JSGT臨床試験トレーニングコース2016
3. Session III ケース・スタディ：企業治験の経験

腫瘍溶解性ウイルス療法HF10の実用化に向けた臨床開発

Clinical Development of HF10, Oncolytic Virus Immunotherapy

タカラバイオ株式会社
田中 舞紀

2016 JSGCT臨床試験トレーニングコース
COI開示

発表責任者：　田中 舞紀

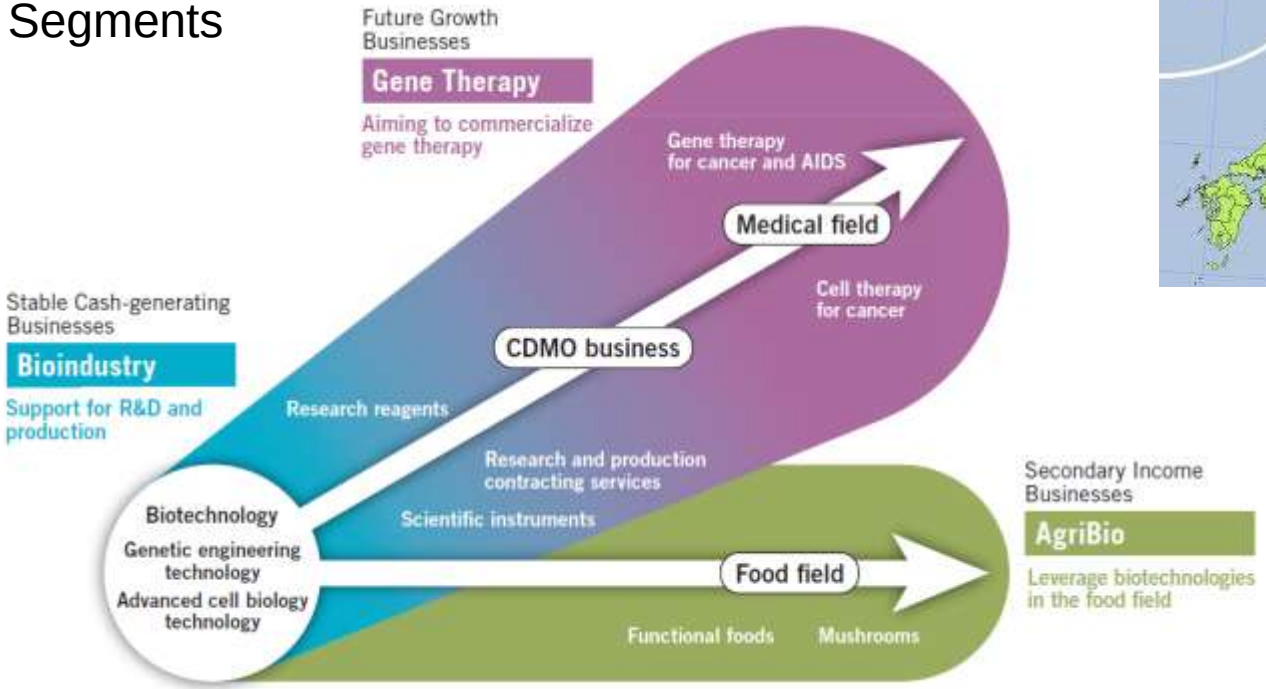
発表者はタカラバイオ株式会社の社員です。

Agenda

1. Introduction
   - Takara Bio Inc.
2. Oncolytic Virus Immunotherapy
   - What is OV?
   - Pipeline - HF10
3. Experiences in Regulatory process in the US and Japan

TAKARA BIO at a Glance

- Trade Name ：TAKARA BIO INC.
- Established ：April 1, 2002
- Issued Capital ：¥ 14,965 million (As of March 31, 2016)
- Head Office ：Kusatsu, Shiga, Japan
- Number of Employees of Takara Bio Group：1,273 (As of March 31, 2016)
- Business Segments



Center for Gene & Cell Processing
(Kusatsu, Shiga, Japan)

Total floor space: 6,500 m^2,

1st floor:

- **Cell banking (e.g. *E. coli*)**
- **Plasmid vector manufacturing**
- ***E. coli* culture for protein production**
- **QC test (sterility, Mycoplasma)**
- **Cell bank storage**

2nd floor:

- **Viral vector production**
  gamma retrovirus, lentivirus, HSV, adenovirus, AAV, HVJ , etc.
- **Cell culture, Media preparation**
- **Protein purification**
- **Aseptic filling**

