

YMTHE, Volume 31

Supplemental Information

Safety and dose escalation of the targeted oncolytic adenovirus OBP-301 for refractory advanced liver cancer: Phase I clinical trial

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Supporting Information

Table S1. Overview of adverse events related to the investigational product*

EVENT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (N = 20)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Influenza like illness	1 (5%)	6 (30%)	0 (0%)	0 (0%)	0 (0%)	6 (30%)
Pyrexia	2 (10%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	3 (15%)
Fatigue	1 (5%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	2 (10%)
INVESTIGATIONS						
Blood bilirubin increased	0 (0%)	1 (5%)	1 (5%)	1 (5%)	0 (0%)	1 (5%)
Hepatitis B DNA increased	1 (5%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Platelet count decreased	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (10%)
Alanine aminotransferase increased	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Aspartate aminotransferase increased	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)
Lymphocyte count decreased	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)
Neutrophil count decreased	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)
White blood cell count decreased	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
Anemia	0 (0%)	1 (5%)	2 (10%)	0 (0%)	0 (0%)	2 (10%)
GASTROINTESTINAL DISORDERS						
Abdominal distension	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (10%)
Abdominal pain	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Diarrhea	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
METABOLISM AND NUTRITION DISORDERS						
Decreased appetite	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)

Table S2. Prior hepatocellular carcinoma therapies received by enrolled patients*

	Cohort-1 N=3	Cohort-2 N=3	Cohort-3 N=3	Cohort-4 N=3	Cohort-5 N=8	Total N=20
Any prior therapy	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	8 (100.0)	20 (100.0)
Number of prior therapies						
0	0	0	0	0	0	0
1	0	1 (33.3)	0	0	0	1 (5.0)
2	2 (66.7)	1 (33.3)	0	0	1 (12.5)	4 (20.0)
3	0	1 (33.3)	1 (33.3)	0	1 (12.5)	3 (15.0)
4	0	0	0	0	2 (25.0)	2 (10.0)
5	0	0	0	0	2 (25.0)	2 (10.0)
>5	1 (33.3)	0	2 (66.7)	3 (100.0)	2 (25.0)	8 (40.0)
Any prior non-surgical procedure	3 (100.0)	2 (66.7)	3 (100.0)	3 (100.0)	8 (100.0)	19 (95.0)
Preferred WHO designation						
Radiotherapy	2 (66.7)	2 (66.7)	3 (100.0)	3 (100.0)	7 (87.5)	17 (85.0)
Sorafenib tosylate	0	1 (33.3)	2 (66.7)	2 (66.7)	4 (50.0)	9 (45.0)
Sorafenib	1 (33.3)	1 (33.3)	0	0	2 (25.0)	4 (20.0)
Orantinib (Tsu-68)	2 (66.7)	0	0	0	2 (25.0)	4 (20.0)
Regorafenib	0	0	0	0	2 (25.0)	2 (10.0)
Resminostat	0	0	0	2 (66.7)	0	2 (10.0)
Capecitabine	0	0	1 (33.3)	0	0	1 (5.0)
Cisplatin	0	0	1 (33.3)	0	0	1 (5.0)
Doxorubicin	0	0	1 (33.3)	0	0	1 (5.0)
Ethanol	0	0	1 (33.3)	0	0	1 (5.0)
Investigational drug	0	0	0	1 (33.3)	0	1 (5.0)
Monoclonal antibodies	0	0	0	0	1 (12.5)	1 (5.0)
Nivolumab	0	0	0	0	1 (12.5)	1 (5.0)
Peretinoin	0	0	0	0	1 (12.5)	1 (5.0)
Any prior surgical procedure	3 (100.0)	1 (33.3)	3 (100.0)	3 (100.0)	7 (87.5)	17 (85.0)

*Numbers indicate n (%).

