# Immunological Impact of Canerpaturev (C-REV, formerly HF10), an Oncolytic Viral Immunotherapy, with or without Ipilimumab for Advanced Solid Tumor Patients

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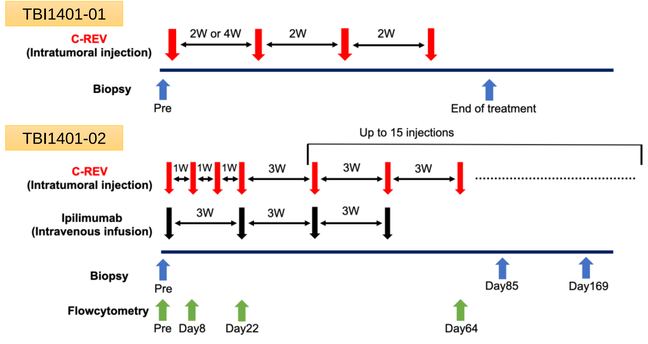
## Background

- Canerpaturev (C-REV), an oncolytic, spontaneous mutant of Herpes Simplex Virus type 1 (HSV-1), is a cancer immunotherapy agent that combine direct tumor cell killing with immune modulation.
- A phase I study for solid tumors with cutaneous and/or superficial lesions treated with C-REV monotherapy and a phase II study for unresectable or metastatic melanoma treated with C-REV and Ipilimumab combination therapy were conducted.
- This study was conducted to investigate the immune profile after C-REV injections and its correlation with the tumor response.

## Methods

- A phase I study (TBI1401-01: n=6) included solid tumor patients with cutaneous and/or superficial lesions treated with C-REV monotherapy (1 x $10^6$ and 1 x $10^7$ $TCID_{50}$/mL/dose; 4 injections q2-4wk).
- In phase II study (TBI1401-02: n = 28), C-REV (1 x $10^7$ $TCID_{50}$/mL/dose; 4 injections q1wk; then up to 15 injections q3wk) was injected into each tumor for advanced melanoma patients who were refractory or intolerant to prior therapies. Four Ipilimumab infusions (3 mg/kg) were administered at q3wk.
- Immune-monitoring was conducted before and after treatment in tumor microenvironment using paired biopsy samples by multiplex immunohistochemistry (mIHC) and in peripheral blood by flow cytometry.

**Figure 1. Design of study protocol**




## Results

### TBI1401-01

**Table 1. Patient characteristics:** Samples were obtained from 5 of 6 patients

| Patient ID | Age | Sex | Cancer type | Stage | Previous treatment |
|---|---|---|---|---|---|
| 4181-001 | 73 | M | Sweat gland cancer | IV | Surgery, CDDP+ADM, FECOM, DTX |
| 4181-003 | 67 | F | Melanoma | IIIB | Surgery, IFNβ |
| 4181-004 | 76 | M | Squamous cell carcinoma | IV | Surgery, CPT-11 |
| 4181-006 | 54 | F | Conjunctival melanoma | IV | Surgery, Nivolumab, CBCDA+PTX, Ipilimumab |
| 4181-008 | 79 | F | Vulva melanoma | II | RTx |

FECOM: 5FU+CBDCA+VCR+EPI+MMC, RTx: Radiation

**Figure 2. The representative figure of mIHC in TBI1401-01 (ID: 4181-006)**

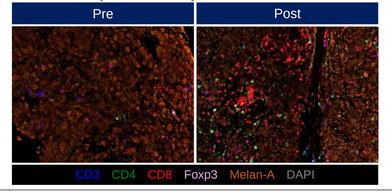
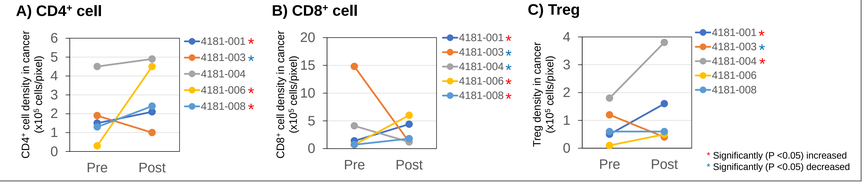



**Figure 3. The change of tumor infiltrating T cells after C-REV injection:** Significant infiltrations of CD8⁺and CD4⁺ T cells were observed at tumor local site in 3 (60%) of 5 patients.