3rd floor:

- **Cell processing**
- **QC test (test for cells & viruses, qPCR, bio assay, etc.)**

FOYA 2016
Facility of the Year Awards
CATEGORY WINNER
Facility Integration

ISPE Facility of
The Year 2016 Awarded

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Clinical Development Pipeline

	Region	Preclinical	Phase I	Phase II	Phase III
Oncolytic Virus					
HF10 anti-cancer therapy	US			Phase II (to complete by Mar 2017)	
	Japan		Phase I (to complete by Mar 2017)		
Engineered T-cell Therapy					
NY-ESO-1 siTCR gene therapy	Japan		Phase I (to complete by Mar 2017)		
MAGE-A4 siTCR gene therapy	Japan		Phase I (to complete by Mar 2017)		
CD19 CAR gene therapy	Japan		Phase I (to start by Mar 2017)		

Takara sponsored clinical trial

Investigators-initiated clinical trial

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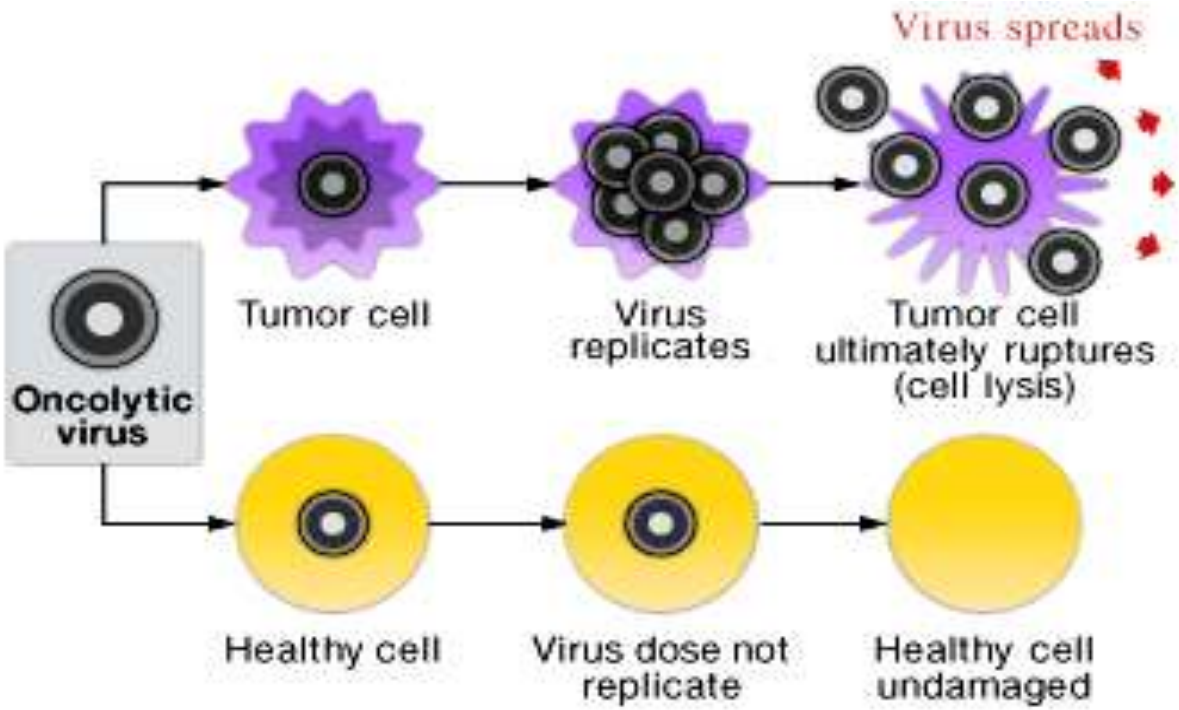
Oncoloytic Virus Immunotherapy

What is Oncolytic Virus?

Oncolytic virus（腫瘍溶解性ウイルス）

正常組織に過度の損傷を与えることなく腫瘍組織内で選択的に増殖、拡散し、腫瘍組織を破壊するウイルス　（ICH considerations on Oncolytic Viruses　和訳より）



History of OV

1954-55 Thirty patients with locally advanced cervical carcinoma were treated with intratumoral injection of wild-type human adenoviruses.

The National Cancer Institute. Cancer 9 (1956)

子宮頸がんに対してアデノウイルス接種

1960~ A large number of oncolytic viruses were studied in cancer patients, including mumps, measles, bovine enterovirus, Newcastle disease virus, etc.