Table S3. Adverse events related to an investigational product

Statistic	Cohort					Total (N=20)
	Cohort I (N=3)	Cohort II (N=3)	III (N=3)	Cohort IV (N=3)	Cohort V (N=8)	
General disorders and administration site conditions						
Influenza like illness	0	0	0	1 (33.3%)	5 (62.5%)	6 (30%)
Pyrexia	0	0	1 (33.3%)	1 (33.3%)	1 (12.5%)	3 (15%)
Fatigue	1 (33.3%)	0	0	0	1 (12.5%)	2 (10%)
Investigations						
Platelet count decreased	1 (33.3%)	1 (33.3%)	0	0	0	2 (10%)
Alanine aminotransferase increased	0	0	0	0	1 (12.5%)	1 (5%)
Aspartate aminotransferase increased	0	0	0	0	1 (12.5%)	1 (5%)
Blood bilirubin increased	0	0	0	0	1 (12.5%)	1 (5%)
Hepatitis B DNA increased	0	1 (33.3%)	0	0	0	1 (5%)
Lymphocyte count decreased	0	0	0	1 (33.3%)	0	1 (5%)
Neutrophil count decreased	0	0	0	1 (33.3%)	0	1 (5%)
White blood cell count decreased	0	1 (33.3%)	0	0	0	1 (5%)
Gastrointestinal disorders						
Abdominal distension	1 (33.3%)	0	0	0	1 (12.5%)	2 (10%)
Abdominal pain	0	0	0	1 (33.3%)	0	1 (5%)
Diarrhea	0	0	0	0	1 (12.5%)	1 (5%)
Blood and lymphatic system disorders						
Anemia	0	0	0	2 (66.7%)	0	2 (10%)
Metabolism and nutrition disorders						
Decreased appetite	0	0	0	1 (33.3%)	0	1 (5%)

Table S4. TEAEs occurred in this study.

EVENT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (N = 20)
INVESTIGATIONS						
Aspartate aminotransferase increased	2 (10%)	3 (15%)	4 (20%)	3 (15%)	0 (0%)	6 (30%)
Alanine aminotransferase increased	1 (5%)	1 (5%)	2 (10%)	1 (5%)	0 (0%)	3 (15%)
Blood bilirubin increased	1 (5%)	2 (10%)	2 (10%)	1 (5%)	0 (0%)	3 (15%)
Platelet count decreased	3 (15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (15%)
Gamma-glutamyltransferase increased	1 (5%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Hepatitis B DNA increased	1 (5%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
White blood cell count decreased	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Activated partial thromboplastin time prolonged	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Blood alkaline phosphatase increased	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Glucose urine present	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Lipase increased	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	1 (5%)
Lymphocyte count decreased	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)
Neutrophil count decreased	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Influenza-like illness	2 (10%)	6 (30%)	0 (0%)	0 (0%)	0 (0%)	7 (35%)
Pyrexia	3 (15%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	5 (25%)
Injection site pain	1 (5%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	2 (10%)
Fatigue	1 (5%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	2 (10%)
Oedema peripheral	0 (0%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	2 (10%)
Injection site erosion	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Non-cardiac chest pain	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
GASTROINTESTINAL DISORDERS						
Abdominal pain	2 (10%)	5 (25%)	0 (0%)	0 (0%)	0 (0%)	6 (30%)
Nausea	0 (0%)	4 (20%)	0 (0%)	0 (0%)	0 (0%)	4 (20%)
Abdominal distension	2 (10%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	3 (15%)
Ascites	0 (0%)	3 (15%)	0 (0%)	0 (0%)	0 (0%)	3 (15%)
Diarrhea	1 (5%)	1 (5%)	1 (5%)	0 (0%)	0 (0%)	3 (15%)
Dyspepsia	1 (5%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	3 (15%)
Vomiting	1 (5%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	2 (10%)
Abdominal discomfort	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Abdominal pain upper	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Constipation	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Upper gastrointestinal hemorrhage	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	1 (5%)
METABOLISM AND NUTRITION DISORDERS						
Hypoalbuminemia	0 (0%)	4 (20%)	0 (0%)	0 (0%)	0 (0%)	4 (20%)
Decreased appetite	0 (0%)	3 (15%)	0 (0%)	0 (0%)	0 (0%)	3 (15%)
INFECTIONS AND INFESTATIONS						
Hepatitis viral	2 (10%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	2 (10%)
Cholangitis infective	0 (0%)	0 (0%)	1 (5%)	0 (0%)	1 (5%)	1 (5%)
Implant site infection	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Periodontitis	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Pneumonia bacterial	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	1 (5%)

