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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Presenter disclosure

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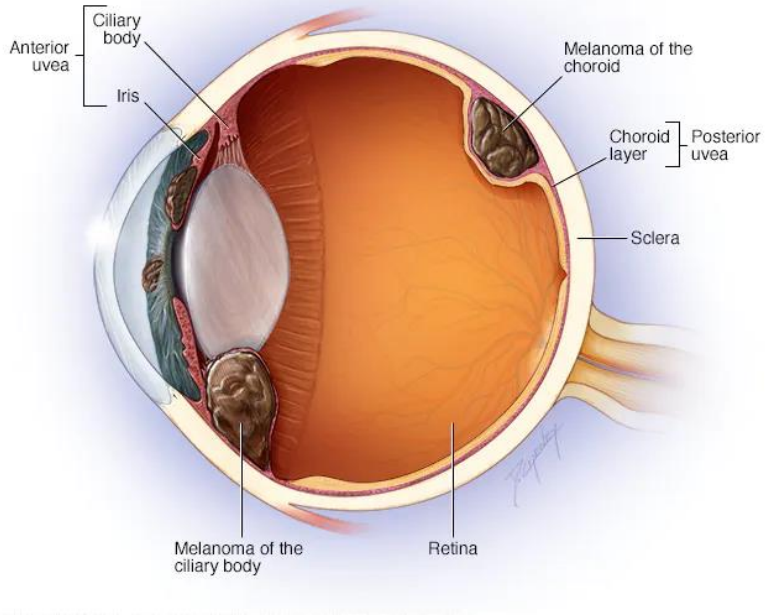
Uveal melanoma

- Uveal melanoma:
  - The most common form of intraocular primary malignancy
  - Accounts for **~90%** of all cases of **ocular melanoma** and up to 5% of all melanomas[1-4]
  - Approximately **50% of patients** will develop **distant metastases**
    - The **liver** represents **~90%** of sites of metastatic disease[1,2]
    - Following metastasis, median OS is <1 year[1,5]
- Uveal melanoma is an **immunologically "cold" tumor type** that does not respond well to immunotherapy[1]
  - Single-agent immune checkpoint inhibitor therapies typically exhibit low response rates (~5%–10%) in patients with metastatic uveal melanoma[6,7]
  - Combination therapies have shown higher response rates (12%–18%) but at the expense of significant toxicities[8,9]
- Tebentafusp is the first FDA–approved agent for the treatment of unresectable/metastatic uveal melanoma, but its use is restricted to HLA-A*02:01–positive patients[10]



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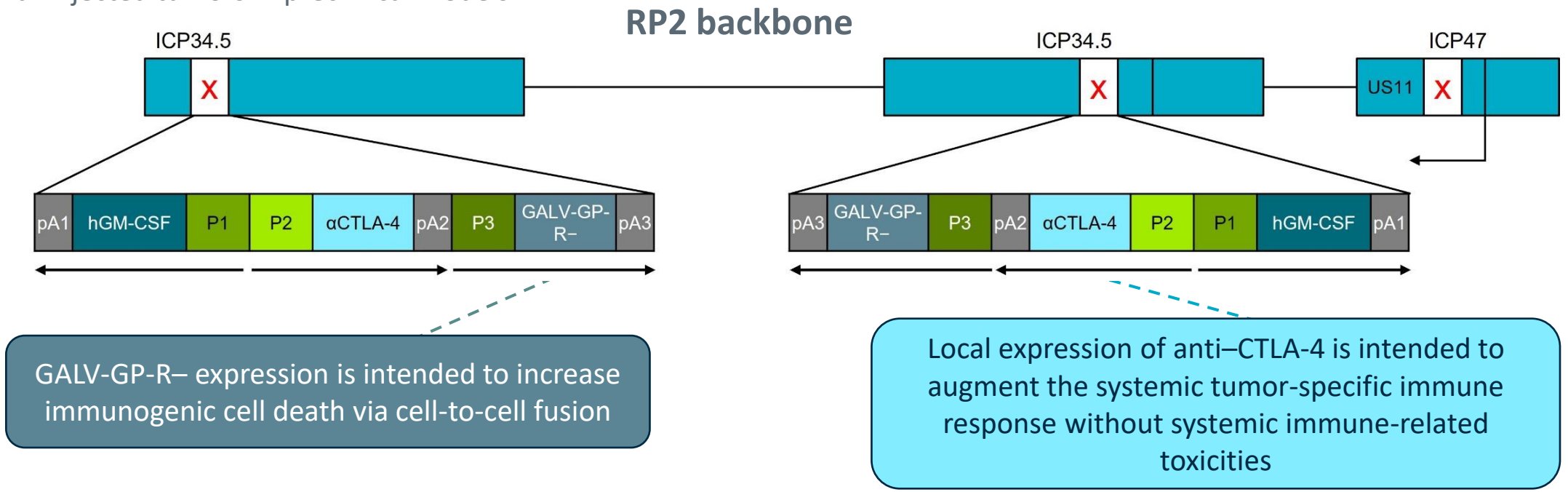
Unmet need: *Treatments with higher efficacy and tolerability, especially for patients who have failed to respond to or progressed on tebentafusp or anti–PD-(L)1 and/or anti–CTLA-4 directed therapies*