Mumps : Asada, T. Cancer 34 (1974)

Measles : Gross, S. Lancet 1 (1971)

1991 ~ Virotherapy has been re-evaluated

HSV : Martuza, RL et al. Science 252 (1991).

AdV : Bischoff, JR et al. Science 274 (1996).

ウイルス療法の再評価

Various OV

- Type
  - Wild-type OV
    野生型
  - Naturally attenuated OV
    自然変異弱毒型
  - Genetically modified OV
    遺伝子改変型
- Examples of OV
  - Adenovirus
  - Vaccinia virus
  - Herpes simplex virus
  - Measles virus
  - Vesicular stomatitis virus (VSV)
  - Reovirus
  - Newcastle disease virus

10

New Treatment Option – Oncolytic Virus Immunotherapy

IMLYGIC™ (talimogene laherparepvec)

- Amgen社開発、通称T-VEC
- Phase 3 結果：n=436、DRR T-VEC 16% vs GM-CSF 2%、OS 23.3mo vs 18.9mo (p=0.051）
- 2015年10月米国承認、12月欧州承認

NIH NATIONAL CANCER INSTITUTE

NCI Treatment Option Overview

Five types of standard treatment are used:

- Surgery
- Chemotherapy
- Radiation therapy
- Biologic therapy
- Targeted therapy
  - Signal transduction inhibitor therapy
  - **Oncolytic virus therapy**
  - Monoclonal antibody therapy
  - Angiogenesis inhibitors

OV開発例	開発現況
T-VEC	ﾒﾗﾉｰﾏ：米国・欧州承認
CAVATAK	ﾒﾗﾉｰﾏ：米国 Phase 2
HF10	ﾒﾗﾉｰﾏ：米国 Phase 2、日本 Phase 1 膵癌：日本Phase 1準備中
G47Δ	ｸﾞﾘｵｰﾏ：日本 医師主導Phase 2
Telomelysin	食道がん：日本 医師主導Phase 1

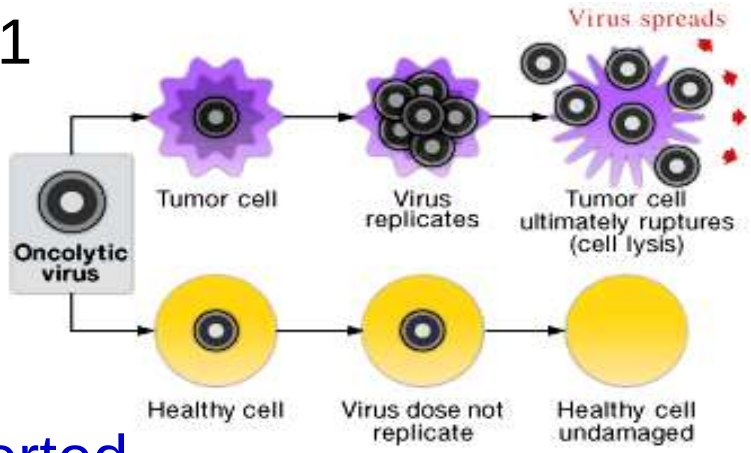
HF10 – An Oncoloytic Herpes Simplex Virus (HSV-1) for treatment of cancer

HF10 – Oncolytic HSV-1

- Spontaneous mutant strain of HSV-1 with no external gene.

