Results from Phase I study of the oncolytic viral immunotherapy agent Canerpaturev (C-REV) in combination with Gemcitabine plus Nab-paclitaxel for Unresectable Pancreatic Cancer

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Abstract # 325

Introduction

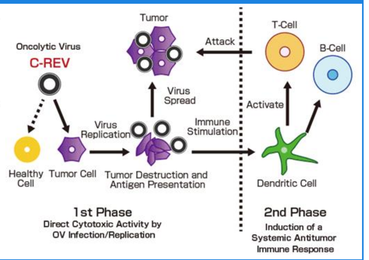
Canerpaturev (C-REV, formerly HF10) is an oncolytic, spontaneous mutant Herpes Simplex Virus type 1, and is one of immunotherapies that combine direct tumor cell killing with immune modulation. This study was designed to determine the recommended dose of C-REV in combination with chemotherapy (Gemcitabine + Nab-paclitaxel; G-nP) in Japanese patients with stage III or IV unresectable pancreatic cancer. The dose escalation in 2 dose levels of C-REV was performed according to the standard 3 + 3 design.

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)

Secondary and Other Endpoints

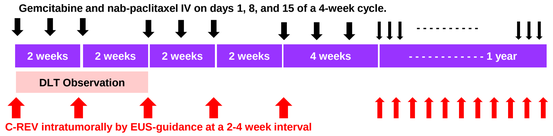
- Safety using CTCAE 4.0
- Best overall response rate(BORR) using RECIST 1.1 at Week 16 and study completion
- Progression-free survival(PFS)
- Viral Shedding: whole blood, saliva, urine and feces by qPCR
- Overall survival(OS), 1 year survival rate

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 if eligible for injection.



Results

Patient Demographics

Patient Demographics

Characteristics	n (%) Dose level 1 n=3	n (%) Dose level 2 n=3	N (%) ALL N=6
Age (y.o.)			
Median	69	64	67.5
Range	66 - 71	63 - 72	63 – 72
ECOG PS			
0	3 (100%)	2 (66.7%)	5 (83.3%)
1	0 (0.0%)	1 (33.3%)	1 (16.7%)
Sex			
Male	2 (66.7%)	0 (0.0%)	2 (33.3%)
Female	1 (33.3%)	3 (100%)	4 (66.7%)
Stage			
III	1 (33.3%)	1 (33.3%)	2 (33.3%)
IV	2 (66.7%)	2 (66.7%)	4 (66.7%)
Primary site			
Pancreatic head	1 (33.3%)	2 (66.7%)	3 (50.0%)
Pancreatic body	1 (33.3%)	1 (33.3%)	2 (33.3%)
Pancreatic tail	1 (33.3%)	0 (0.0%)	1 (16.7%)
Stage IV - Metastatic lesions			
Liver		2	2
Lung	1		1
Ascites fluid	1		1
Tumor marker (baseline)			
CA19-9 (U/mL)	562.9 - 4936.7	2.0 - 1130	2.0 - 4936.7
Span-1 (U/mL)	130 - 480	56 - 180	56 - 480
DUPAN-2 (U/mL)	1100 - 1600	350 - 1600	350 - 1600
CEA (ng/mL)	1.9 - 22.2	1.2 - 31.6	1.2 - 31.6
HSV-1 antibody			
(+)	1 (33.3%)	2 (66.7%)	3 (50.0%)
(-)	2 (66.7%)	1 (33.3%)	3 (50.0%)

Safety

Summary of ≥ Grade 3 Treatment-Emergent AEs

Adverse Events Term (Based on MedDRA/J Preferred Term (v21.1)) N=6, n (%)	Any Relationship	C-REV-Related	G-nP-Related
Any TEAEs	6 (100%)	1 (16.7%)	6 (100%)
Neutropenia	4(66.7%)	0 (0.0%)	4(66.7%)
Dermatitis exfoliative generalized	1(16.7%)	0 (0.0%)	1(16.7%)
Decreased appetite	1(16.7%)	0 (0.0%)	1(16.7%)
Neuropathy peripheral	1(16.7%)	0 (0.0%)	1(16.7%)
Pancreatitis acute	1(16.7%)	1*(16.7%)	0 (0.0%)
Rash	1(16.7%)	0 (0.0%)	1(16.7%)
Vomiting	1(16.7%)	0 (0.0%)	1(16.7%)
White blood cell count decreased	1(16.7%)	0 (0.0%)	1(16.7%)

*After DLT assessment period.

No DLTs occurred.