EVENT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (N = 20)
HEPATOBIILIARY DISORDERS						
Hyperbilirubinemia	0 (0%)	2 (10%)	1 (5%)	0 (0%)	0 (0%)	2 (10%)
Bile duct obstruction	0 (0%)	0 (0%)	1 (5%)	0 (0%)	1 (5%)	1 (5%)
Cholangitis acute	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
Bone pain	0 (0%)	1 (5%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)
Arthralgia	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Flank pain	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Musculoskeletal pain	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Neck pain	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
Anemia	0 (0%)	1 (5%)	2 (10%)	0 (0%)	0 (0%)	2 (10%)
NERVOUS SYSTEM DISORDERS						
Depressed level of consciousness	0 (0%)	1 (5%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)
Seizure	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Somnolence	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS						
Dyspnea	0 (0%)	2 (10%)	1 (5%)	0 (0%)	0 (0%)	2 (10%)
Hypoxia	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Eczema	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Prurigo	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Pruritus	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
EYE DISORDERS						
Ocular icterus	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Visual impairment	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
INJURY, POISONING, AND PROCEDURAL COMPLICATIONS						
Skin abrasion	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
PSYCHIATRIC DISORDERS						
Delirium	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
RENAL AND URINARY DISORDERS						
Dysuria	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)

Table S5. Tumor local responses.

Result	Statistic	Best local response					
		Cohort-1 N=3	Cohort-2 N=3	Cohort-3 N=3	Cohort-4 N=3	Cohort-5 N=8	Total N=20
CR	n (%)	0	0	0	0	0	0
PR	n (%)	0	0	0	0	0	0
SD	n (%)	3 (100)	2 (66.7)	3 (100)	3 (100)	3 (50)	14 (77.8)
PD	n (%)	0 (0)	1 (33.3)	0 (0)	0 (0)	3 (50)	4 (22.2)
Time to disease control (weeks)		4.00(4.0- 4.1)	4.14(3.3- 4.1)	4.14(4.1- 4.1)	4.14(4.0- 4.3)	8.14(8.0- 10.1)	4.14(3.3- 10.1)

Abbreviations here and below: CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.

Table S6. Overall tumor responses.

Result	Statistic	Best overall response					
		Cohort-1 N=3	Cohort-2 N=3	Cohort-3 N=3	Cohort-4 N=3	Cohort-5 N=8	Total N=20
CR	n (%)	0	0	0	0	0	0
PR	n (%)	0	0	0	0	0	0
SD	n (%)	2 (66.7)	1 (33.3)	3 (100)	1 (33.3)	0 (0)	7 (38.9)
PD	n (%)	1 (33.3)	2 (66.7)	0 (0)	2 (66.7)	6 (100)	11 (61.1)
Time to disease control (weeks)		4.00(4.0- 8.0)	4.14(3.3- 4.1)	4.14(4.1- 5.4)	4.14(4.0- 4.3)	8.14(8.0- 10.1)	4.21(3.3- 10.1)
Time to progression (weeks)		19.14(4.14- 74.29)	4.14(3.29- 8.00)	8.14(8.14- 20.14)	4.29(4.14- 8.14)	8.14(8.00- 10.14)	8.14(4.29- 8.14)
Overall survival (weeks)		2/3(-,-)	0/3 40.86 (6.29- 102.57)	2/3(-,-)	1/3 12.86 (-,-)	0/6 23(14.14- 26.00)	8/18 26.00 (-,-)