→ Greater replication ability = effective dose is lower

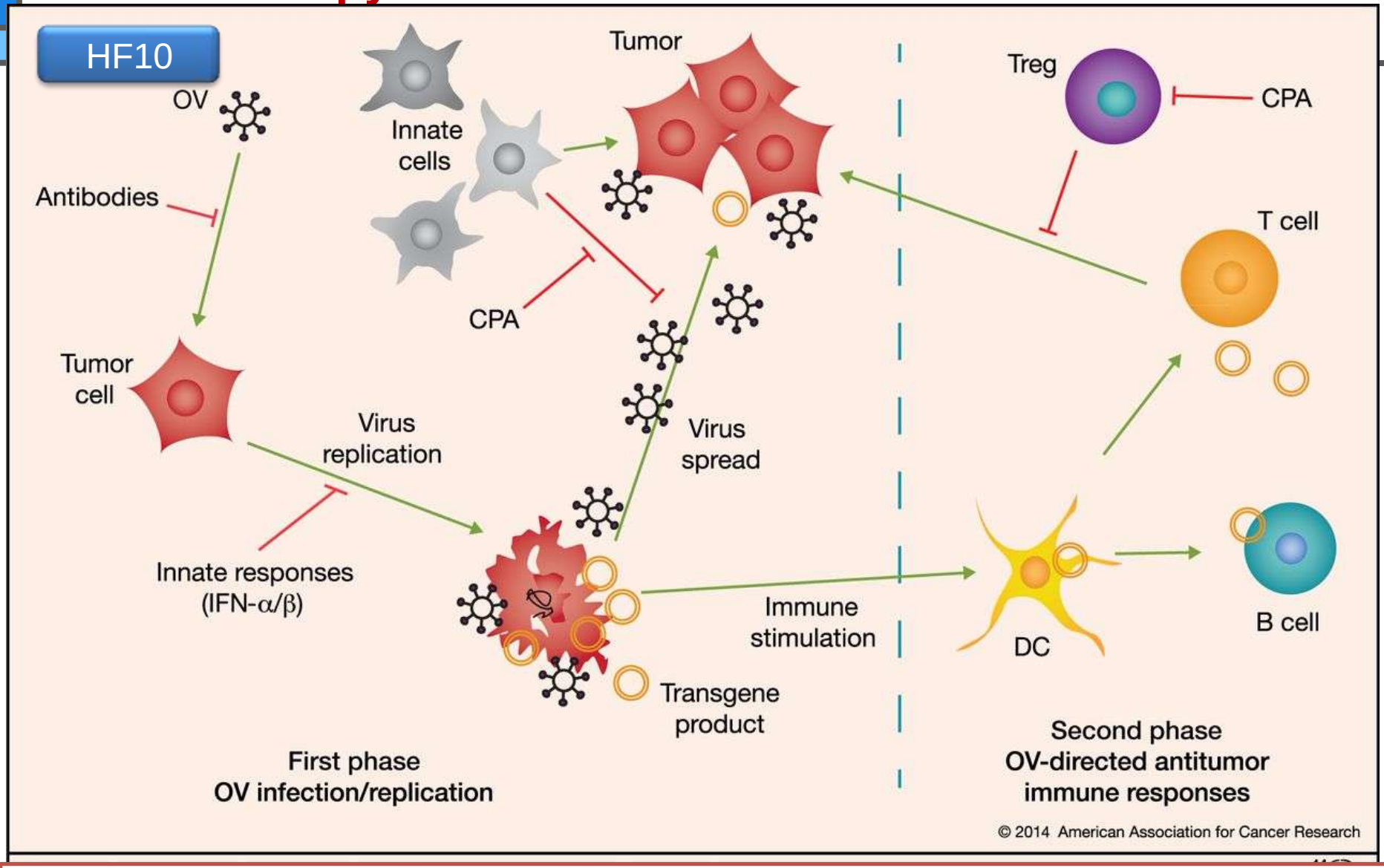
→ No toxicity to be caused by exogenous gene (ex. GM-CSF) inserted.



- In addition to local oncolytic tumor destruction, systemic anti-tumor immune response observed.
- Established by Dr. Nishiyama at Nagoya University
- Licensed rights for the global development of HF10 from Nagoya University

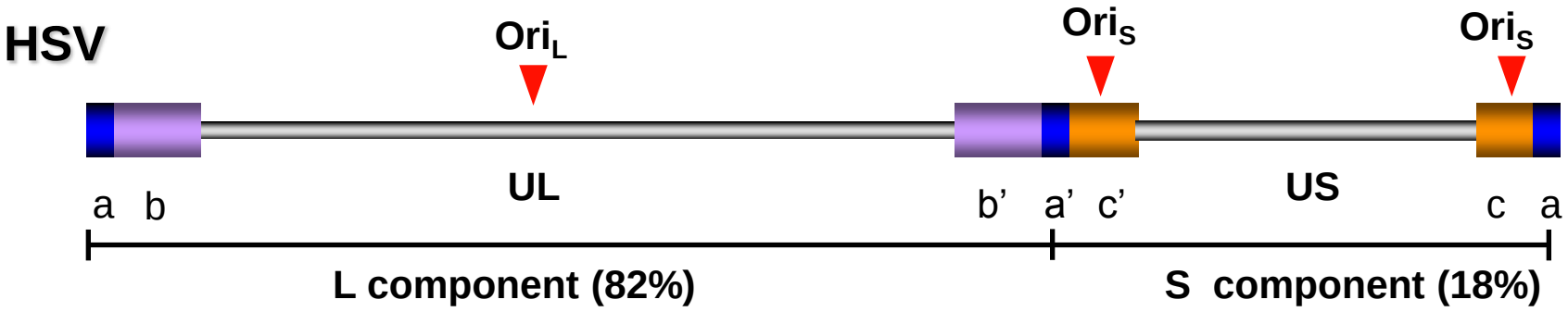
Oncolytic viruses and their application to cancer immunotherapy

Cancer Immunol Res. 2014 Apr;2(4):295-300.

