# Topline Results from Phase II of Combination Treatment with Canerpaturev (HF10), an Oncolytic Viral Immunotherapy, and Ipilimumab in Patients with Unresectable or Metastatic Melanoma after Anti-PD-1 Therapy

**# 1267P**

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## Introduction

Canerpaturev (C-REV, formerly HF10) is an oncolytic, spontaneous mutant of HSV-1, and is one of immunotherapies that combine direct tumor cell killing with immune modulation. Preclinical studies in tumor-bearing mouse model demonstrated that anti-CTLA-4 antibody with C-REV showed a higher rate of complete tumor disappearance and significant improvement in the median overall survival compared to either monotherapy. The Phase II trial of combination treatment with C-REV and ipilimumab (Ipi: anti-CTLA-4 antibody) was designed to assess the efficacy and safety of patients with pretreated unresectable or metastatic malignant melanoma .

## Methods

### Study Design

**SCREENING**

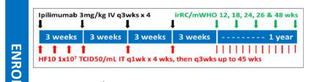
Key Eligibility Criteria
Patients with
- pretreated unresectable or metastatic melanoma (Stage IIIB, IIIC, or IV:AJCC 7th edition)
- Injectable/ measurable lesion
- Adequate organ function
- ECOG PS 0-2
- Expected life ≥ 24w
- No known bleeding diathesis or coagulopathy

**ENROLLMENT**

**ENROLLMENT**

Ipilimumab 3mg/kg IV

C-REV up to 5 mL
1x10$^7$ TCID$_{50}$/mL IT




Primary endpoint:
- Best overall response rate by irRC at week 24

Key secondary endpoints:
- Safety and tolerability
- Objective response rate by irRC, mWHO criteria and RECIST (Ver.1.1)
- Progression-free survival

**END OF TREATMENT**

**FOLLOW-UP**

## Results

| Analysis set, n | Enrollment, 28 | Safety analysis set, 28 | Efficacy analysis set, 27* |
|---|---|---|---|

*Did not have a post baseline tumor assessment; n=1

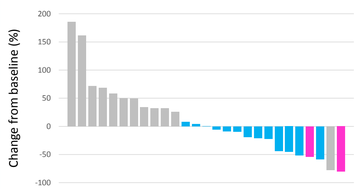
| Patient Characteristics (N=28) | n (%) |
|---|---|
| Sex – n (%) Female / Male | 16 (57%) / 12 (43%) |
| Age, median (min, max) -years | 67 (31, 81) |
| Elderly – n (%) < 65 / 65 ≤ | 11 (39.3%) / 17 (60.7%) |
| ECOG-PS –n(%) 0 / 1 / 2 | 23 (82.1%) / 4 (14.3%) /1 (3.6%) |
| Disease stage (AJCC 7th edition) –n(%) | |
| IIIB / IIIC / IV | 2 (7.1%) / 8 (28.6%) / 18 (64.3%) |
| M0 /M1a / M1b / M1c | 10 (35.7%) /6 (21.4%) / 2 (7.1%) /10 (35.7%) |
| Prior anti-cancer therapies –n(%) | |
| Anti-PD1 ab / Except for Anti-PD1 ab | 25 (89.3%) / 3 (10.7%) |
| Clinical Type –n (%) | |
| ALM / NM / SSM / Mucosal | 11 (39.3%) / 5 (17.9%) / 3 (10.7%) / 6 (21.4%) |

## Phase II Overall Results

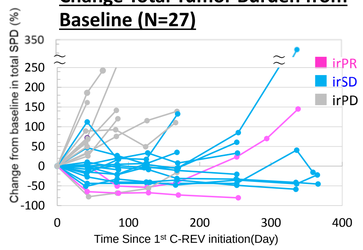
### Safety Summary (N=28)

| Treatment-Emergent Adverse Events (TEAEs) | n (%) |
|---|---|
| Any grade TEAEs | 28 (100.0%) |
| Grade 3 or 4 TEAEs | 14 (50.0%) |
| Any Severe TEAEs | 16 (57.1%) |
| Grade 3 or 4 C-REV + Ipi-Related TEAEs | 10 (35.7%) |
| Grade 3 or 4 C-REV-Related TEAEs | 6 (21.4%) |
| Grade 3 or 4 Ipi-Related TEAEs | 10 (35.7%) |
| TEAEs-Related death | 0 (0.0%) |

