2024 ASCO® ANNUAL MEETING

# SAFETY, EFFICACY, AND BIOMARKER RESULTS FROM AN OPEN-LABEL, MULTICENTER, PHASE 1 STUDY OF RP2 ALONE OR COMBINED WITH NIVOLUMAB IN A COHORT OF PATIENTS WITH UVEAL MELANOMA

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# Key takeaways

## Efficacy

- RP2 as monotherapy or combined with nivolumab was associated with **durable antitumor activity in a cohort of pretreated patients with metastatic uveal melanoma (n = 17),** with an **objective response rate of 29.4%** and **disease control rate of 58.8%**

## Safety

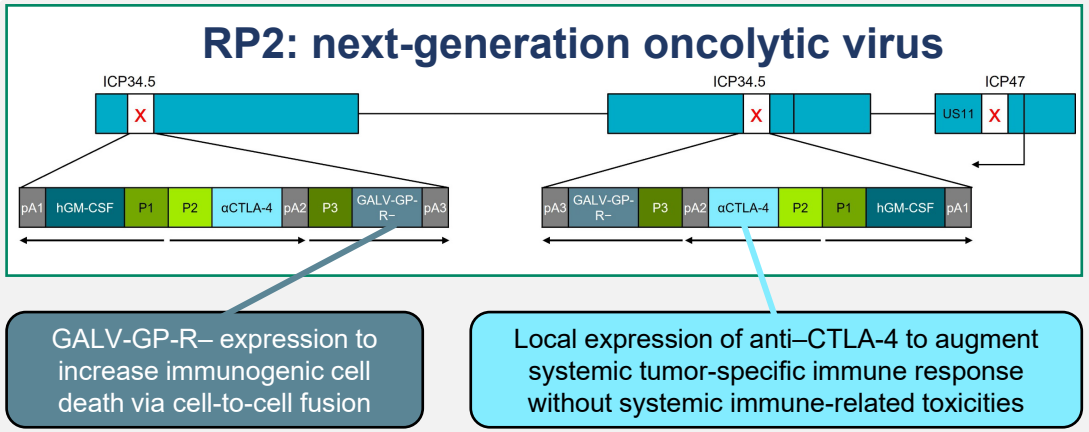
- The treatment showed a favorable safety profile, including in the majority of patients who underwent intrahepatic injection; treatment-related adverse events were mostly grade 1 or 2, with no grade 4 or 5 events observed

# Background: Uveal melanoma and RP2

- Uveal melanoma (UM) is the most common form of ocular primary malignancy, accounting for ~5% of all melanomas[1-4]
  - ~50% of patients develop distant metastases[1,2]
    - ~90% to the liver[1,2]
    - After metastasis, median OS is ~1 year[1,5]
- Metastatic UM is immunologically "cold" and does not respond well to immunotherapy[1]
  - Single-agent ICIs exhibit low response rates (<10%)[6]
  - ICI combination therapies show slightly higher response rates (12%–18%) at the expense of significant toxicities[7,8]
- While tebentafusp and HEPZATO KIT™ have been licensed for metastatic UM, both apply to select patient populations and survival benefit remains modest

***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*

## RP2: next-generation oncolytic virus

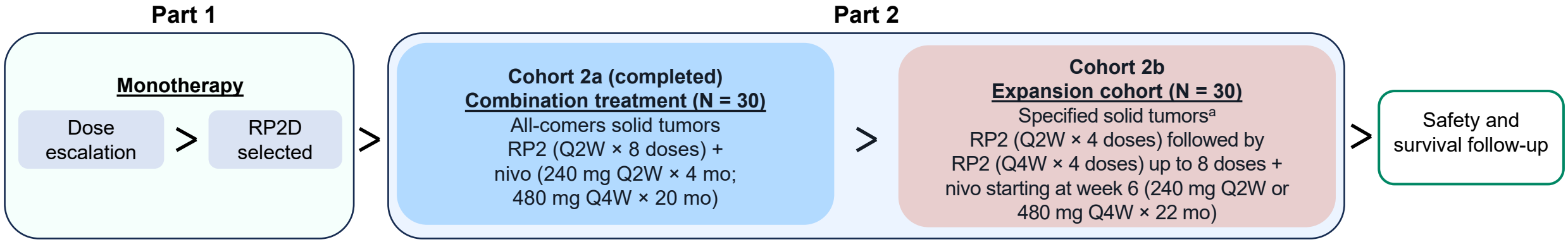



**RP2** is a genetically modified HSV-1 that encodes GM-CSF, the fusogenic protein GALV-GP-R–, and an anti–CTLA-4 antibody-like molecule[9]