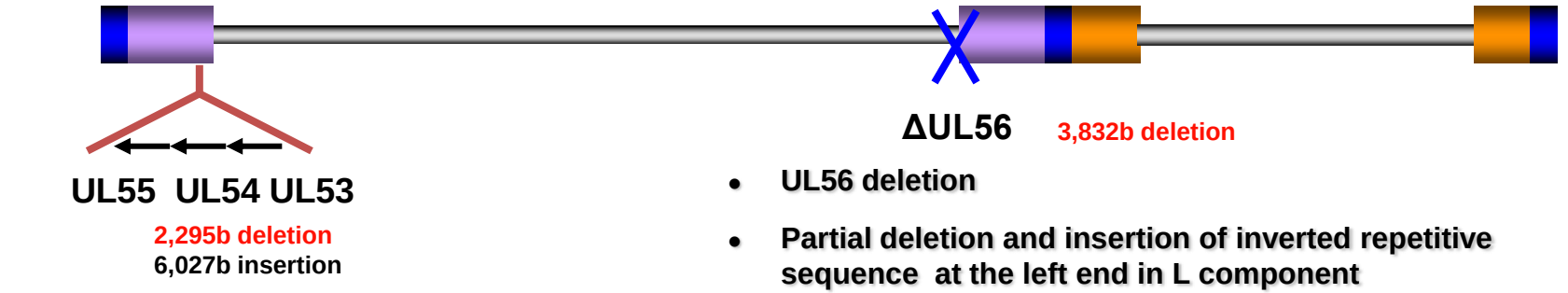


From topical treatment to systemic anti-tumor effects

HSV Genome Structure & HF10



- Since 1988, DNA all base sequence
- UL: 65, US: 14, Inverted repetitive sequence: 10 (Total 89)
- Accessory genes: 45



- UL56 deletion
- Partial deletion and insertion of inverted repetitive sequence at the left end in L component
- Stability of genome in transfer of cultured cells

Lack of UL56 gene decreases HSV-1 pathogenicity without affecting viral replication ability

Attenuated virulence of HF10

Virulence of HSV-1 & 2 after Intraperitoneal Administration to Adult Mice (LD_{50} (pfu))

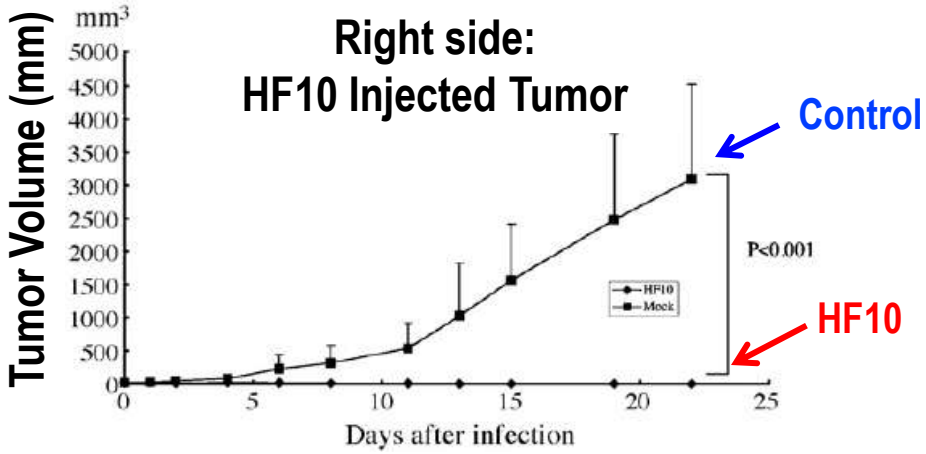
Virus	Characteristics	LD_{50} (pfu)	Ratio
HSV-1 KOS	**Wild-type**	**2,200**	**1**
HSV-1 hrR3	UL39-deletion	> 5,000,000	> 2,272.7
HSV-1 SP23	**Wild-type**	**5,600**	**2.5**
HSV-1 N38	US9,10,11,12-deletion	100,000	45.5
HSV-1 HF 10	**3.9kb-deletion including UL56**	**> 5,000,000**	**> 2,272.7**
HSV-2 186	Wild-type	63	0.03
HSV-2 L1BR1	US3-deletion	> 1,000,000	> 454.5
HSV-2 Y7	Clinical isolate	21	0.01
HSV-2 YN	Clinical isolate	55	0.03

