Abstract: 128628

Case report: Complete response in a patient with mucoepidermoid carcinoma of the parotid gland treated with RP2 oncolytic immunotherapy

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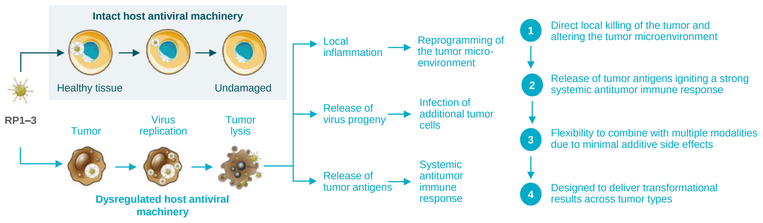
Background

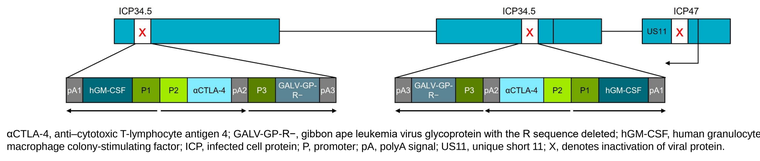
- Head and neck cancers were estimated to account for >50,000 new cancer diagnoses and >11,000 deaths in the US in 2022.[1]
- Salivary gland malignancies account for approximately 3% of all head and neck cancers and are histologically heterogeneous.[2]
- Mucoepidermoid carcinoma (MEC) is the most common malignancy of the major salivary glands, usually developing in the parotid gland and, less commonly, in the submandibular or sublingual glands.[3]
- High-grade MEC correlates with poor prognosis, owing to both locoregional recurrence and distant metastasis, even following adjuvant therapy.[4-6]
- Standards of care for malignant salivary gland tumors include adequate surgical resection and definitive irradiation; systemic therapies include chemotherapy regimens, targeted therapies, and/or immunotherapies (anti–programmed cell death protein 1 [PD-1]) in certain circumstances.[7]
- However, many patients do not benefit from these therapies and/or experience substantial toxicity.[7] Therefore, an unmet need exists for new approaches to the treatment of MEC and other rare head and neck cancers.
- Tumor-directed oncolytic immunotherapies (TDOIs) consist of naturally occurring or genetically modified viruses proposed to kill tumors via a dual mechanism of action (**Figure 1**)[8]:
  - Direct viral killing of the tumor and alteration of the tumor microenvironment.
  - Release of tumor antigens to potentially ignite a strong and durable systemic immune response.
- RP2 is the second agent in a platform of herpes simplex virus type 1 (HSV-1)–based TDOIs under clinical development (**Figure 2**); it is an enhanced potency, modified version of HSV-1 expressing human granulocyte-macrophage colony-stimulating factor, the fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP-R−), and an anti–cytotoxic T-lymphocyte antigen 4 antibody-like molecule (**Figure 2**).
- Clinical studies demonstrate preliminary activity of RP2 in advanced solid tumors as monotherapy (**Figure 3A**) or in combination with nivolumab (anti–PD-1; **Figure 3B**).
- RP2 administered alone or in combination with nivolumab is generally well tolerated, causing low-grade toxicities, and showing little or no overlapping toxicities with those of chemotherapy and other common anti-cancer modalities.
- Here we report a durable complete response (CR) in a patient with recurrent inoperable MEC of the left parotid gland treated with RP2 monotherapy.

