Final Results from Phase II of Combination with Canerpaturev (formerly HF10), an Oncolytic Viral Immunotherapy, and Ipilimumab in Unresectable or Metastatic Melanoma in 2nd or later line treatment.

 # 1365P

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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
・Life expectancy ≥ 24w
・No significant tumor bleeding or coagulation abnormality

ENROLLMENT

TREATMENT

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

Table 1: Patient Characteristics

(N=28)	n (%)
Sex – n (%) Female / Male	16 (57.1%) / 12 (42.9%)
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-PD-1 ab therapies –n(%)	
Yes / No	25 (89.3%) / 3 (10.7%)
Subtypes –n (%)	
ALM / NM / SSM / Mucosal	11 (39.3%) / 5 (17.9%) / 3 (10.7%) / 6 (21.4%)

Phase II Overall Results

Safety (N=28)

Table 2: Summary

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%)

Efficacy (N=27)

Table 4: Summary

† typo was corrected after ESMO2019

Overall Response	irRC (24wks)	irRC (48wks)	RECIST v.1.1 (24wks)
ORR [(ir)CR + (ir)PR]	2 (7.4%)	3 (11.1%†)	2 (7.4%)
DCR [(ir)CR + (ir)PR + (ir)SD]	15 (55.6%)	15 (55.6%)	11 (40.7%)
BORR			
irCR / CR	0 (0.0%)	0 (0.0%)	0 (0.0%)
irPR / PR	2 (7.4%)	3 (11.1%†)	2(7.4%)
irSD / SD	13 (48.2%)	12 (44.4%)	9(33.3%)
irPD/ PD	12 (44.4%)	12 (44.4%)	16 (59.3%)

Fig.1: Kaplan-Meier analysis of OS

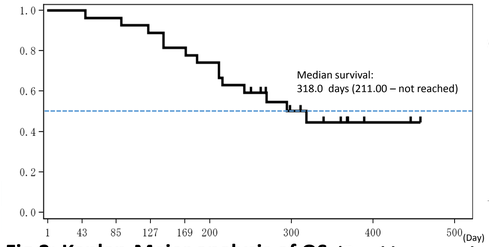
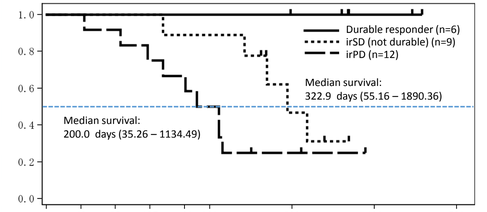


Fig.2: Kaplan-Meier analysis of OS (Durable responder)



Adjusted for baseline LDH and baseline tumor burden

Table 3: Incidence of Study treatment-related ≥ Grade 3 TEAEs (N=28)

TEAEs	n (%)	TEAEs	n (%)
Hyponatraemia	3 (10.7%)	Lipase increased	1 (3.6%)
Adrenal insufficiency	2 (7.1%)	Malaise	1 (3.6%)
Colitis	1 (3.6%)	Muscular weakness	1 (3.6%)
Amylase increased	1 (3.6%)	Nausea	1 (3.6%)
Constipation	1 (3.6%)	Toxic skin eruption	1 (3.6%)
Hepatic function abnormal	1 (3.6%)	White blood cell count decreased	1 (3.6%)

MedDRA/J Preferred Term (ver.21.0)

Fig.3: Best Change from Baseline

Fig.3-1: Whole Measurable Lesion

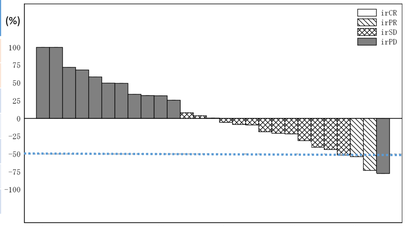


Fig.3-2: Injected Lesion

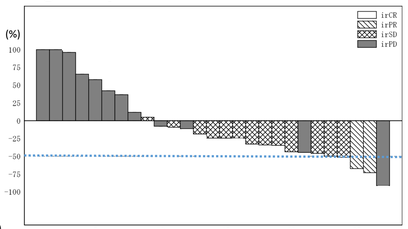


Fig.3-3. Non-Injected Lesion

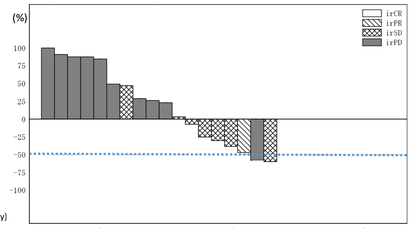


Table 5: Subgroup Analysis (N=27, irRC, 48wks)