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 GM-CSF; HSV-1, herpes simplex virus type 1; ICI, immune checkpoint inhibitor; ICP, infected cell protein; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 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. Wessely A, et al. *Int J Mol Sci* . 2020;21(3):879. 7. Piulats A, et al. *J Clin Oncol*. 2021;39(6):586-98. 8. Pelster M, et al. *J Clin Oncol*. 2021;39(6):599-607. 9. Thomas S, et al. *J Immunother Cancer*. 2019;7(1):214.

# Methods: Study design




## RP2 administration

RP2 is administered via direct intratumoral injection into:

- Superficial/subcutaneous lesions, or
- Deep/visceral lesions using image guidance (eg, ultrasound or CT)

## Key eligibility criteria

### Inclusion

- Age ≥18 years
- Advanced or metastatic non-neurological solid tumors **(including uveal melanoma)**
- Progressed on or cannot tolerate standard therapy
- At least 1 measurable and injectable tumor ≥1 cm
- ECOG PS 0–1

### Exclusion

- Prior treatment with OI
- History of HBV, HCV, or HIV infection
- Active significant herpetic infections/ prior complications of HSV-1 infection
- Active CNS metastases and/or carcinomatous meningitis
- Major surgery ≤2 weeks prior to starting study drug[b]

## Key endpoints

**Primary**

- Safety/tolerability of RP2 ± nivo (TEAEs, SAEs)
- ORR with RP2 ± nivo

**Secondary**

- DOR, CR rate, DCR, and PFS
- One- and 2-year OS

**Exploratory**

- Biomarker analyses

For part 2, the treatment period lasts up to 24 months. OS will be recorded for up to 3 years from cycle 1 day 1. The RP2D was identified as $1 \times 10^6$ PFU/mL once, followed by up to 7 doses of $1 \times 10^7$ PFU/mL per dosing day. A second course of up to 8 additional RP2 injections is permitted if prespecified criteria are met.

[a]Patients in cohort 2b must have histologically or cytologically confirmed diagnosis of advanced or metastatic uveal melanoma, lung cancer, breast cancer, squamous cell carcinoma of the head and neck, or gastrointestinal cancers (including but not limited to colorectal cancer [microsatellite stable], hepatic cellular carcinoma, and gastric, gastroesophageal junction, or esophageal cancers). [b]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; CR, complete response; CT, computed tomography; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV-1, herpes simplex virus type 1; nivo, nivolumab; OI, oncolytic immunotherapy; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; PFU, plaque-forming unit; Q2W, every 2 weeks; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; SAE, serious adverse event; TEAE, treatment-emergent adverse event.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# Results: Uveal melanoma patient demographics and baseline characteristics

- Overall, 17.6% (3/17) of patients received ≥3 prior lines of therapy
- The majority of patients (70.6% [12/17]) received both prior anti–PD-1 and anti–CTLA-4 therapy

| | 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) |

Data cutoff: August 2023. [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: Clinical activity in uveal melanoma

- The ORR was 29.4% (all PRs) and DCR was 58.8%
  - At data cutoff, median (range) DOR was 11.5 (2.8–21.2)[a] months

| | 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) |
| NE[b] | 1 (33.3) | 1 (33.3) | 2 (11.8) |
| **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)** |

| HLA-A*02:01 status | Positive (n = 6) | Negative (n = 11) | Total (N = 17) |
|---|---|---|---|
| **Best overall response**, n (%) | | | |
| 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) |

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

[a]From first dose to disease progression; response is ongoing. [b]Two patients died before any assessment.
CR, complete response; DCR, disease control rate; DOR, duration of response; HLA, human leukocyte antigen; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.