FDA, US Food and Drug Administration; HLA, human leukocyte antigen; OS, overall survival; PD-1, programmed cell death protein 1.

1. Jager MJ, et al. *Nat Rev Dis Primers*. 2020;6(1):24. 2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Melanoma: Uveal. Version 1.2023. 3. Mahendraraj K, et al. *Clin Ophthalmol*. 2017;11:153-60. 4. Branisteanu DC, et al. *Exp Ther Med*. 2021;22(6):1428. 5. Khoja L, et al. *Ann Oncol*. 2019;30(8):1370-80. 6. Rossi E, et al. *Cancer Immunol Immunother*. 2019;68(7):1179-85. 7. Algazi AP, et al. *Cancer*. 2016;122(2):3344-53. 8. Pelster MS, et al. *J Clin Oncol*. 2021;39(6):599-607. 9. Piulats JM, et al. *J Clin Oncol*. 2021;39(6):586-98. 10. Montazeri K, et al. *Drug Des Devel Ther*. 2023;17:333-9.

RP2

- RP2 is a genetically modified HSV-1 that encodes GM-CSF, the fusogenic protein GALV-GP-R–, and a human anti–CTLA-4 antibody-like molecule[1]
  - Constructed using a potent new clinical strain of HSV-1 with superior oncolytic activity in vitro and further modified to enhance immunogenic tumor cell death[1]
  - Deletion of the viral gene ICP34.5 improves tumor selectivity[1]
  - Addition of GALV-GP-R– to the HSV-1 backbone enhanced immunogenic cell death and induced regression of both injected and uninjected tumors in preclinical models[1]

