaneous, bone	Not done (non-evaluable)
4401-0014	Combination	None	Liver	SD
4402-0007	Combination	Nivolumab	Orbital mass, bone (pelvis, vertebral), cheek	PR
4401-0021	Combination	Selumetinib + paclitaxel, pembrolizumab, ipilimumab, melphalan intrahepatic chemoperfusion	Liver, gastrointestinal, lymph nodes, abdominal wall, leg	SD
4401-0022	Combination	Ipilimumab, dacarbazine	Liver	Not captured
4402-0014	Combination	Ipilimumab, pembrolizumab	Retroperitoneal, SCF	PR
4403-0014	Combination	Tebentafusp	Liver	PD
4403-0015	Combination	Tebentafusp, nivolumab + ipilimumab	Lung, liver, vertebra	SD
4401-0026	Combination	Ipilimumab + nivolumab, chemosaturation	Liver	PD
4403-0017	Combination	Ipilimumab + nivolumab	Liver	PR
4402-0018	Combination	None	Liver	SD
4402-0019	Combination	Ipilimumab, pembrolizumab	Liver, perirenal	PD
4403-0018	*Combination*	*Nivolumab + ipilimumab*	*Liver*	*SD*
4403-0019	*Combination*	*Ipilimumab + nivolumab*	*Liver*	*Not done yet*
3412-0001	*Combination*	*Ipilimumab + nivolumab, IL-2, carboplatin, paclitaxel*	*Liver, lung*	*Not done yet*

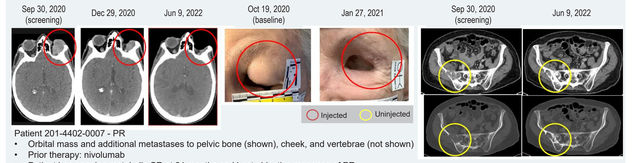
Red outlined boxes indicates responding patients. Yellow shading indicates patients ongoing on treatment for whom the outcome is not yet known.
CR, complete response; IL, interleukin; PD, progressive disease; PET, positron emission tomography; PR, partial response; SCF, supraclavicular fossa nodal failure; SD, stable disease.

Figure 4. Duration of Response



CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

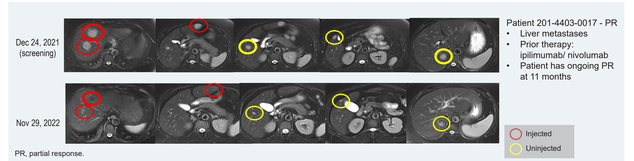
Figure 5. Patient who progressed on prior nivolumab (RP2 + nivolumab)



Patient 201-4402-0007 - PR
- Orbital mass and additional metastases to pelvic bone (shown), cheek, and vertebrae (not shown)
- Prior therapy: nivolumab
- Patient has ongoing metabolic CR at 21 months and best objective response of PR

CR, complete response; PR, partial response.

Figure 6. Patient who progressed on prior ipilimumab/nivolumab (RP2 + nivolumab)



Patient 201-4403-0017 - PR
- Liver metastases
- Prior therapy: ipilimumab/ nivolumab
- Patient has ongoing PR at 11 months

PR, partial response.

Safety

- The most common grade 1 or 2 treatment-related adverse events (TRAEs; ≥20%) overall in both cohorts combined were pyrexia, chills, fatigue, and hypotension (**Table 4**)
  - The only grade 3 TRAE occurring in >1 patient was hypotension (2 patients receiving RP2 + nivolumab)
  - No grade 4 or 5 TRAEs were observed
- Out of the 11 patients who received liver injections, 2 patients experienced Grade 3 TEAEs (4 total events) assessed as related to procedure and RP2. The first patient experienced Grade 3 hypotension 1 day after cycle 2 and alanine aminotransferase increased 3 days after Cycle 3. The second patient experienced Grade 3 hypotension 15 days after cycle 1 and again 1 day after cycle 3. All events resolved with standard medical management; both patients were in the combination cohorts and continued on the study.
- There were no Grade 4 or 5 TEAEs in patients who received liver injections which were assessed as related to procedure and RP2, or nivolumab.

All data presented as n (%).TRAEs include events deemed related to RP2 only, nivolumab only, or both RP2 and nivolumab.
[a]Grade 1 or 2 TRAEs occurring in >10% and grade =3 TRAEs occurring in patients with uveal melanoma are shown.
TRAE, treatment-related adverse event.

Table 4. TRAEs

Patients with ≥1 TRAE	Grade 1–2	Grade 3	Grade 4–5
RP2 monotherapy (n = 3)	2 (66.7)	0	0
Hypotension	2 (66.7)	0	0
Chills	1 (33.3)	0	0
Hyperhidrosis	1 (33.3)	0	0
Pyrexia	1 (33.3)	0	0
Rash	1 (33.3)	0	0
Vomiting	1 (33.3)	0	0
RP2 + nivolumab (n = 14)[a]	13 (92.9)	6 (42.9)	0
Pyrexia	11 (78.6)	0	0
Chills	7 (50.0)	0	0
Fatigue	4 (28.6)	0	0
Pruritus	3 (21.4)	0	0
Hypotension	2 (14.3)	2 (14.3)	0
Infusion-related reaction	2 (14.3)	1 (7.1)	0
Headache	2 (14.3)	0	0
Influenza-like illness	2 (14.3)	0	0
Nausea	2 (14.3)	0	0
Vitiligo	2 (14.3)	0	0
Alanine aminotransferase increased		1 (7.1)	0
Arthralgia		1 (7.1)	0
Immune-mediated hepatitis		1 (7.1)	0
Lipase increased		1 (7.1)	0

Conclusions

- Preliminary data from RP2 monotherapy and RP2 + nivolumab demonstrate a favorable safety profile and meaningful antitumor activity in patients with metastatic uveal melanoma, an immunologically "cold" tumor type that has few effective treatment options, including in patients with liver metastases
- These data continue to support the hypothesis that intratumoral oncolytic immunotherapy expressing anti–CTLA-4 antibody, in combination with an anti–PD-1 agent, may provide a clinically meaningful benefit and a favorable toxicity profile in patients with hard-to-treat/unresponsive tumors

This study is currently 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 (NCT04336241).

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