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Phase I clinical trial of OBP-301, a novel telomerase-specific oncolytic virus, in combination with radiotherapy in esophageal cancer patients

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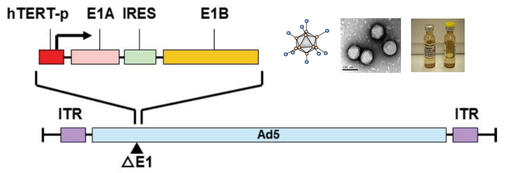
Background

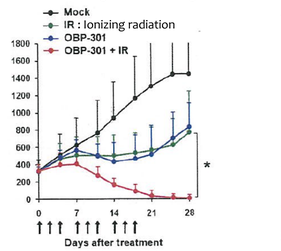
- OBP-301 is a novel condition-restricted, replication-competent adenovirus derived from human adenovirus type 5 (Ad-5) that incorporates a human telomerase reverse transcriptase (hTERT) promoter.
- The majority of malignant tumors express telomerase activity[1], hTERT promoter regulates the hTERT gene expression that is correlated with telomerase activity. Thus, telomerase may be a plausible target for cancer therapy.

OBP-301:



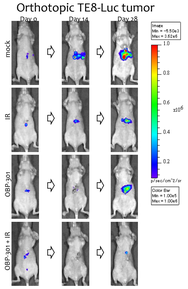
- The safety of OBP-301 monotherapy has been confirmed in patients with advanced solid tumor in Phase I clinical trial in US[2].
- OBP-301 infection led to E1B-55 kDa viral protein that degraded the complex related to DNA repair, and finally improved the radio sensitivity of human cancer cell, and produced the synergy effect between OBP-301 and radiation[3].

TE8 human esophageal cancer xenografts



OBP-301 1x10[8] PFU+Radiation 2Gy, 3 times/wk for 3wks

Orthotopic TE8-Luc tumor



- OBP-301 administration induced the immune response, and CD8+ and CD4+ T cell increased not only OBP-301 injection tumor, but also non-injection tumor[4].
- Esophageal cancer increases in incidence with age, peaking in the seventh and eighth decades of life. In general, elderly patients may have a limit with their ability to tolerate intensive treatments such as radical surgery or definitive chemoradiotherapy[5] .

Reference

1) *Shay JW and Bacchetti SA. Eur J Cancer 1997; 33:787-91*
2) *Nemunaitis J et al., Mol Ther 2010; 18:429-34*
3) *Kuroda S et al., Plos One 2010; 18: 429-34*
4) *Fujita et al., Oncology Report 2008; 20: 1363-1368*
5) *Bonavina L et al., Dis Esophagus 2003; 16:90-3*

Method

Subject:

- Patient with esophageal cancer who is not eligible to standard surgery or chemotherapy

Study Design:

- 3+3 design, 2 cohorts, single arm, open label

Objective:

Primary objective:

- To evaluate the tolerability and safety of OBP-301 in combination with radiation therapy

Secondary objective:

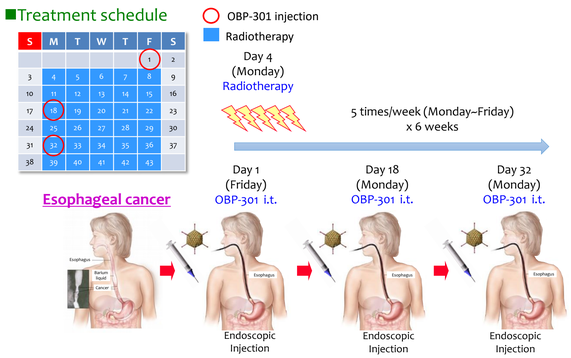
- To examine the therapeutic effect of OBP-301 in combination with radiation therapy

Exploratory objective:

- To explorer the biodistribution and viral shedding of OBP-301, and tumor immunological effect

Regimen:

- OBP-301 is locally injected 3 times through endoscopy.
- Radiotherapy is administered 5 times/week x 6 week (Total 60 Gys).



DLT definition:

The dose limiting toxicity (DLT) was defined as 1 or more of the following events related to OBP-301 administration:

- A non-hematological toxicity corresponding to Grade 3 or higher of CTCAE v4.0
- A hematological toxicity corresponding to Grade 4 or higher of CTCAE v4.0

However, even if a lymphopenia reached Grade 4, it was not to be deemed as a DLT unless another Grade 3 (hematological toxicity: Grade 4) AE caused by a lymphopenia occurred concurrently.

Result

Safety:

- OBP-301 in combination with radiation were well tolerated. No DLT was observed, and maximum tolerable dose (MTD) of OBP-301 was over 1x10[12] VP/injection.
- Most common adverse events related to OBP-301 were Lymphopenia (83.3%), Pyrexia (83.3%).

