Abstract # 704P

Results from phase I study of the oncolytic viral immunotherapy agent Canerpaturev (C-REV) in combination with gemcitabine plus nab-paclitaxel as first-line treatment of unresectable pancreatic cancer

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Introduction

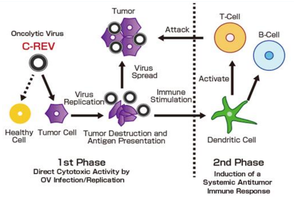
Canerpaturev (C-REV, formerly HF10) is an oncolytic, spontaneous mutant Herpes Simplex Virus type 1, and is one of immunotherapies that combine direct tumor cell killing with immune modulation. This study was designed to determine the recommended dose of C-REV in combination with chemotherapy (Gemcitabine + Nab-paclitaxel; G-nP) in Japanese patients with stage III or IV unresectable pancreatic cancer. 3+3 pts with Stage III or IV enrolled to determine the recommended dose (RD) (Dose escalation cohort), followed by 10 pts with stage III enrolled at RD (Expansion cohort).

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

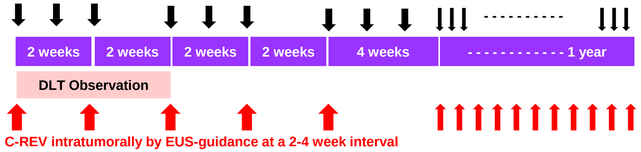
Primary Endpoint
- Dose Limiting Toxicity (DLT) (Dose escalation cohort)
- Safety using CTCAE 4.0 (Expansion cohort)

Secondary and Other Endpoints
- Safety using CTCAE 4.0
- Best overall response rate(BORR) using RECIST 1.1 at Week 16 and study completion
- Progression-free survival(PFS)
- Viral Shedding: whole blood, saliva, urine and feces by qPCR
- Overall survival(OS), 1 year survival rate

Key Eligibility Criteria
- Written informed consent
- Stage III or IV JPS 7th edition
- Injectable on EUS/ measurable pancreatic lesion
- ECOG PS 0-1
- Life expectancy ≥ 12w
- Without bleeding diathesis or coagulopathy

Study Treatment
- C-REV at 1x10^6 TCID$_{50}$/mL [Dose level 1] or 1x10^7 TCID$_{50}$/mL [Dose level 2] (up to 2mL, depending on tumor size) intratumorally by EUS-guidance at a 2-week interval in addition to 1000 mg/m^2 gemcitabine and 125 mg/m^2 nab-paclitaxel by intravenous infusion on days 1, 8, and 15 of a 4-week cycle.
- The study treatment could continue up to 1 year till disease progression or intolerability if eligible for injection.

Gemcitabine and nab-paclitaxel IV on days 1, 8, and 15 of a 4-week cycle.



Results

Patient Demographics

Characteristics	n (%) Dose escalation n=6	n (%) Expansion cohort n=10	N (%) ALL N=16
Age (y.o.)			
Median/ Range	67.5/63-72	67/51-72	67/51-72
ECOG PS			
0/1	5 (83.3)/1 (16.7)	9 (90.0)/1 (10.0)	14 (87.5)/2(12.5)
Sex			
Male/Female	2 (33.3)/4(66.7)	5 (50.0)/5(50.0)	7 (43.8)/9(56.2)
Stage			
III/IV	2 (33.3)/4(66.7)	10 (100.0)/0(0.0)	12 (75.0)/4(25.0)
Stage IV-metastatic lesion			
Liver	2	-	2
Lung	1	-	1
Ascites fluid	1	-	1
Pancreatic tumor location			
Pancreatic head	3 (50.0)	6 (60.0)	9 (56.2)
Pancreatic body	2 (33.3)	4 (40.0)	6 (37.5)
Pancreatic tail	1 (16.7)	0 (0.0)	1 (6.3)
Tumor size (mm)			
Median/Range	32.6/20.0-77.8	30.2/24.0-41.9	31/20.0-77.8
Tumor marker (Range)			
CA19-9 (U/mL)	2.0 - 4936.7	8.5 - 343.0	2.0 - 4936.7
Span-1 (U/mL)	56.0 - 480.0	11.0 - 732.2	11.0 - 732.2
DUPAN-2 (U/mL)	350.0 - 1600.0	12.5 - 11719.0	12.5 - 11719.0
CEA (ng/mL)	1.2 - 31.6	1.1 - 13.8	1.1 - 31.6
HSV-1 antibody			
(-)/(+)	3(50.0)/3(50.0)	9(90.0)/1(10.0)	12(75.0)/4(25.0)
Dose level			
level 1/level 2	3(50.0)/3(50.0)	0(0.0)/10(100.0)	3(18.8)/13(81.2)

Safety (Cutoff Date: 5th Aug2019)

Summary of ≥ Grade 3 Treatment-Emergent AEs in at least 10% of patients

Adverse Events Term Based on MedDRA/J Preferred Term (v22.0) N=16, n (%)	Any Relationship*	C-REV Related**	G-nP Related***
Any TEAEs	15(93.8)	5(31.3)	15(93.8)
Neutropenia	13(81.3)	2(12.5)	13(81.3)
Platelet count decreased	4(25.0)	1(6.3)	4(25.0)
White blood cell count decreased	4(25.0)	2(12.5)	4(25.0)
Anaemia	2(12.5)	1(6.3)	2(12.5)
Rash	2(12.5)	0(0.0)	2(12.5)
Febrile neutropenia	2(12.5)	0(0.0)	2(12.5)

