Abstract # 714P

Phase I study of the oncolytic viral immunotherapy agent Canerpaturev (C-REV) with S-1 in patients with stage IV pancreatic cancer

Susumu Hijioka[1], Makoto Ueno[2], Tatsuya Ioka[3], Yoshiki Hirooka[4], Eizaburo Ohno[5], Masato Ozaka[6], Takuji Okusaka[1], Yuta Maruki[1], Satoshi Kobahashi[2], Reiko Ashida[3], Jun Yashika[5], Junji Furuse[7], Masafumi Ikeda[8], Hideki Kasuya[9], Maki Tanaka[10], Yusuke Hashimoto[8]

[1]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Japan ; [2]Department of Gastroenterology, Hepatobiliary and Pancreatic Medical Oncology Division, Kanagawa Cancer Center, Japan; [3]Cancer survey and Gastrointestinal Oncology, Osaka International Cancer Institute, Japan; [4]Liver, Biliary Tract and Pancreas Diseases, Fujita Health University, Japan; [5]Gastroenterology, Nagoya University Hospital, Japan ; 6 Hepato-Biliary-Pancreatic Medicine Department, Gastroenterology Center, The Cancer Institute Hospital of JFCR; [7]Cancer center, Kyorin University Hospital, Japan; [8]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Japan; [9]Department of Surgery II, Nagoya University Hospital, Japan; [10]TaKaRa Bio. Inc, Japan

Introduction

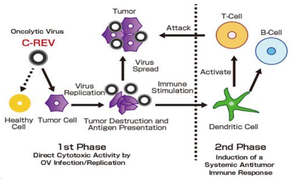
Canerpaturev (C-REV, former HF10) is an oncolytic, spontaneous mutant Herpes Simplex Virus type 1, and is one of immunotherapies that combine direct tumor cell killing with immune modulation. The purpose of this study is to evaluate the safety, tolerability and efficacy of C-REV with S-1 in patients with gemcitabine-refractory advanced pancreatic cancer as well as to assess whether the immune modulation can work in pancreatic cancer by direct tumor cell killing. Also, to compare the safety and efficacy of C-REV injected in liver metastasis or not.

Mode of Actions

C-REV selectively replicates in tumor cells and break them down without damaging to normal cells.

When locally injected into a tumor, C-REV shows two different effects as described below.

- Direct cytotoxic effects by viral replication.
- Systemic anti-tumor effects by activated cytotoxic T-lymphocytes following tumor destruction



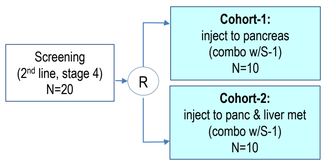
Methods

Primary Endpoint
- Safety using CTCAE 4.0

Secondary and Other Endpoints
- Best overall response rate(BORR) using RECIST 1.1
- Progression-free survival(PFS)
- Viral Shedding: whole blood, saliva, urine and feces by qPCR
- Overall survival(OS), 1 year survival rate

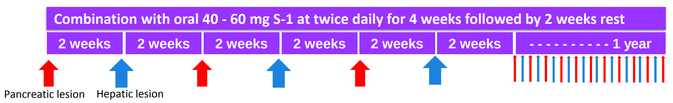
Study Treatment
- C-REV at 1x10^7 $TCID_{50}$/mL (up to 2mL, depending on tumor size) intratumorally by EUS-guidance or by ultrasound-guidance at a 2-week interval in combination with oral 40 - 60 mg S-1 at twice daily for 4 weeks followed by 2 weeks rest.
- The study treatment could continue up to 1 year till disease progression or intolerability if eligible for injection.