Figure 1. Proposed dual mechanism of action of TDOI



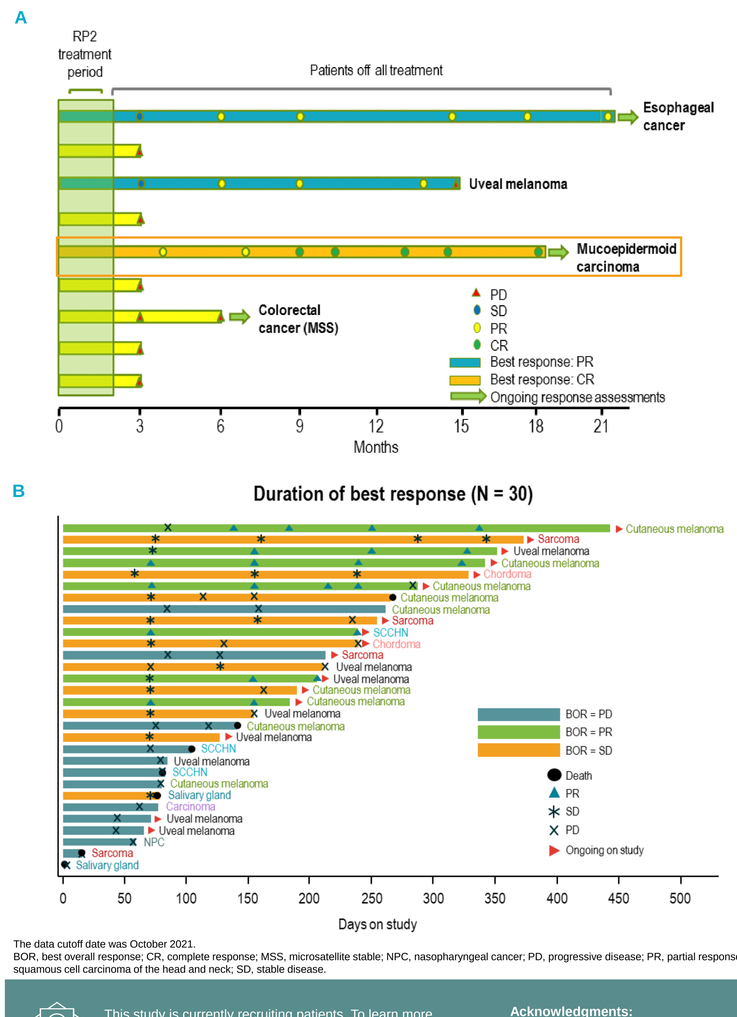
TDOI, tumor-directed oncolytic immunotherapy.

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.

Figure 3. Clinical activity of (A) RP2 monotherapy and (B) RP2 + nivolumab in advanced tumor types



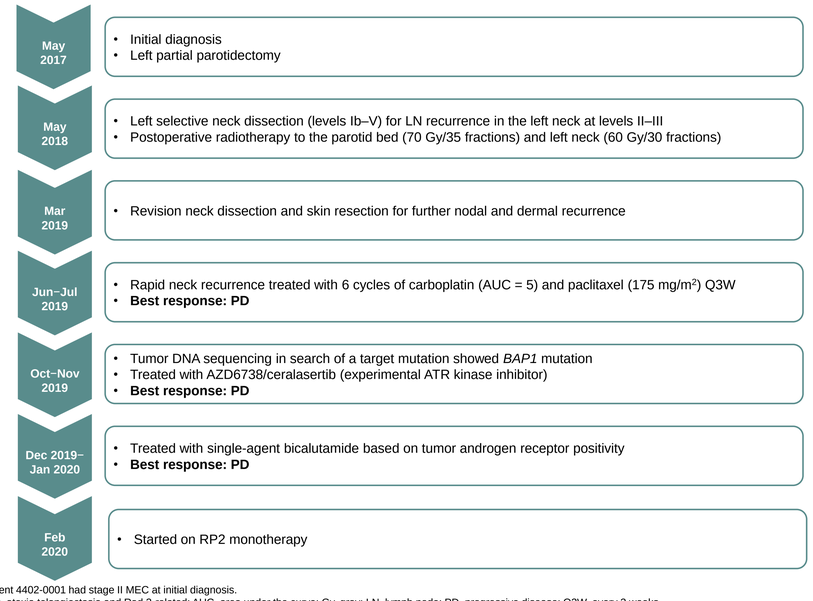
The data cutoff date was October 2021.
BOR, best overall response; CR, complete response; MSS, microsatellite stable; NPC, nasopharyngeal cancer; PD, progressive disease; PR, partial response; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease.

Case description

Oncologic history and clinical course

- Patient 4402-0001 is a 36-year-old male who was diagnosed in May 2017 with stage II MEC of the left parotid gland.
- Despite multiple resections, definitive radiation, several rounds of systemic treatment with combination chemotherapy, and 2 different targeted therapies (genetically driven treatments targeting specific tumoral mutations), progressive disease was consistently observed.
- The oncologic history and clinical course are illustrated in **Figure 4**.
- RP2 monotherapy was initiated 33 months after initial diagnosis, as part of an ongoing phase 1, multicenter, open-label, first-in-human trial (NCT04336241)[9]:
  - Five intratumoral injections were administered every 2 to 3 weeks over 2 months to all target lesions in the left cervical lymph node chain and left supraclavicular fossa (**Table 1**).

Figure 4. Timeline of oncologic history and clinical course prior to RP2 monotherapy



Patient 4402-0001 had stage II MEC at initial diagnosis.
ATR, ataxia telangiectasia and Rad 3-related; AUC, area under the curve; Gy, gray; LN, lymph node; PD, progressive disease; Q3W, every 3 weeks.