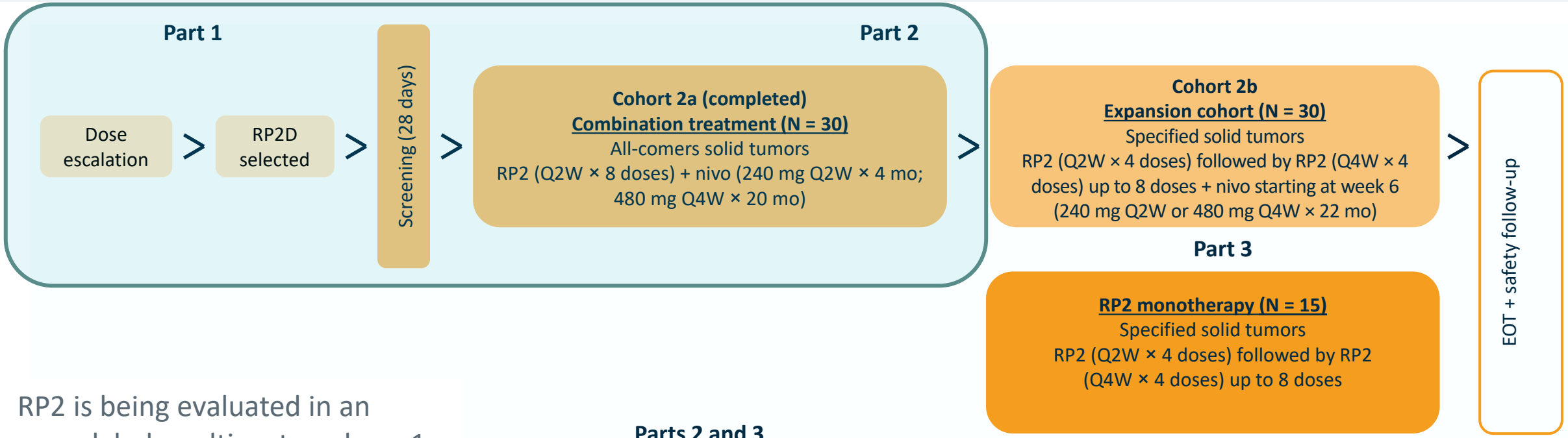


αCTLA-4, anti–CTLA-4; CTLA-4, cytotoxic T-lymphocyte antigen 4; GALV-GP-R–, gibbon ape leukemia virus glycoprotein with the R sequence deleted; GM-CSF, granulocyte-macrophage colony-stimulating factor; hGM-CSF, human granulocyte-macrophage colony-stimulating factor; HSV-1, herpes simplex virus type 1; ICP, infected cell protein; P, promoter; pA, polyA signal; US11, unique short 11; X, denotes inactivation of viral protein.

1. Thomas S, et al. *J Immunother Cancer*. 2019;7(1):214.

Methods

Study design



- 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)

Parts 2 and 3

Treatment period (24 mo)

Overall survival (up to 3 y from C1D1)

RP2 is administered via direct intratumoral injection into superficial/subcutaneous lesions or into deep/visceral lesions using image guidance (eg, ultrasound or CT)

The RP2D was identified as 1×10^6 PFU/mL once, followed by up to 7 doses of 1×10^7 PFU/mL per dosing day. A second course of up to 8 additional RP2 injections is permitted if prespecified criteria are met.
C1D1, cycle 1 day 1; CT, computed tomography; EOT, end of treatment; nivo, nivolumab; PD-1, programmed cell death protein 1; PFU, plaque-forming unit; Q2W, every 2 weeks; Q4W, every 4 weeks; RP2D, recommended phase 2 dose.

Objective and eligibility

- **Primary objective**: To assess the safety, tolerability, and ORR of RP2 alone and in combination with nivolumab

Key eligibility criteria

Inclusion

- Age ≥18 years
- Histologically or cytologically confirmed advanced or metastatic non-neurological solid tumors (including uveal melanoma)
- Progressed on or cannot tolerate standard therapy
- Must have ≥1 measurable and injectable tumor ≥1 cm in longest diameter (or shortest diameter of lymph nodes)
- ECOG PS 0–1

Exclusion

- Prior treatment with OI
- Known history of hepatitis B (hepatitis B surface antigen reactive), hepatitis C virus (hepatitis C RNA detected), or HIV infection
- Active significant herpetic infections or prior complications of HSV-1 infection
- Known active CNS metastases and/or carcinomatous meningitis
- 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; HIV, human immunodeficiency virus; HSV-1, herpes simplex virus type 1; OI, oncolytic immunotherapy; ORR, objective response rate.

Uveal melanoma: 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)

- Here, we present updated safety and efficacy data of RP2 ± nivolumab in a subset of patients with uveal melanoma
- As of August 2023, 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

[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.

Uveal melanoma: Efficacy findings

	RP2 monotherapy (n = 3)	RP2 + nivolumab (n = 14)	Total (N = 17)
Best overall response, n (%)			
CR	0	0	0
PR	1 (33.3)	4 (28.6)	5 (29.4)
SD	0	5 (35.7)	5 (29.4)
PD	1 (33.3)	4 (28.6)	5 (29.4)
ORR (CR + PR)	**1 (33.3)**	**4 (28.6)**	**5 (29.4)**
DCR (CR + PR + SD)	1 (33.3)	9 (64.3)	10 (58.8)

- **ORR:** 29.4% (all PRs)
- **DCR:** 58.8%
- **Median (range) DOR** at the data cutoff: 11.47 (2.78–21.22)[a] months