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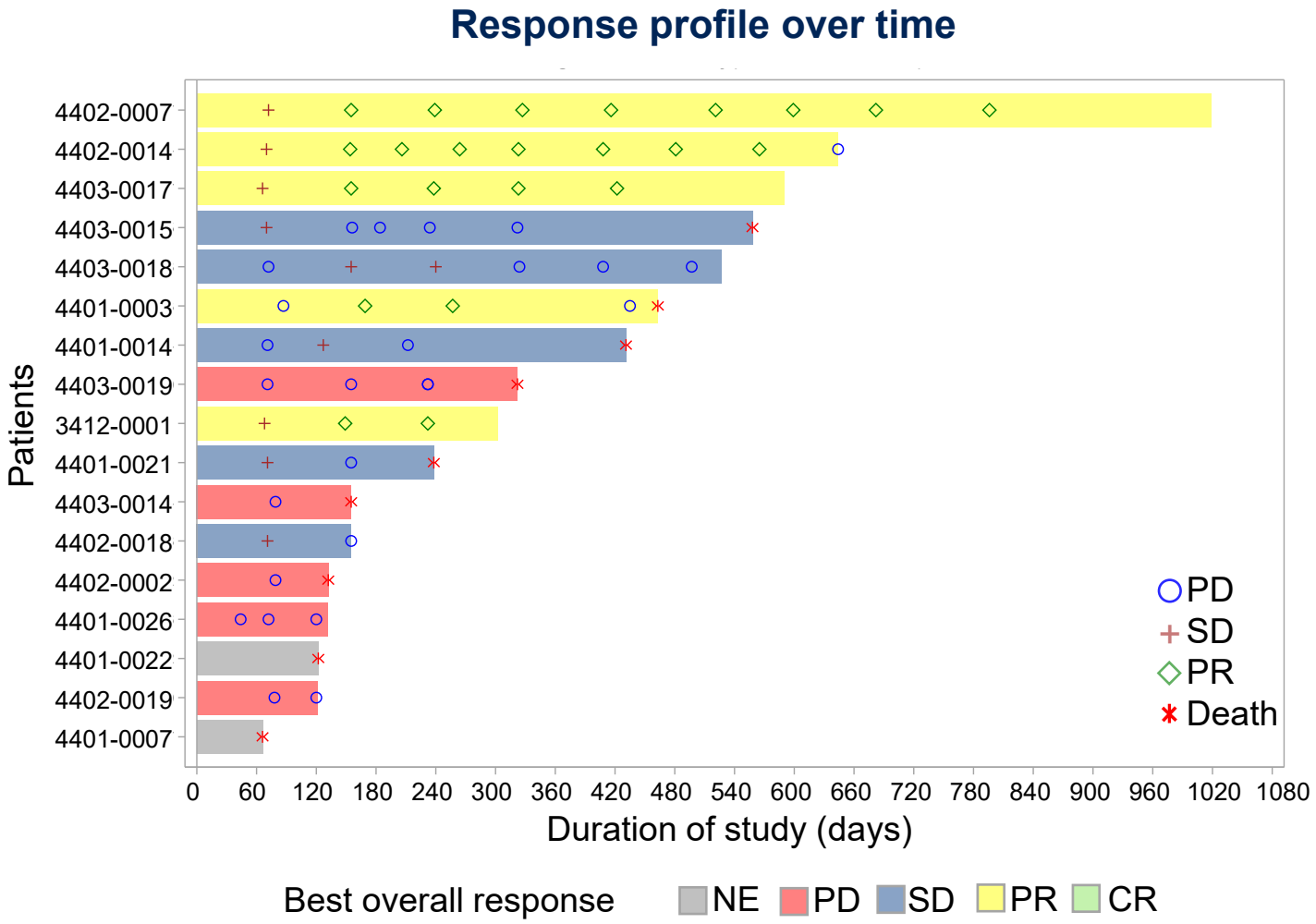
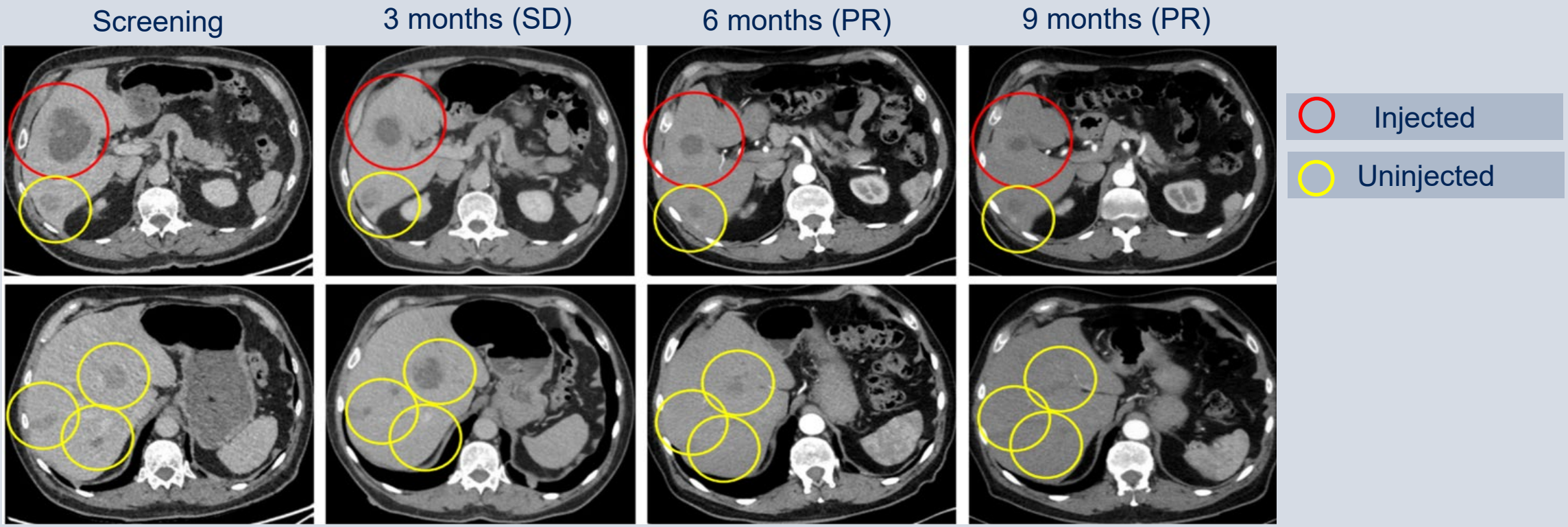
# Results: Clinical activity in uveal melanoma