Key Eligibility Criteria
- Written informed consent
- Stage IV JPS 7th edition
- Injectable on EUS/ measurable pancreatic and hepatic lesion
- Pts had first-line gemcitabine-based chemotherapy
- ECOG PS 0-1
- Life expectancy ≥ 12w
- Without bleeding diathesis or coagulopathy



Cohort 1

Cohort 2



Results (Cut-off Date: Aug 05,2019)

Patient Demographics

Characteristics (Baseline)	N (%) Cohort 1 (n=10)	Cohort 2 (n=10)
Age (y.o.)		
Median/Range	62/37-77	66/41-71
ECOG PS		
0/1	5 (50)/5 (50)	9 (90)/1 (10)
Sex		
Male/Female	6 (60)/4(40)	4 (40)/6(60)
Pancreatic tumor location		
Pancreas (NOS)	1 (10)	0 (0)
Pancreatic head	1 (10)	2 (20)
Pancreatic body	5 (50)	2 (20)
Pancreatic tail	3 (30)	4 (40)
Metastatic lesion		
Liver	10 (100)	10 (100)
Lung	-	1 (10)
Bone	-	2 (20)
Lymph node	-	2 (20)
Pleural effusion	1 (10)	-
Tumor size (mm)		
Median/Range	42.5/31.0-131.0	85/40-181.9
Tumor marker (Range)		
CA19-9 (U/mL)	2.1 - 15877.0	1.4 - 100000.0
Span-1 (U/mL)	6.6 - 8400.0	1.0 - 10000.0
DUPAN-2 (U/mL)	12.5 - 3169.0	34.0 - 16000.0
CEA (ng/mL)	1.0 - 4584.4	5.0 - 477.3
Prior anti-cancer therapies		
Gemcitabine + nab-paclitaxel	10 (100)	10 (100)
HSV-1 antibody		
(-)/(+)	5 (50)/5(50)	5 (50)/5(50)

Safety

Summary of ≥ Grade 3 Treatment-Emergent AEs

Adverse Events Term Based on MedDRA/J Preferred Term (v22.0)	Cohort 1 (n=10) n(%) Any Relationship	C-REV Related	S-1 Related	Cohort 2 (n=10) n(%) Any Relationship	C-REV Related	S-1 Related
Any TEAEs	3 (30)	1 (10)	2 (20)	3 (30)	1 (10)	3 (30)
Pancreatic abscess	1 (10)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhoea	1 (10)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
Bone marrow failure	1 (10)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
Anaemia	0 (0)	0 (0)	0 (0)	1 (10)	1 (10)	1 (10)
Neutropenia	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	1 (10)
Platelet count decreased	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	1 (10)

Viral Shedding

Whole blood, urine, saliva	Feces
1st injection, 2nd injection of C-REV Day 1(pre), Day 2, Day 3, Day8	pre-treatment, prior to 2nd and later injection of C-REV
3rd and later injection of C-REV Day 1(pre)	
End of study 28 days after the last injection of C-REV	

The samples were collected from 20 pts. In 8 pts, HF10 virus DNA was detected by qPCR in whole blood, urine, saliva. each case was only once, and was rapidly cleared.

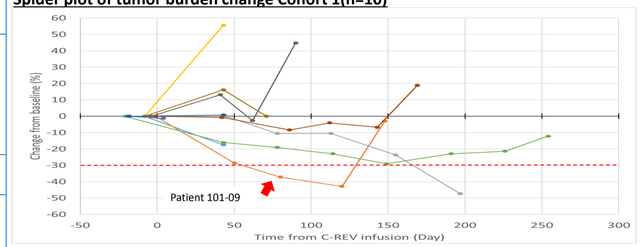
Efficacy

Best Overall Response Rate

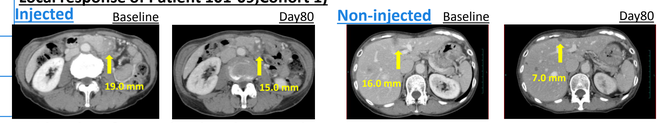
Response	N(%) Cohort 1 (n=10)	Cohort 2 (n=9*)
Objective response (CR +PR)	1 (10)	0 (0)
Disease control rate (CR +PR +SD)	5 (50)	6 (66.7)
Complete Response (CR)	0 (0)	0 (0)
Partial Response (PR)	1 (10)	0 (0)
Stable Disease (SD)	4 (40)	6 (66.7)
Progressive Disease (PD)	4 (40)	3 (33.3)
Not Evaluable (NE)	1 (10)	1 (11.1)

* :One patient did not have image evaluation after administration.