Table 1: Adverse events related to OBP-301 (n=6)

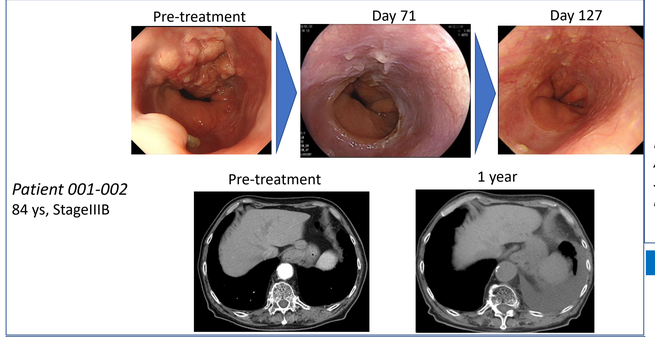
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Total
Lymphopenia	1(17%)	1(17%)	3(50%)	1(17%)	5(83%)
Pyrexia	3(50%)	2(33%)	0	0	5(83%)
Esophagitis	0	1(17%)	0	0	1(17%)
Decreased appetite	1(17%)	0	0	0	1(17%)
Upper respiratory tract infection	1(17%)	0	0	0	1(17%)
Malaise	1(17%)	0	0	0	1(17%)
Weight decreased	1(17%)	0	0	0	1(17%)
Radiation esophagitis	1(17%)	0	0	0	1(17%)

Efficacy:

- Local response: 4 CR (66.7%), 2 non-CR/PD (33.3%).
- Even though 2 patients recurred after CR conformation, less invasive therapy such as endoscopic submucosal dissection (ESD), was performed for aftertreatment.

Table 2: Demographic and local response

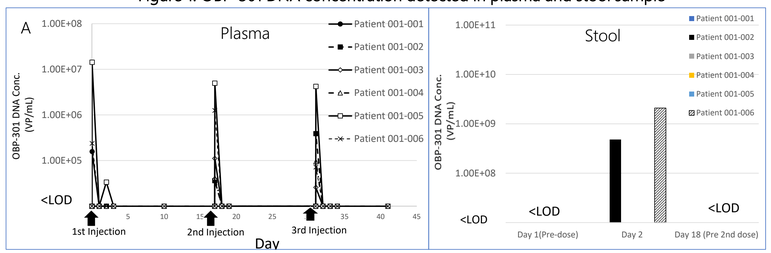
Cohort (Dose)	Patient No.	Age	Gender	TMN	Stage (TMN Ver.7)	Histology	Local Response
Cohort 1 (1x10[11] VP)	001-001	82	M	T1bN0M0	IA	Squamous cell ca	CR
	001-002	84	M	T3N2M0	IIIB	Adeno ca & Squamous cell ca	CR
	001-003	82	M	T1bN1M0	IIB	Squamous cell ca	CR
Cohort 2 (1x10[12] VP)	001-004	79	M	T1bN0M0	IA	Squamous cell ca	CR
	001-005	66	M	T3N1M0	IIIA	Squamous cell ca	Non-CR/PD
	001-006	85	M	T2N0M0	IB	Squamous cell ca	Non-CR/PD



Biodistribution and Viral Shedding:

- OBP-301 DNA special sequence (*IRES*) was detected in all patient's plasma 30 min after OBP-301 injection, and reduced below the limit of detection (LOD) after that.
- OBP-301 DNA was detected in 2 patients' stool 24 hrs after OBP-301 injection, but not detected in all saliva, sputum, and urine samples.

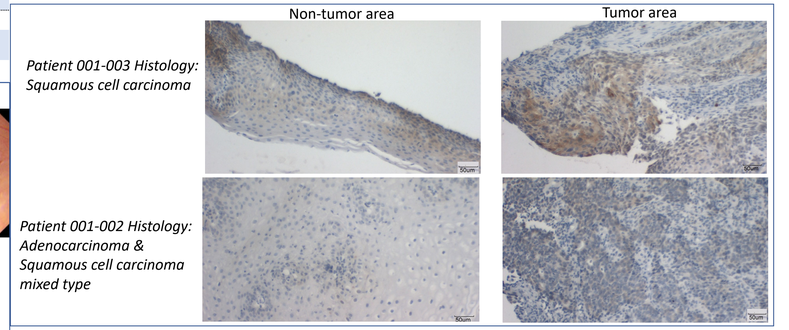
Figure 1: OBP-301 DNA concentration detected in plasma and stool sample



Sensitivity of OBP-301 infection in biopsy tissue :

- The expression of Coxsackievirus and adenovirus receptor (CAR) was high in biopsy tissue of patients with Squamous cell carcinoma, including tumor and non-tumor area.
- In biopsy tissue of patient 001-002 with Adenocarcinoma & Squamous cell carcinoma mixed type, CAR was not expressed in non-tumor area but highly expressed in tumor area.

Figure 2: Immunohistochemistry of CAR in biopsy tissue



Conclusion

- The combination of OBP-301 and radiotherapy was well tolerated.
- OBP-301 in combination with radiotherapy are able to provide definite clinical benefits in patients with esophageal cancer who are not applicable for surgery or standard chemotherapy.
- The combination therapy might be one of promising therapies for patient who is not eligible to standard surgery or/and chemotherapy, and the pivotal trial of OBP-301 in combination with radiation in Japanese patients ongoing.

Acknowledgments

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