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

# Results: Patient with liver metastases who progressed on prior ipilimumab and nivolumab and received RP2 monotherapy

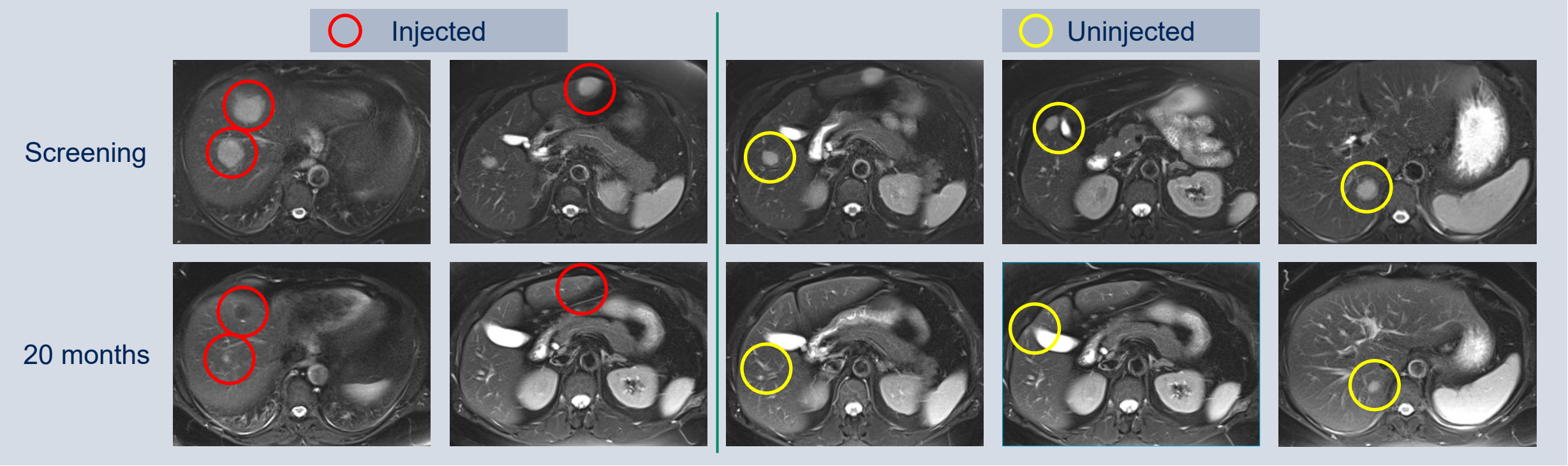
- **Patient 4401-0003**: PR




PR, partial response, SD, stable disease.