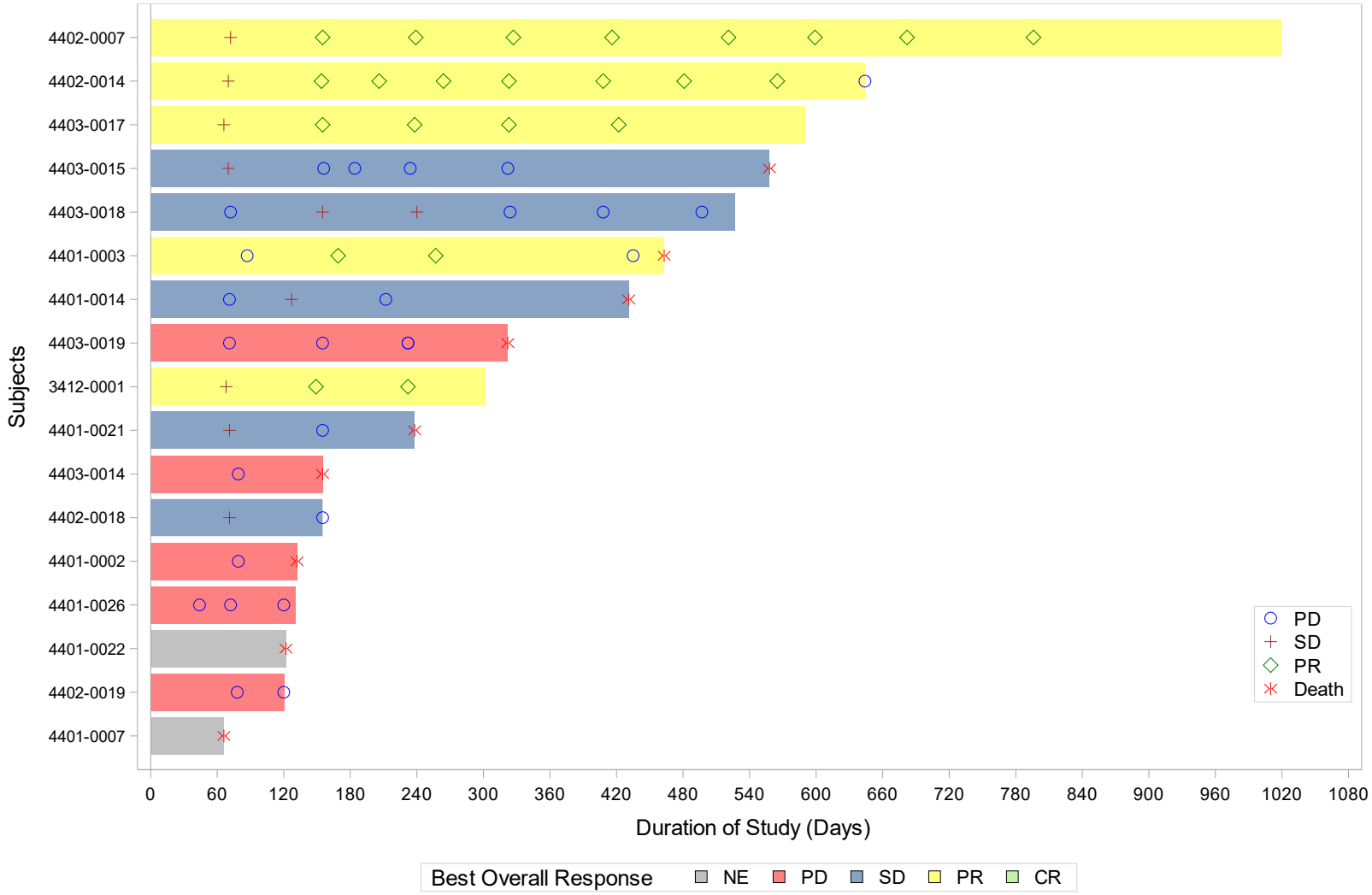
[a]Response is ongoing.
CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Patients with uveal melanoma dosed with RP2

Patient #	RP2 monotherapy or combination with nivolumab	Prior therapies	Sites of disease	Best response
4401-0002	Monotherapy	Ipilimumab + nivolumab, temozolomide, selumetinib + vistusertib, carboplatin, paclitaxel	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	Liver metastasis resection	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	Liver metastasis resection	Liver	SD
4402-0019	Combination	Ipilimumab, pembrolizumab	Liver, perirenal	PD
4403-0018	Combination	Nivolumab + ipilimumab	Liver	SD
4403-0019	Combination	Ipilimumab + nivolumab	Liver	PD
3412-0001	Combination	Ipilimumab + nivolumab, IL-2, carboplatin, paclitaxel	Liver, lung	PR

Red outlined boxes indicate responding patients.
IL, interleukin; PD, progressive disease; PR, partial response; SCF, supraclavicular fossa nodal failure; SD, stable disease.