Table 1. RP2 monotherapy treatment regimen

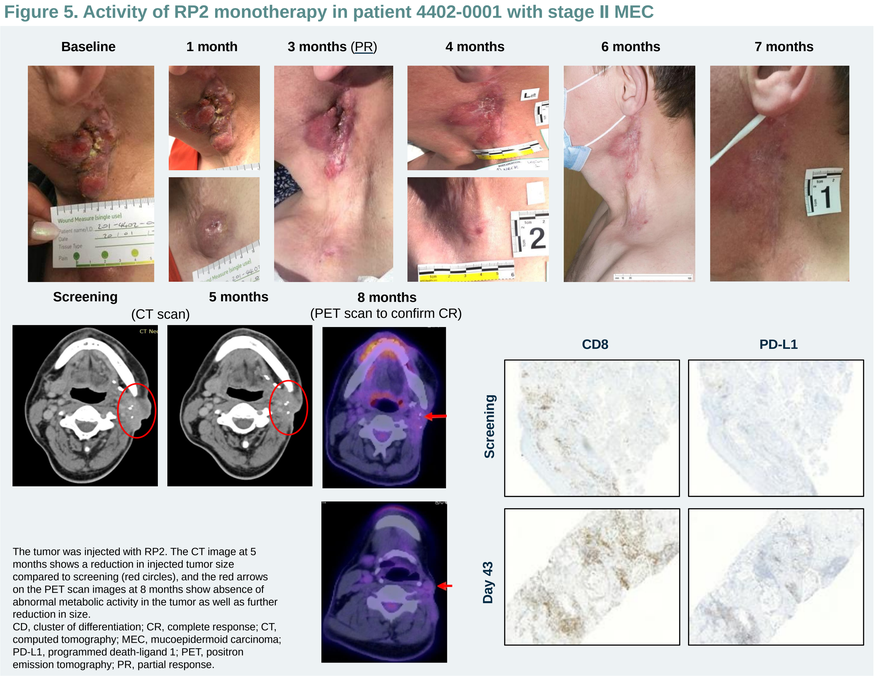
Injection number	Timing	Location	Volume
1	02/18/2020	LCLN LSCF	4 mL 6 mL
2	03/03/2020	LCLN LSCF	4 mL 6 mL
3	03/24/2020	LCLN LSCF	5 mL 5 mL
4	04/07/2020	LCLN LSCF	5 mL 5 mL
5	04/28/2020	LCLN LSCF	7 mL 3 mL

LCLN, left cervical lymph node; LSCF, left supraclavicular fossa.

Activity of RP2 monotherapy

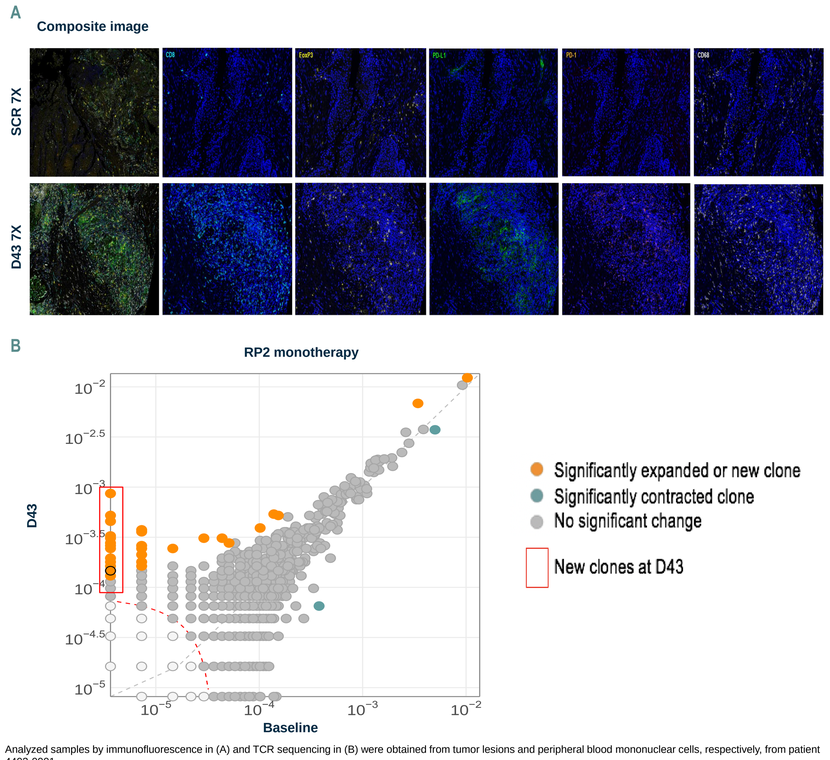
- A partial response (PR) per Response Evaluation Criteria in Solid Tumors version 1.1 was observed 3 months after the first RP2 injection, with a 31% reduction in target lesion size and a further lesion size reduction at 6 months (61%; **Figure 5**).
- Functional positron emission tomography-computed tomography (PET-CT) scan showed no evidence of disease at 8 months (functional CR; 64% reduction in lesion size; **Figure 5**).
- Fifteen months after the first RP2 injection, the patient achieved a CR, which was ongoing at the last follow-up (May 2023; overall duration of response >35 months). The patient remains in clinical and metabolic CR, in addition to radiographic CR.
- Immunohistochemistry of day 43 biopsies demonstrated a striking influx of CD8+ T cells compared to screening, indicative of a reversal of baseline T-cell exclusion (**Figure 5**).
  - RP2 monotherapy induced remodeling of the tumor microenvironment as well as an expansion of existing T-cell clones and the generation of new tumor-specific T-cell clones (**Figure 6**).