# Results: Patient with liver metastases who progressed on prior ipilimumab and nivolumab and received RP2 + nivolumab

- **Patient 4403-0017**: PR




PR, partial response.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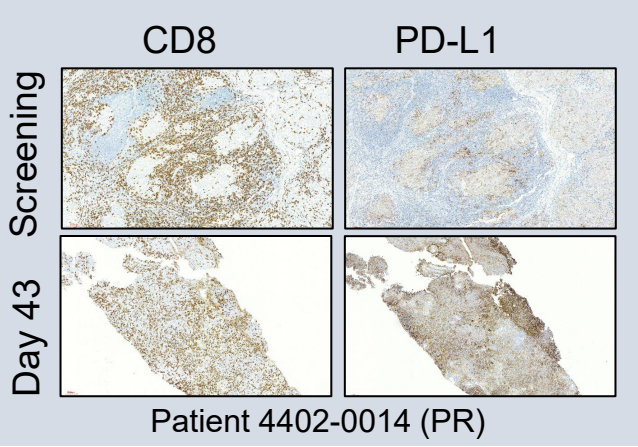
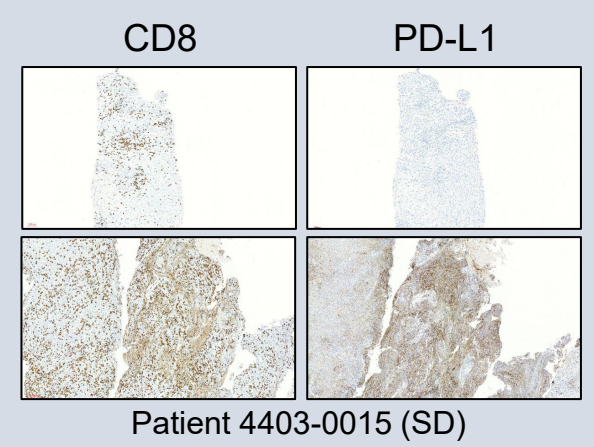
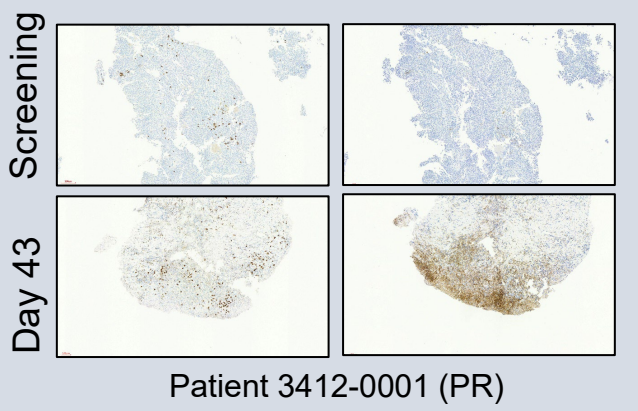
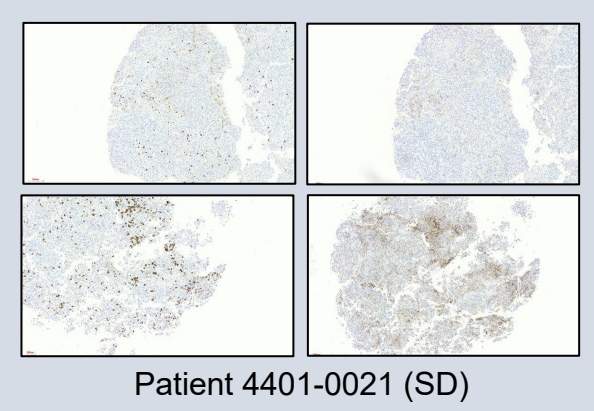
# Results: RP2 + nivolumab leads to immune activation

- IHC shows increases in CD8+ T cells and PD-L1 expression at day 43 in 4 evaluable tumor biopsies from patients treated with RP2 + nivolumab who achieved disease control