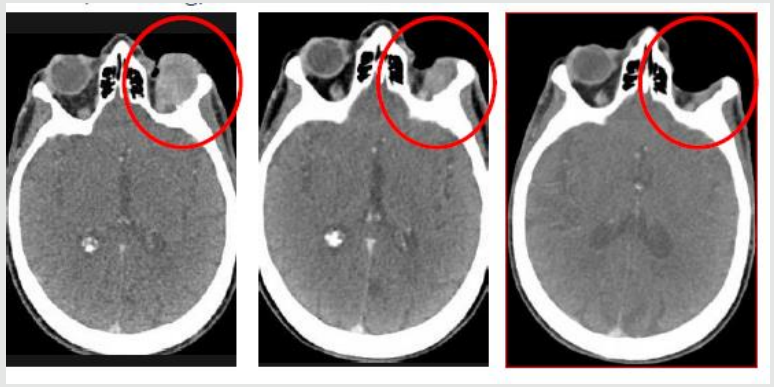
Uveal melanoma: Duration of response



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

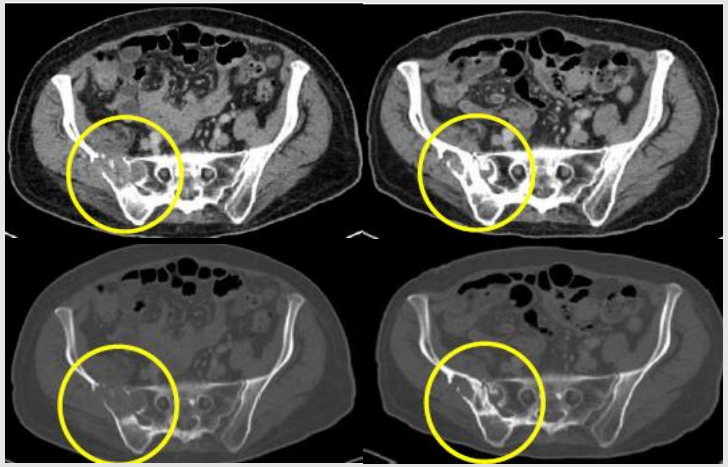
Patient who progressed on prior nivolumab (RP2 + nivolumab)