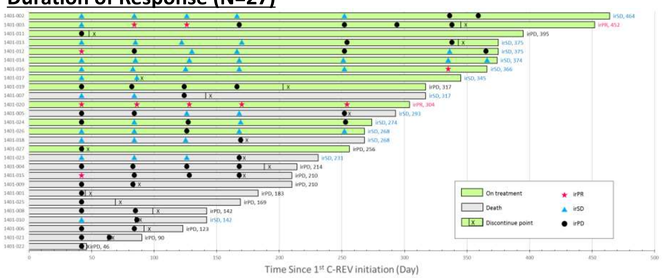
### Best Percent Changes of Tumor Burden in Total Tumor (N=27)




### Change Total Tumor Burden from Baseline (N=27)




### Duration of Response (N=27)




### Incidence of Study Treatment-Related ≥ Grade 3 TEAEs (N=28)

| TEAEs | n (%) |
|---|---|
| Hyponatraemia | 3 (10.7%) |
| Adrenal insufficiency | 2 (7.1%) |
| Colitis | 1 (3.6%) |
| Amylase increased | 1 (3.6%) |
| Constipation | 1 (3.6%) |
| Hepatic function disorder | 1 (3.6%) |
| Lipase increased | 1 (3.6%) |
| Malaise | 1 (3.6%) |
| Muscle weakness lower limb | 1 (3.6%) |
| Nausea | 1 (3.6%) |
| Toxicoderma | 1 (3.6%) |
| White blood cell decreased | 1 (3.6%) |

### Efficacy Summary (N=27)

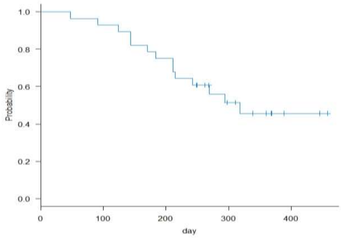
| Overall Response - irRC | n (%) |
|---|---|
| Objective Response Rate (ORR*) / 90% CI | 2 (7.4%) /1.3-21.5 |
| Disease Control Rate (DCR**) / 90% CI | 15 (55.6%) / 38.2-72.0 |
| **Best Overall Response Rate (BORR)** | |
| Complete Response (irCR) | 0 (0.0%) |
| Partial Response (irPR) | 2 (7.4%) |
| Stable Disease (irSD) | 13 (48.2%) |
| Unconfirmed Progressive Disease (unconfirmed irPD) | 6 (22.2%) |
| Confirmed Progressive Disease (confirmed irPD) | 6 (22.2%) |

*ORR: irCR + irPR, **DCR: irCR + irPR + irSD

### Subgroup Analysis: M-Stage, Clinical Type (N=27)

| | n | irPR n (%) | irSD n (%) | irPD n (%) |
|---|---|---|---|---|
| **M-Stage** | | | | |
| M0 | 10 | 2 (20.0%) | 5 (50.0%) | 3 (30.0%) |
| M1a | 5 | 0 (0.0%) | 3 (60.0%) | 2 (40.0%) |
| M1b | 2 | 0 (0.0%) | 1 (50.0%) | 1 (50.0%) |
| M1c | 10 | 0 (0.0%) | 4 (40.0%) | 6 (60.0%) |
| **Clinical Type** | | | | |
| ALM | 10 | 1 (10.0%) | 6 (60.0%) | 3 (30.0%) |
| NM | 5 | 0 (0.0%) | 3 (60.0%) | 2 (40.0%) |
| SSM | 3 | 0 (0.0%) | 0 (0.0%) | 3 (100%) |
| Mucosal | 6 | 1 (16.7%) | 2 (33.3%) | 3 (50.0%) |
| Others | 3 | 0 (0.0%) | 2 (66.7%) | 1 (33.3%) |