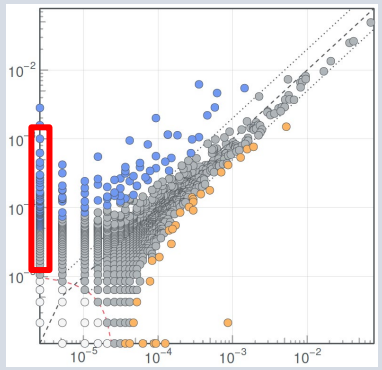


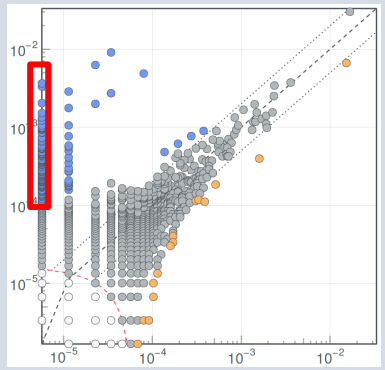



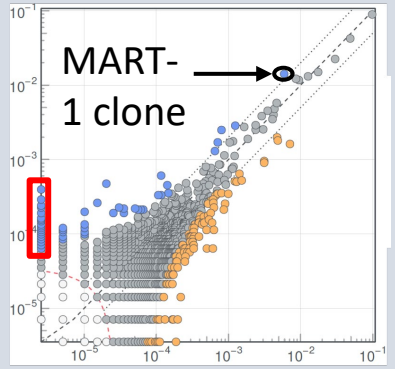



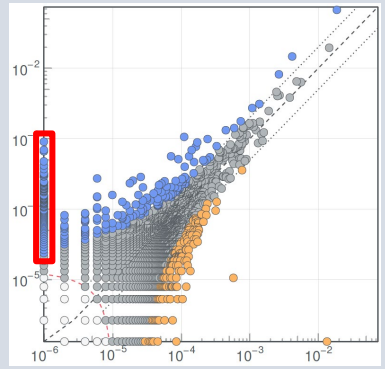



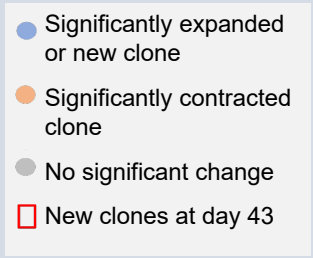

- TCR sequencing of PBMCs demonstrates expansion of existing T-cell clones and generation of new tumor-specific clones following treatment with RP2 + nivolumab




- Numerous clones that exhibited expansion were first identified on day 43
- Expansion of new or pre-existing clones in peripheral blood did not show correlation with clinical response

Day 43 biopsies were taken before nivolumab treatment was initiated.
IHC, immunohistochemistry; MART-1, melanoma-associated antigen recognized by T cells 1; PBMC, peripheral blood mononuclear cell; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; TCR, T-cell receptor.

# Results: Safety profile in uveal melanoma

| 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%) in both cohorts combined were pyrexia, chills, fatigue, hypotension, and pruritus
- Both cases of grade 3 hypotension were transient and readily managed with crystalloid repletion
- There were no grade 4 or 5 TRAEs
- In patients who underwent intrahepatic injections, there were no clinically significant bleeding events

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.
TRAE, treatment-related adverse event.

# Conclusions

- RP2 monotherapy or RP2 + nivolumab treatment resulted in an **ORR of 29.4%** and a **DCR of 58.8%** in a cohort of patients with metastatic uveal melanoma
- Clinical activity was seen regardless of HLA status or specific prior ICI regimen
- The data indicate a **favorable safety profile and durable antitumor activity** in metastatic uveal melanoma, both in patients with liver and extrahepatic metastases
- Biomarker data indicate increased **immune cell infiltration** and **increased PD-L1 expression in tumors** and changes in the peripheral T-cell repertoire following RP2 + nivolumab
- The data show that intratumoral oncolytic immunotherapy expressing an anti–CTLA-4 antibody, in combination with an anti–PD-1 agent, can provide **clinically meaningful benefit with a favorable toxicity profile** in patients with advanced, ICI-resistant malignancies
- Based on these results, **preparations are underway for a pivotal study**

CTLA-4, cytotoxic T-lymphocyte antigen 4; DCR, disease control rate; HLA, human leukocyte antigen; ICI, immune checkpoint inhibitor; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programed death-ligand 1.

# Acknowledgments


- 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 Vineetha Edavana, 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).