### TBI1401-02

**Table 2. Best overall response by irRC**

| Best overall response | n (%) |
|---|---|
| irPR | 2 (7) |
| irSD | 14 (52) |
| irPD | 11 (41) |

*One patient did not have post injected evaluation of tumor size.
*Disease type: 39.3% acral lentiginous and 21.4% mucosal melanoma

**Table 3.**

| Patient ID | Age | Sex | Performance status | Stage | Previous treatment | Detection of HSV-1 virus at Day 85 or 169 | Best overall response | Survival period (days) |
|---|---|---|---|---|---|---|---|---|
| 1401-001 | 66 | F | 1 | IV | Surgery, RTx, IFNβ, Nivolumab, DTIC | - | irPD | 184 |
| 1401-002 | 31 | M | 0 | IIIc | Surgery, PEG-IFNα, Nivolumab, IFNβ | + | irSD | 458 |
| 1401-003 | 60 | M | 0 | IIIc | Surgery, IFNβ, Nivolumab | + | irPR | 446 |
| 1401-005 | 66 | M | 0 | IV | Surgery, PEG-IFNα, Nivolumab | + | irSD | 294 |
| 1401-006 | 63 | F | 1 | IV | Surgery, RTx, PEG-IFNα, Nivolumab, IFNβ | - | irPD | 124 |
| 1401-010 | 57 | M | 2 | IIIc | Surgery, RTx, PEG-IFNα, Nivolumab | + | irSD | 143 |
| 1401-013 | 56 | F | 0 | IV | Surgery, Pembrolizumab | - | irSD | 369 |
| 1401-016 | 67 | F | 0 | IV | Surgery, IFNβ, Nivolumab | + | irSD | 360 |
| 1401-018 | 69 | M | 0 | IIIc | Nivolumab | - | irSD | 269 |
| 1401-019 | 80 | F | 0 | IV | Surgery, DTIC, VCR, ACNU, IFNβ | - | irPD | 311 |
| 1401-027 | 71 | F | 0 | IIIc | Surgery, Nivolumab | - | irPD | 250 |

RTx: Radiation

**Table 3. The patient characteristics and treatment response:** Tumor biopsy samples (n = 11) revealed that five patients (45%) among 11 patients were confirmed persistent infection of C-REV at the injected site by qPCR. Disease control rate of patients with the virus DNA detected on Days 85/169 was higher than that without it (100% [n = 5, irPR; 1, irSD; 4] vs. 33% [n = 6, irSD; 2, irPD; 4]). Furthermore, average OS of patients with or without the DNA detected was 342 or 251 days respectively.

**Figure 4 Tumor volume change and CD4/CD8 density (Patient ID: 1401-003)**

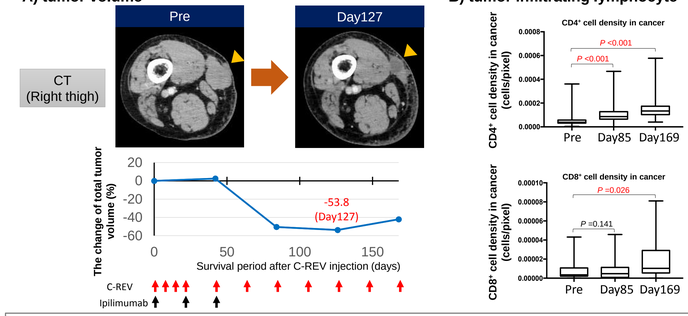
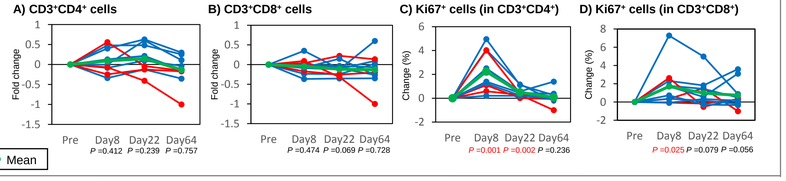



**Figure 5. Flowcytometry analysis of peripheral blood:** CD3⁺CD4⁺ cells and CD3⁺CD8⁺ cells were not increased after treatment (A, B) However, frequencies of Ki67⁺ cells in CD3⁺CD4⁺ and CD3⁺CD8⁺ cells were significantly increased at day 8 (C, D) compared with pretreatment blood sample.




## Conclusion

After C-REV monotherapy, significant infiltrations of CD8⁺ and CD4⁺ T cells were observed at tumor local site in 60% of patients. In combination with Ipilimumab, disease control rate of patients with persistent C-REV infection at the injected site was better than that without it. This observation suggests that C-REV injection contributed to prolonging survival.

## Acknowledgements

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