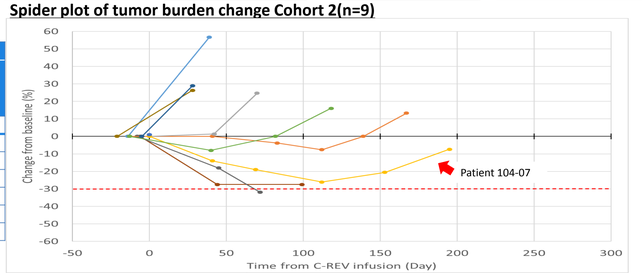
Spider plot of tumor burden change Cohort 1(n=10)



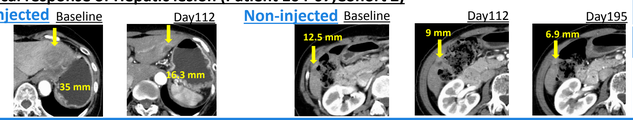
Local response of Patient 101-09,Cohort 1)



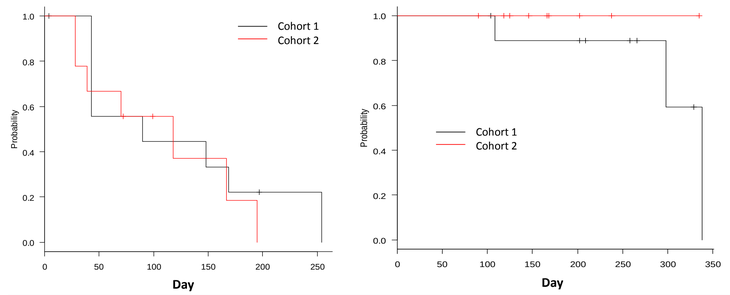
Spider plot of tumor burden change Cohort 2(n=9)



Local response of Hepatic lesion (Patient 104-07,Cohort 2)



Kaplan-Meier Estimates of Progression-free Survival and Overall Survival



Variable	Cohort 1 (n=10)	Cohort 2 (n=9)
PFS, median, day /95% CI	90/ 43-NA	118/ 28-NA
OS, median, day /95% CI	338/ 108-NA	Not reached
6 month OS, % /95% CI	88.9/ 43.3-98.4	100/ 100-100
Follow-up time, median, day	258	166

Summary of Results

- Ten patients (pts) were enrolled and treated in each cohort. In Cohort 2, one patient was excluded from the efficacy analyses.
- There was no difference in the incidence of ≥Gr3 AEs between Cohorts, were similar as the AEs previously reported in S-1 therapy.
- Objective response rate was 10% (1 PR) in Cohort 1 and 0% in Cohort 2, Disease control rate was 50%(1 PR and 4 SDs) and 66.7%(6 SDs), respectively.
- Median PFS was 90 days in Cohort 1 and 118 days in Cohort 2. There was no difference in efficacy between cohorts. Median OS was 338 days in Cohort 1, and was not reached in Cohort 2.

Discussion

While preliminary, OS tended to be prolonged despite no significant improvement in ORR or PFS. Furthermore, one patient in Cohort 1 and two pts in Cohort 2 had PRin after the cut-off date. The updated data will be available early next year.

Conclusions

Intratumoral C-REV serial injections are safe and well-tolerated in combination with S-1. The majority of S-1-related ≥Gr3 AEs were similar as the AEs previously reported in S-1 therapy. Assessment of C-REV plus S-1 as a potential new second-line treatment for stage IV pancreatic cancer is ongoing in this study.

Acknowledgements

- Patients, their families and caregivers
- Dr. Yukihiro Nishiyama (Nagoya University), originally established HF10
- TaKaRa Bio Inc., funded this study

Corresponding author : Susumu Hijioka, E-mail : shijioka@ncc.go.jp