Table S7. Intention-to-treat analysis of overall survival*

Measurement	Statistic	Cohort-1 N=3	Cohort-2 N=3	Cohort-3 N=3	Cohort-4 N=3	Cohort-5 N=8	Total N=20
Number of Patients by Censoring Status:							
Total Patients	n (%)	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	6 (100.0)	18 (100.0)
Not Censored (Dead)	n (%)	1 (33.3)	3 (100.0)	1 (33.3)	2 (66.7)	3 (50.0)	10 (55.6)
Censored	n (%)	2 (66.7)	0	2 (66.7)	1 (33.3)	3 (50.0)	8 (44.4)
Overall Survival (weeks)	25th Percentile (95% CI)	19.29 (-, -)	6.29 (6.29,102.57)	20.43 (-, -)	7.14 (-, -)	14.14 (14.14,26.00)	19.29 (6.29,26.00)
	Median (95% CI)	- (-, -)	40.86 (6.29,102.57)	- (-, -)	12.86 (-, -)	23.00 (14.14,26.00)	26.00 (-, -)
	75th Percentile (95% CI)	- (-, -)	102.57 (6.29,102.57)	- (-, -)	- (-, -)	26.00 (14.14,26.00)	- (-, -)
Survival Rate at							
Week-1		1.00	1.00	1.00	1.00	1.00	1.00
Week-2		1.00	1.00	1.00	1.00	1.00	1.00
Week-3		1.00	1.00	1.00	1.00	1.00	1.00
Week-4		1.00	1.00	1.00	1.00	1.00	1.00
Week-8		1.00	0.67	1.00	0.67	1.00	0.89
Week-12		1.00	0.67	1.00	0.67	1.00	0.89

Abbreviations: CI: confidence interval, mRECIST: modified Response Evaluation Criteria in Solid Tumors, N: number of patients in the cohort.

*The percentage in each category was relative to the total number of patients in the relevant analysis set. The 25th percentile, median, and 75th percentile for overall survival and survival rate were based on Kaplan-Meier estimates. For patients not reported as dead at the time of analysis, the final known date of survival was used as the censoring date.

Table S8. OBP-301 viral DNA in blood and urine samples (safety set).*

Table S9. Neutralizing antibodies (Anti-Ad5) in the safety set.

Table S10. NK, MDSC, and Tregs in Cohort-5

type	Patient#	Pre-dose	1 week	2 weeks	3 weeks	4 weeks	5 weeks	8 weeks	early terminate
NK	501	13.04	10.43	14.9	14.01	11.67	11.61	14.72	14.72
	502	19	11	12	14	16	15		15
	503	32.65	34.48	31.16	31.59	31.37	19.88	24.46	24.46
	504	9.06	1.78	6.12	7.05	7.81	5.1	6.13	6.13
	505	18.9	14.08	12.33	21.14	19.15	15.81	19.96	19.96
	506	10.42	8.13	1.88					9.37
	507	25.52	20.8	15.62	15.73				
	508	10.31	16.03	14.2	9.04	14.59	15.2	14.32	14.32
	Mean ± S.D.	17.36±8.37	14.59±9.80	13.53±8.55	16.08±8.23	16.77±8.13	13.77±4.99	15.92±6.88	14.85±6.12
	Media (range)	15.97 (9.1-32.7)	12.54 (1.8-34.5)	13.27 (1.9-31.2)	14.01 (7.1-31.6)	15.3 (7.8-31.4)	15.1 (5.1-19.9)	14.7 (6.1-24.5)	14.7 (6.1-24.5)
MDSC	501	0.47	0.35	0.31	0.39	0.42	0.54	0.17	0.17
	502	17	19.5	16.9	47.87	7.51	14.77		18
	503	0.09	0.09	0.1	0.05	0.11	0.24	0.14	0.14
	504	0.18	0.6	0.14	0.15	0.15	0.23	0.13	0.13
	505	0.34	0.39	0.5	0.28	0.34	0.32	0.47	0.47
	506	0	0.2						0.11
	507	0.14	0.05	0.26	0.23				
	508	1	9.69	2.41	53.85	0.43	0	0.46	0.46
	Mean ± S.D.	2.40±5.90	3.86±7.13	2.95±6.21	14.69±24.78	1.49±2.95	2.68±5.92	0.27±0.18	2.90±7.03
	Media (range)	0.26 (0.0-17.0)	0.37 (0.1-19.5)	0.31 (0.1-16.9)	0.28 (0.1-53.9)	0.38 (0.1-7.5)	0.28 (0.0-14.8)	0.17 (0.1-0.5)	0.17 (0.1-18.8)
Treg	501	1.03	0.57	1.77	1.29	0.23	1.53	0.79	0.79
	502	10.9	8.4	3.4	3.98	11.77	12.2		13.47
	503	0.09	0.3	0.28	0.06	0.09	0.21	0.2	0.2
	504	0.16	0.16	0.1	0.23	0.11	0.14	0.1	0.1
	505	0.44	1.26	0.13	0.17	0.01	0.2	0.34	0.34