Sep 30, 2020 (screening) | Dec 29, 2020 | Jun 9, 2022



Oct 19, 2020 (baseline) | Jan 27, 2021

Sep 30, 2020 (screening) | Jun 9, 2022



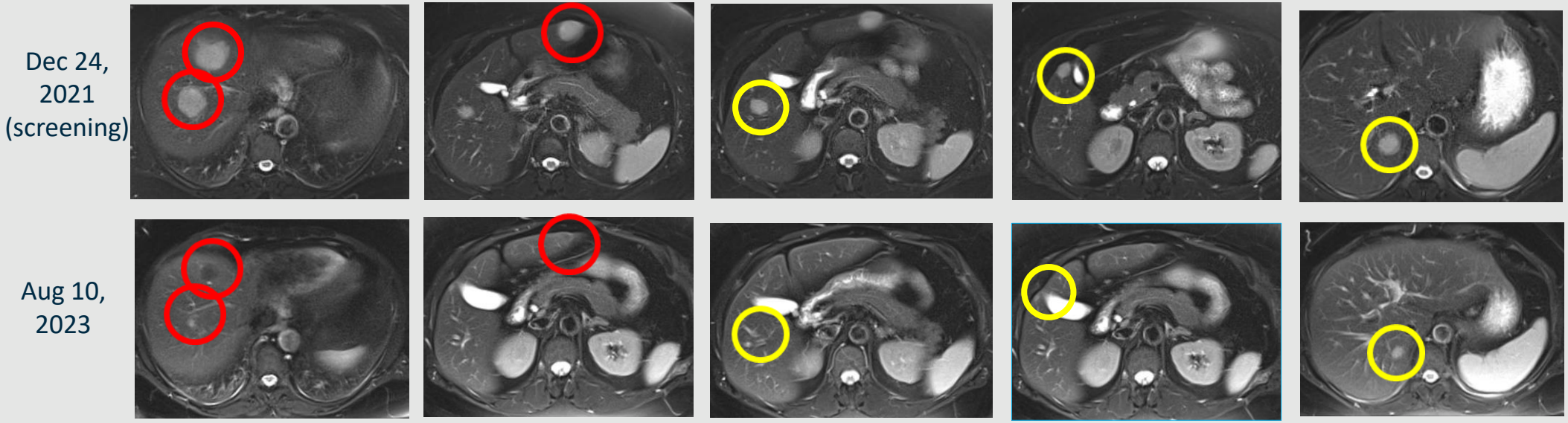
Patient 201-4402-0007: PR

- Orbital mass and additional metastases to the 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

Injected | Uninjected

CR, complete response; PR, partial response.

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 19 months

Injected

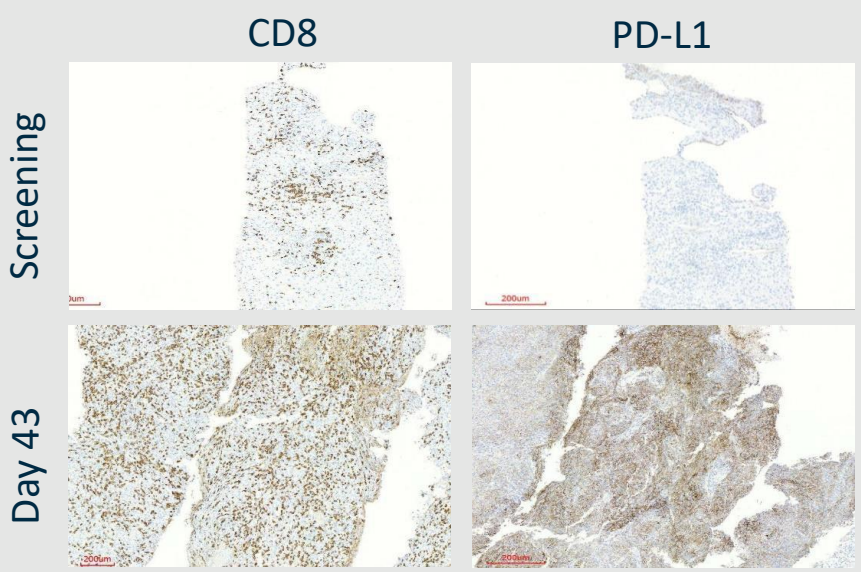
Uninjected

PR, partial response.

RP2 + nivolumab generated local and systemic anti-tumor immune response

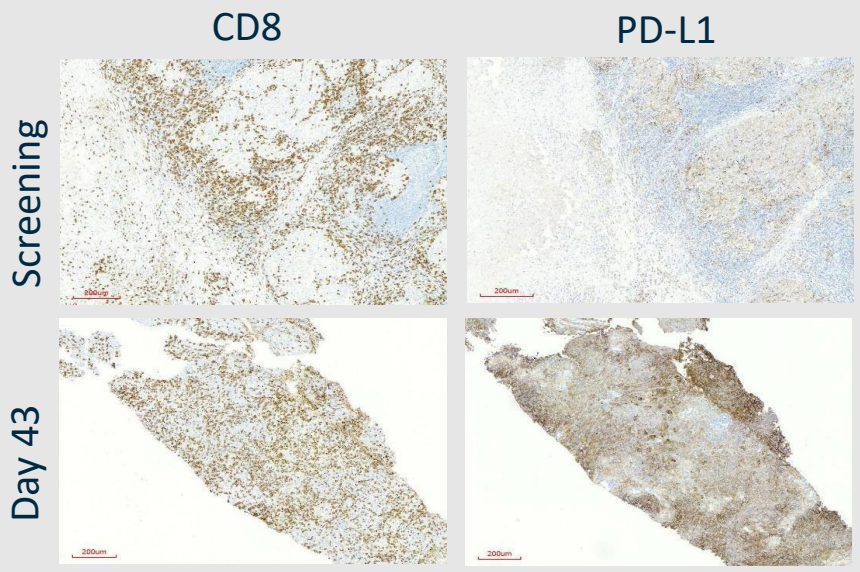
Immunohistochemistry of day 43 tumor biopsy