	n	ORR n (%)	DCR n (%)
Disease Stage (AJCC 7th edition)			
IIIB, IIIC, IV-M1a	15	3 (20.0%)	10 (66.7%)
IV-M1b	2	0 (0.0%)	1 (50.0%)
IV-M1c	10	0 (0.0%)	4 (40.0%)
Subtypes			
ALM	10	2 (20.0%)	7 (70.0%)
Mucosal	6	1 (16.7%)	3 (50.0%)
NM	5	0 (0.0%)	3 (60.0%)
SSM	3	0 (0.0%)	0 (0.0%)
Others	3	0 (0.0%)	2 (66.7%)
Liver metastasis			
Yes	5	0 (0.0%)	0 (0.0%)
No	22	3 (13.6%)	15 (68.2%)
LDH level (baseline)			
≤ ULN	17	3 (17.6%)	11 (64.7%)
ULN <	10	0 (0.0%)	4 (40.0%)
Tumor burden (baseline)			
< Median	13	2 (15.4%)	10 (76.9%)
Median ≤	14	1 (7.1%)	5 (35.7%)
Prior anti-PD-1 ab			
Yes	24	3 (12.5%)	14 (58.3%)
No	3	0 (0.0%)	1 (33.3%)
BRAF mutation status			
Positive	2	0 (0.0%)	0 (0.0%)
Negative	21	3 (14.3%)	14 (66.7%)
Unknown	4	0 (0.0%)	1 (25.0%)
Anti-HSV-1 ab (baseline)			
Seropositive	16	3 (18.8%)	10 (62.5%)
Seronegative	11	0 (0.0%)	5 (45.5%)

Correlation between persistent infection and the response (N=11*)

Table 6: Summary

Patient ID	Detection of C-REV DNA at Day 85 or 169	BORR**	Survival period (days)**
1401-003	+	irPR	446
1401-002	+	irSD	458
1401-005	+	irSD	294
1401-010	+	irSD	143
1401-016	+	irSD	360
1401-013	-	irSD	369
1401-018	-	irSD	269
1401-001	-	irPD	184
1401-006	-	irPD	124
1401-019	-	irPD	311
1401-027	-	irPD	250

Table 7: Survival period

C-REV DNA detection	DCR (%)	Survival period – mean (days)**
Yes (N=5)	100% (irPR=1, irSD=4)	342
No (N=6)	33% (irSD=2, irPD=4)	251

DCR of pts 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.

*Both baseline and post treatment samples of the injected lesions were obtained from the 11 pts.

** Cut-off date: 31st August, 2018

Summary of Results/ Conclusion

RESULTS:

- From March 2017 to December 2018, 28 pts were enrolled.
- Disease stages were IIIB (7.1%), IIIC (28.6%) and IV (64.3%).
- Acral lentiginous was 39.3% and mucosal melanoma was 21.4%.
- Anti-PD-1 antibody was previously used in 89.3%.
- Grade 3 or worse AEs related to the study treatment was 35.7 %.
- Of 27 efficacy evaluable pts, BORR and DCR by irRC were 11.1%† and 55.6%, respectively.
- 6 pts (22.2%) were confirmed in durable response and had no deaths (follow-up period: 298 – 446 days).
- The median OS was 318.0 days (95% C.I. 211.00 – not reached).
- Tumor biopsy samples (n=11) analysis showed that the difference of DCR and survival period for pts with or without C-REV DNA detection at injected lesions.

* Durable response: Patients with irPR and durable irSD longer than 24 wks

CONCLUSION:

In melanoma, various immunotherapies and molecular targeted drugs have been approved for treatment options, but there are still unmet medical needs in particular in pts who failed in the 1st line therapy. In this trial, C-REV did not show the exacerbation in ipi toxicity and patients with irPR and durable irSD contributed to prolonging OS. Thus, C-REV plus ipi has potential to become a new treatment option for melanoma in ≥2nd line setting.

Reference

Table 8: 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 / DCR / MST	2 (3.6%) / 9 (16.3%) / 223 Days	0 (0.0%) / 1 (11.1%) / ND

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

Acknowledgements

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

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