506	0.03	0.01						0.15
507	0.05	0.03	0.08	0.01				
508	0.08	0.05	0.12	0.03	0.01	0	0	0
Mean ± S.D.	1.60±3.77	1.35±2.88	0.84±1.28	0.82±1.46	2.04±4.77	2.38±4.84	0.29±0.31	2.15±4.99
Media (range)	0.13 (0.0- 10.9)	0.23 (0.0-8.4)	0.13 (0.1-0.4)	0.17 (0.0-4.0)	0.10 (0.0- 11.8)	0.21 (0.0- 12.2)	0.20 (0.0- 0.8)	0.20 (0.0- 13.5)

Table S11. Schedule of assessments for the single-injection cohorts and the alternative single-dose cohort.

		Treatment		Follow-up						
Visit	Screening	1	2	3	4	5	6	7	8	
Week	-2~0	0	0	1	2	3	4	8	12	
Day	-14~ -1	Baseline/-1~0		1	7±1	14±1	21±1	28±2	56±2	84±2
		Pre-dose	Post-dose							
Informed Consent	X									
Inclusion/Exclusion criteria	X	X								
Demography	X									
Medical history	X	X								
Pregnancy test (urine)	X									
HIV, Hep B, Hep C screening ^a	X									
Safety parameters										
EKG	X							X	X	
Vital Signs ^b	X	X	X ^b	X	X	X	X	X	X	
Physical examination	X	X		X	X	X	X	X	X	
Hematology	X	X		X	X	X	X	X	X	
Serum chemistry	X	X		X	X	X	X	X	X	
Urinalysis	X	X						X	X	
Subject wellbeing										
Performance status	X	X		X	X	X	X	X	X	
Pain score (VAS)		X	X	X	X	X	X	X	X	
Biomarkers										
AFP and DCP	X							X	X	
Immune phenotypes*										
CD4, CD8, and NK		X			X			X	X	
Neutralizing Antibody										
Anti-adenovirus type 5		X			X			X	X	
Virus dissemination										
Viral DNA ^{c,d}		X	X ^d	X	X	X	X	X	X	
HBV-DNA and HCV-RNA		X		X	X	X	X	X	X	

		Treatment		Follow-up						
Visit	Screening	1	2	3	4	5	6	7	8	
Week	-2~0	0	0	1	2	3	4	8	12	
Day	-14~ -1	Baseline/-1~0		1	7±1	14±1	21±1	28±2	56±2	84±2
		Pre-dose	Post-dose							
Tumor response										
Image Studies ^e	X							X	X	X
Biopsy ^f		X ^f								
Study drug administration ^g		X								
Drug accountability ^g		X								
Adverse events ^h			X	X	X	X	X	X	X	X
Concomitant medication	X	X		X	X	X	X	X	X	X

Abbreviations: Ad5: adenovirus type 5; AFP: alpha-fetoprotein; CD4: cluster of differentiation 4; CD8: cluster of differentiation 8; CT: computed tomography; DNA: deoxyribonucleic acid; DCP: des- γ -carboxy prothrombin; EKG: electrocardiogram; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; NK: natural killer; RNA: ribonucleic acid; VAS: visual analog scale.

* Only Cohort-4 was assessed.

^a HBsAg and HCV antibody testing.

^b Vital signs were examined 30 min (\pm 5), 1 h (\pm 10 min), 3 h (\pm 10 min), and 6 h (\pm 10 min) after injection.

^c Blood and urine samples were collected and Ad5 viral DNA tests were performed.

^d Ad5 viral DNA tests were performed 30 min (\pm 5), 1 h (\pm 10 min), 3 h (\pm 10 min), and 6 h (\pm 10 min) after injection. Only blood samples were collected.

^e Image studies include chest CT, abdominal CT, and other necessary image studies at the investigators' discretion.

^f Biopsy for targeted tumor within 8 weeks prior to OBP-301 treatment as a baseline and biopsy at 5 days for the last treatment as post OBP301 were suggested but not mandatory.