*:In Dose escalation Cohort(n=6), No DLTs occurred.
**TEAEs expressed in less than 10%:Bacteraemia, Pancreatitis acute, Peritonitis
*** TEAEs expressed in less than 10%: AST increased, Bacteraemia, Cholangitis acute, Decreased appetite, Dermatitis exfoliative generalized, Hyperkalaemia, Hypertension, Liver abscess, Neuropathy peripheral, Vomiting

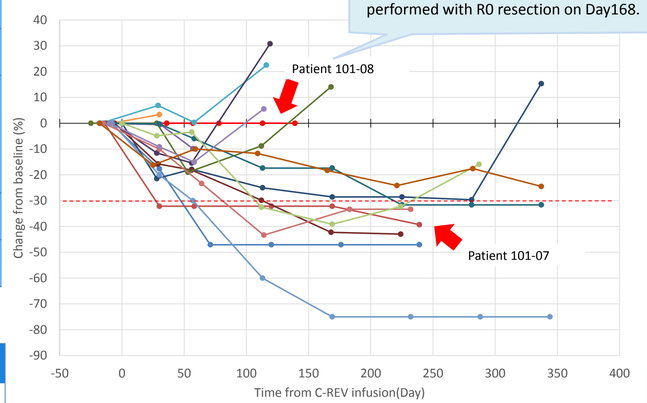
Efficacy

Overall Survival, Progression-free Survival, Best Overall Response Rate

Efficacy Variable (Cutoff Date: 5th Aug2019)	Dose escalation n=6	Expansion cohort n=10	ALL n=16
Median Overall Survival/ Median Follow-up time (mo)	Not reached /17.8	Not reached /10.2	Not reached /11.1
1-year Survival rate (%)	83.3	90.0	86.5
Median Progression-free Survival (mo)	9.4	5.5	7.6
Best Overall Response Rate using RECIST 1.1 (n (%))			
Objective response (CR+ PR)	4(66.7)	3(30.0)	7(43.8)
Disease control rate (CR+ PR+ SD)	6(100.0)	9(90.0)	15(93.8)
Complete Response (CR)	0(0.0)	0(0.0)	0(0.0)
Partial Response (PR)	4(66.7)	3(30.0)	7(43.8)
Stable Disease (SD)	2(33.3)	6(60.0)	8(50.0)
Progressive Disease (PD)	0(0.0)	0(0.0)	0(0.0)
Not Evaluable (NE)	0 (0.0)	1(10.0)	1(6.3)

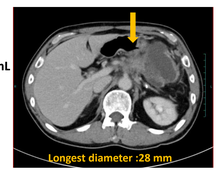
Spider plot of tumor burden change(N=16)

Patient 101-08: Despite the longest diameter unchanged, the short axis was reduced, followed by conversion surgery performed with R0 resection on Day168.

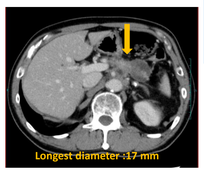


Local response of Patient 101-07 with stage III

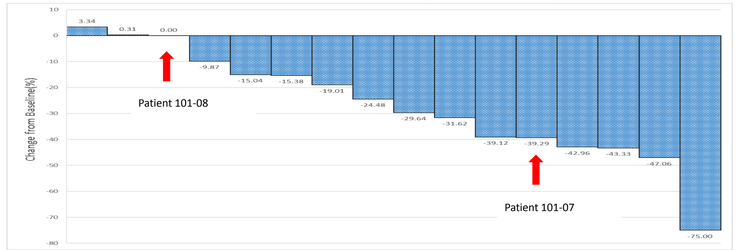
Baseline
CA19-9 : 20.1 U/mL
CEA: 1.8 ng/mL



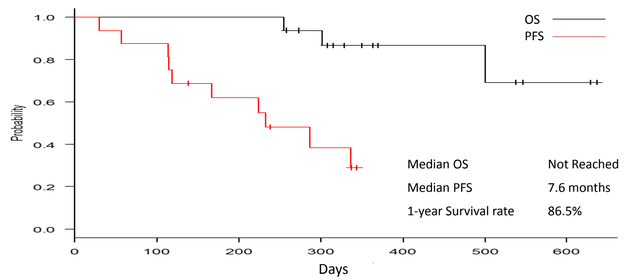
Day 337
CA19-9 : 6.0 U/mL
CEA: 1.4 ng/mL



Maximum percentage changes from baseline in size of target lesions (N=16)



Kaplan-Meier Estimates of Progression-free Survival and Overall Survival (N=16)



Summary of Results

- Sixteen patients (pts) were enrolled and treated.
- Of 6 dose escalation pts, no DLTs were observed.
- As of 5th Aug 2019, 31.3%(5/16) pts had C-REV-related ≥Gr3 AE. 93.8% (15/16) pts had G-nP-related ≥Gr3 AEs, and the majority of ≥Gr3 AEs were similar as the AEs previously reported in G-nP therapy.
- Objective response rate was 43.8% (7 PRs), disease control rate was 93.8% (7 PRs and 8 SDs).
- Median PFS was 7.6 months. Median OS was not reached.
- One patient with SD had conversion surgery.

Conclusions

The recommended dose was determined as 1x10^7 TCID$_{50}$/mL. Intratumoral C-REV serial injections are safe. The combination of C-REV and G-nP suggested a favorable benefit/risk profile and encouraging antitumor activity in patients with unresectable pancreatic cancer.

Acknowledgements

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

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European Society for Medical Oncology Congress 2019