Figure 5. Activity of RP2 monotherapy in patient 4402-0001 with stage II MEC



The tumor was injected with RP2. The CT image at 5 months shows a reduction in injected tumor size compared to screening (red circles), and the red arrows on the PET scan images at 8 months show absence of abnormal metabolic activity in the tumor as well as further reduction in size.
CD, cluster of differentiation; CR, complete response; CT, computed tomography; MEC, mucoepidermoid carcinoma; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PR, partial response.

Figure 6. RP2 monotherapy (A) modulates tumor microenvironment and (B) promotes T-cell immunity



Analyzed samples by immunofluorescence in (A) and TCR sequencing in (B) were obtained from tumor lesions and peripheral blood mononuclear cells, respectively, from patient 4402-0001.
CD, cluster of differentiation; D, day; FoxP3, forkhead box P3; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SCR, screening; TCR, T-cell receptor.

Tolerability

- All adverse events (AEs) were nonserious and grade 1/2 in severity (**Table 2**).
- AEs assessed as unrelated to RP2 treatment included wound hemorrhage, decreased appetite, neck pain, cough, dysphonia, and gastroesophageal reflux disease (GERD); most resolved quickly, except cough and dysphonia (103 and 193 days, respectively) and GERD (unresolved at last follow-up; **Table 2**).
- AEs assessed as potentially related to RP2 included fatigue, pyrexia, and influenza-like illness and rapidly resolved, except fatigue (124 days; **Table 2**).

Table 2. AE occurrence following RP2 monotherapy

Preferred term	Start date/time of AE	Standard toxicity grade	Outcome	Causality	Duration, days
Wound hemorrhage	02/17/2020	Grade 1	Resolved	Not related to RP2	1
Pyrexia	02/18/2020	Grade 1	Resolved	Related to RP2	2
Influenza-like illness	02/18/2020	Grade 2	Resolved	Related to RP2	2
Fatigue	02/20/2020	Grade 2	Resolved	Related to RP2	124
Pyrexia	03/03/2020	Grade 2	Resolved	Related to RP2	1
Influenza-like illness	03/03/2020	Grade 2	Resolved	Related to RP2	1
Influenza-like illness	03/04/2020	Grade 1	Resolved	Related to RP2	2
Cough	03/12/2020	Grade 2	Resolved	Not related to RP2	103
Neck pain	04/06/2020	Grade 1	Resolved	Not related to RP2	47
Decreased appetite	04/13/2020	Grade 1	Resolved	Not related to RP2	71
Influenza-like illness	04/28/2020	Grade 1	Resolved	Related to RP2	2
Dysphonia	05/22/2020	Grade 1	Resolved	Not related to RP2	193
Gastroesophageal reflux disease	06/22/2020	Grade 2	Unresolved	Not related to RP2	—

None of the AEs were serious events.
AE, adverse event.

Conclusions

- RP2 monotherapy induced a durable CR in a patient with recurrent inoperable MEC of the parotid gland after disease progression on multiple prior therapies.
- Observed AEs were nonserious and grade 1/2 in severity.
- The expansion portion of the phase 1 study of RP2 as monotherapy or in combination with nivolumab in advanced solid tumor malignancies is ongoing and recruiting patients.

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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Presenter disclosure:
David M. Cohan is an employee and shareholder of Replimune, Inc., Woburn, MA, USA.

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