^g OBP-301 was administered only after all required assessments were completed at each visit.

^h Adverse events were collected after the first dose of OBP-301.

Table S12. Schedule of assessments for the multiple-injection cohort and the alternative multiple-dose cohort.

		Treatment								Follow-up						
Visit	Screening	1	2	3	4*	5	6**	7	8	9	10	11	12			
Week	-2~0	0	0	1	2	3	4	5	6	7	8	12	16			
Day	-14~-1	Baseline/-1~0		1	7±1	13±1	14±1	21±1	27±1	28±1	35±1	42±1	49±1	56±2	84±2	112±2
		Pre	Post			Pre	Post		Pre	Post						
Informed consent	X															
Inclusion/Exclusion criteria	X	X														
Demography	X															
Medical history	X	X														
Pregnancy test (urine)	X															
HIV, Hep B, Hep C screening ^a	X															
Safety parameters																
EKG	X													X		X
Vital signs ^b	X	X	X ^b	X	X	X	X ^b	X	X	X ^b	X	X	X	X	X	X
Physical examination	X	X		X	X	X		X	X		X	X	X	X	X	X
Hematology	X	X		X	X	X		X	X		X	X	X	X	X	X
Serum chemistry	X	X		X	X	X		X	X		X	X	X	X	X	X
Urinalysis	X	X												X	X	X
Subject wellbeing																
Performance status	X	X		X		X			X		X	X	X	X	X	X
Pain score (VAS)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarkers																
AFP and DCP	X													X	X	X
Immune phenotypes																
CD4, CD8, NK, B cell, Treg, and MDSC ^c		X			X	X		X	X		X			X		X
Neutralizing Antibody																
Anti-adenovirus type 5		X			X	X		X	X		X			X		X

		Treatment								Follow-up						
Visit	Screening	1	2	3	4*	5	6**	7	8	9	10	11	12			
Week	-2~0	0	0	1	2	3	4	5	6	7	8	12	16			
Day	-14~ -1	Baseline/-1~0		1	7±1	13±1	14±1	21±1	27±1	28±1	35±1	42±1	49±1	56±2	84±2	112±2
		Pre	Post			Pre	Post		Pre	Post						
Virus dissemination																
Viral DNA ^{d,e}		X	X ^d	X	X	X		X	X		X	X	X	X	X	X
HBV-DNA and HCV-RNA		X		X	X	X		X	X		X	X	X	X	X	X
Tumor response																
Image studies ^f	X													X	X	X
Biopsy ^g		X ^f														
Study drug administration ^h		X				X			X							
Drug accountability ^h		X				X			X							
Adverse events ⁱ			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: Ad5: adenovirus type 5; AFP: alpha-fetoprotein; CD4: cluster of differentiation 4; CD8: cluster of differentiation 8; CT: computed tomography; DNA: deoxyribonucleic acid; DCP: des-γ-carboxy prothrombin; EKG: electrocardiogram; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; MDSC: myeloid-derived suppressor cells; NK: natural killer; RNA: ribonucleic acid; Treg: regulatory T cell; VAS: visual analog scale.

*Pretreatment hematology and serum chemistry tests were performed one day prior to administration and eligibility was reconfirmed by the investigator.

^a HBsAg and HCV antibody tests.

^b Vital signs were examined 30 min (±5), 1 h (±10 min), 3 h (±10 min) and 6 h (±10 min) after injection.

^c Some blood samples were collected and preserved for future research.

^d Blood and urine samples were collected for Ad5 viral DNA tests.

^e Ad5 viral DNA tests were performed 30 min (±5), 1 h (±10 min), 3 h (±10 min), and 6 h (±10 mins) after injection. Only blood samples were collected.

^f Image studies include chest CT, abdominal CT, and other necessary image studies at the investigators' discretion.

^g. Biopsy for targeted tumor within 8 weeks prior to Suratadenoturev treatment as baseline data and biopsy at 5 days for the last treatment as post OBP301 were suggested but not mandatory.

^h. OBP-301 was administered only after all required assessments were completed at each visit.

ⁱ Adverse events were collected after the first dose of OBP-301.