Substantial increase in CD8 T cell infiltration and PD-L1 expression



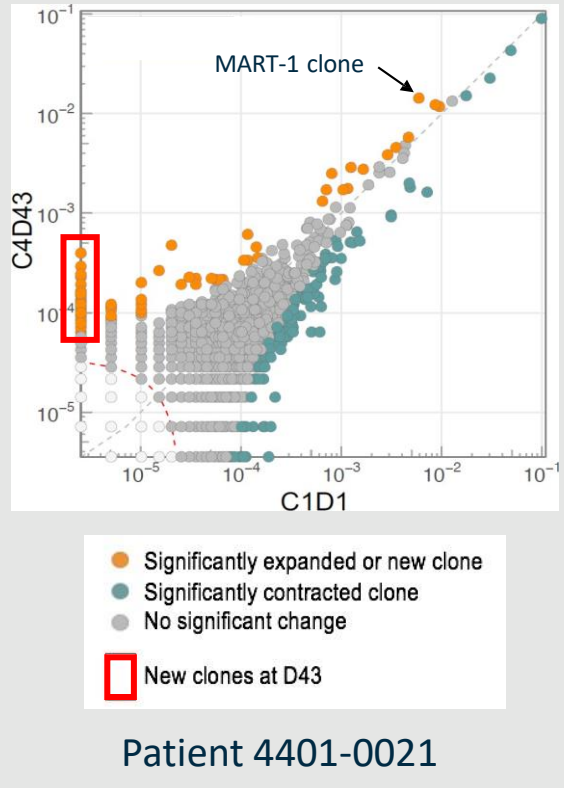
Patient 4403-0015

Discordant CD8 and PD-L1 staining at baseline changing to concordant staining at day 43



Patient 4402-0014

TCR sequencing of PBMCs



Patient 4401-0021

- IHC shows increases in CD8+ T cells and PD-L1 expression levels in tumor biopsies
- TCR sequencing of PBMCs demonstrates expansion of T cell clones

IHC, immunohistochemistry; MART-1, melanoma antigen recognized by T cells 1; PBMC, peripheral blood mononuclear cell; PD-L1, programmed death-ligand 1; TCR, T-cell receptor

Results

Uveal melanoma: Safety profile

Patients with TRAEs	Grade 1–2[a]	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)	13 (92.9)	6 (42.9)[b]	0
Pyrexia	10 (71.4)	0	0
Chills	7 (50.0)	0	0
Fatigue	4 (28.6)	0	0
Pruritus	4 (28.6)	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

- The most common grade 1 or 2 TRAEs (≥20%) overall in both cohorts combined were pyrexia, chills, fatigue, hypotension, and pruritis
- There were no grade 4 or 5 TRAEs

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% of patients are shown.
[b]For the combination therapy cohort, additional grade 3 TRAEs of alanine aminotransferase increase, arthralgia, diarrhea, gamma-glutamyltransferase increase, immune-mediated hepatitis, and lipase increase were reported in 1 patient each.
TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Conclusions

- Metastatic uveal melanoma is an immunologically “cold” tumor type that has few effective treatment options[1]
- **Preliminary data** from RP2 monotherapy and RP2 + nivolumab demonstrate a **favorable safety profile and durable antitumor activity** in **metastatic uveal melanoma**, including in patients with both liver and extra-hepatic metastases
- These data **continue to support** the hypothesis that intratumoral oncolytic immunotherapy expressing an anti–CTLA-4 antibody, in combination with an anti–PD-1 agent, may provide clinically meaningful benefits and a favorable toxicity profile in patients with advanced, immune checkpoint inhibitor-resistant malignancies

CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein 1.

1. Jager MJ, et al. *Nat Rev Dis Primers*. 2020;6(1):24.

Acknowledgements

- We would like to thank the patients for their participation in the trial, as well as their family members
- We would also like to thank the site staff and principal investigators for their critical contributions to this study

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).