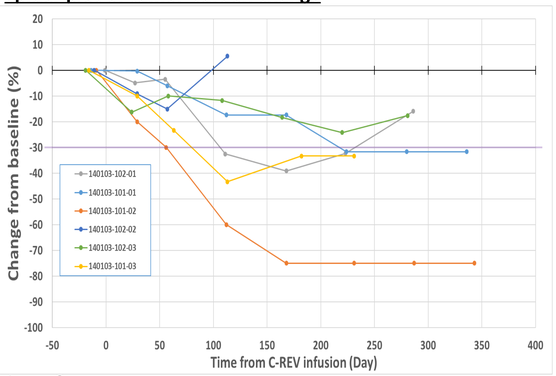
Efficacy

Best Overall Response Rate

Response	N(%) Dose level 1 n=3	N(%) Dose level 2 n=3	N(%) ALL N=6
@ Week 16:			
Objective response (CR +PR)	1 (33.3%)	0 (0.0%)	1 (16.7%)
Complete Response (CR)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Partial Response (PR)	1 (33.3%)	0 (0.0%)	1 (16.7%)
Stable Disease (SD)	2 (66.7%)	3 (100%)	5 (83.3%)
Progressive Disease (PD)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Evaluable (NE)	0 (0.0%)	0 (0.0%)	0 (0.0%)
@ cut-off time*:			
Objective response (CR +PR)	3 (100%)	1 (33.3%)	4 (66.7%)
Complete Response (CR)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Partial Response (PR)	3 (100%)	1 (33.3%)	4 (66.7%)
Stable Disease (SD)	0 (0.0%)	2 (66.7%)	2 (33.3%)
Progressive Disease (PD)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Evaluable (NE)	0 (0.0%)	0 (0.0%)	0 (0.0%)

*Date: Oct 31, 2018

Spider plot of tumor burden change



Viral Shedding

Samples collected/analyzed

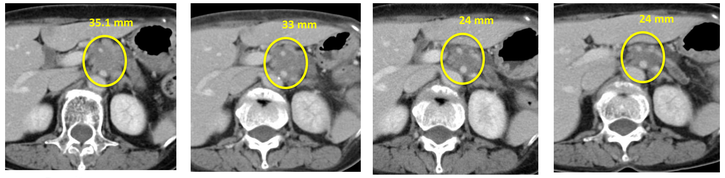
Whole blood, urine, saliva	Feces
1st injection, 2nd injection of C-REV Day 1(pre), Day 2, Day 3, Day8	pre-treatment, prior to 2nd and later injection of C-REV
3rd and later injection of C-REV Day 1(pre)	
End of study 28 days after the last injection of C-REV	

The samples were collected from 6 pts. HF10 virus DNA was not detected by qPCR in any samples analyzed with one exception. In the whole blood on Day 1 of 2nd injection from Patient 102-01, the DNA was detected below Lower Limit Of quantification (LLOQ), and it was transient.

Local response of Patient with Stage III(Patient 101-01)

69y.o., Female, Stage III

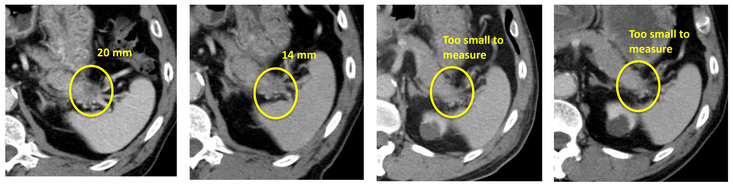
Injected lesion: pancreatic body mass



Local response of Patient with Stage IV(Patient 101-02)

71y.o., Male, Stage IV(metastatic lesion: Lung)

Injected lesion: pancreatic tail mass



Summary of Results/Conclusions

Six patients (pts) were enrolled and treated: 33.3% (2/6) men, age range 63 to 72 y.o., disease stage 33.3% III, 66.7% IV. Of 6 safety evaluable pts, no DLTs were reported. One patient had Grade 3 acute pancreatitis related with C-REV. Six patients had Grade 3 AEs related with G-nP, but no AEs were reported related with C-REV. Of the 6 efficacy evaluable pts, BORR at 16-week was 16% (1 PR), BORR as of cut-off (Oct 31, 2018) was 66.7% (4 PRs). Disease control rate was 100% (4 PRs and 2 SDs), and 1 of 2 SD pt continues the study treatment. HF10 virus DNA was not detected by qPCR in any samples of whole blood, saliva, urine and feces except one whole blood sample transiently detected below LLOQ.

Conclusions:

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

Acknowledgements

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