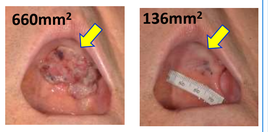
### Kaplan-Meier analysis of overall survival (N=28)




| | | 95% CI |
|---|---|---|
| 1 y survival rate | 45.7% | (25.2 – 64.0) |
| MST | 318Days | (211 - NA) |

### irRC Response (irPR ) of Patient 1401-020

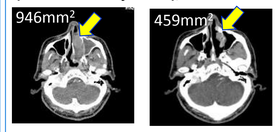
**77 / Male, Stage IIIC, Mucosal Melanoma**
**Prior therapy : Nivolumab**

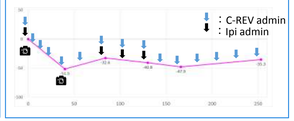




### irRC Response (irSD) of Patient 1401-012

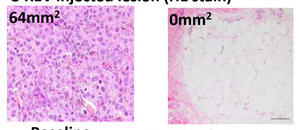
**74 / Male, Stage IIIC, Mucosal Melanoma**
**Prior therapy : Interferon beta (intradermal injection), Nivolumab**

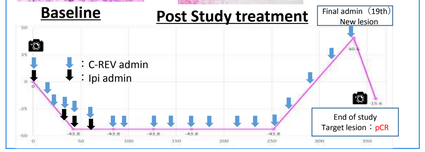



### Pathological Response (pCR) of Patient 1401-002

**31 / Male, Stage IIIC, Nodular Melanoma**
**Prior therapy : PEG-IFNα, Interferon beta (intradermal injection), Nivolumab**
**C-REV injected lesion (HE stain)**




## Summary of Results/Conclusions

**Summary:** Of 28 pts enrolled and treated as of the data cut-off 31 Aug 2018: The median age was 67 yrs (range: 31 to 81) and 43% pts were male. Disease stage was 7.1% IIIB, 28.6% IIIC and 64.3% IV. The most common subtype was 39.3% acral lentiginous and 21.4% mucosal melanoma. All pts were received prior therapies: 89.3% PD-1 monotherapy, 11% DTIC and 7% DAVFeron (DTIC, ACNU, Vincristine, and intradermal Interferon beta). 21.4% had ≥G3 C-REV-related AEs; adrenal insufficiency, constipation, hepatic function disorder, malaise, muscle weakness in lower limb, Nausea, and toxic skin eruption. Although BORR by irRC was 7.4% (2/27), and disease control rate reached relatively high 55.6% (15/27). One of patients with SD achieved pCR at the end of study. Median OS was 318 days.

**Conclusions:** The combination of C-REV with ipi did not show the exacerbate ipi toxicity, and had a favorable benefit/risk profile in Japanese pts who had received prior therapies mainly of PD-1. It is recently well-known that the response to ipi after anti-PD-1 therapy was unsatisfactory and associated with a high frequency of severe irAEs, in particular Asian populations.[1), 2)] The presented response data are encouraging compared to that of the Ipi monotherapy. C-REV+ipi therapy has potential to become a new 2nd line treatment for melanoma.

### Ref) Efficacy of Ipi monotherapy after Nivolumab in Japanese patients with melanoma

| | Fujisawa Y. et al. [1)] | Sato M. et al. [2)] |
|---|---|---|
| Number of Patients | 60 | 9 |
| ≥ Grade 3 AEs | 33 (55.0%) | 2 (22%) |
| ORR | 2 (3.6%) | 0 (0.0%) |
| DCR | 9 (16.3%) | 1 (11.1%) |
| MST | 223 Days | - |

## Acknowledgements

- Patients, their families and caregivers
- Dr. Yukihiro Nishiyama
- Study sponsored by TAKARA BIO INC.

## Reference

1) Fujisawa Y, et al. J Dermatol Sci. 2018 Jan;89(1):60-66.
2) Sato M,et al. J Dermatol. 2018 Apr 14.

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