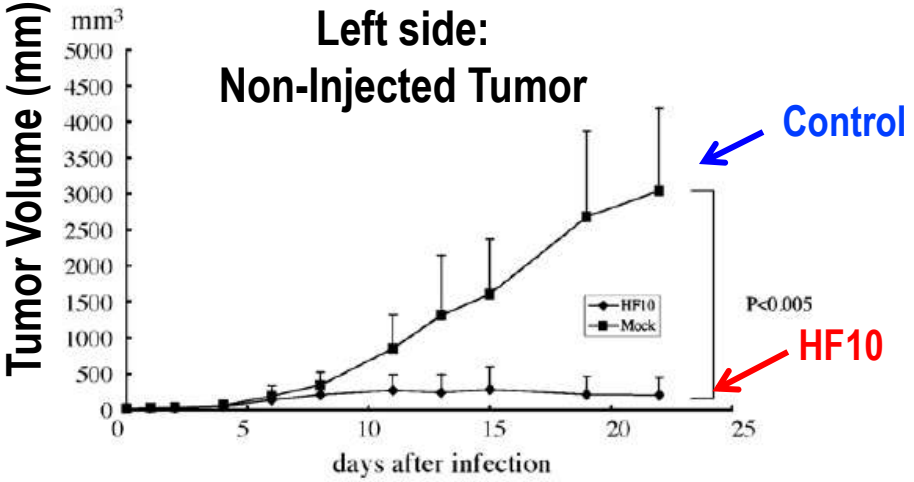
→ LD_{50} reflect mainly neurovirulence

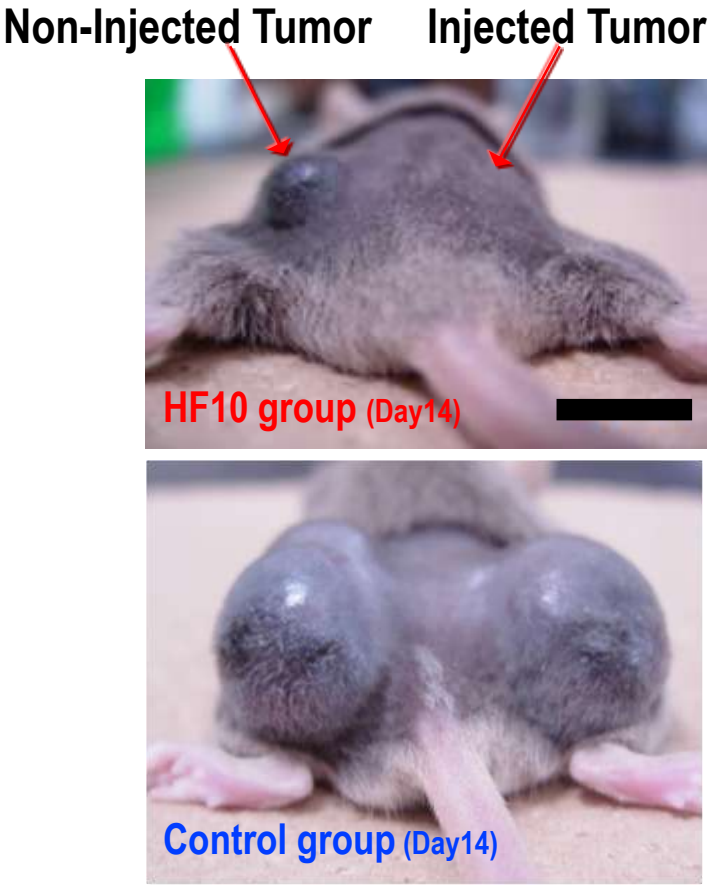
HF10 showed strongly attenuated virulence

Jiang YM. et al. Microbiol Immunol. 39 (11) :905-909.1995

Tumor Immunity in Bilateral Subcutaneous Tumor Model







HF10 reduced tumor growth in non-injected tumor

Watanabe D et al, J Dermatol Sci. 50(3), 185-196, 2008

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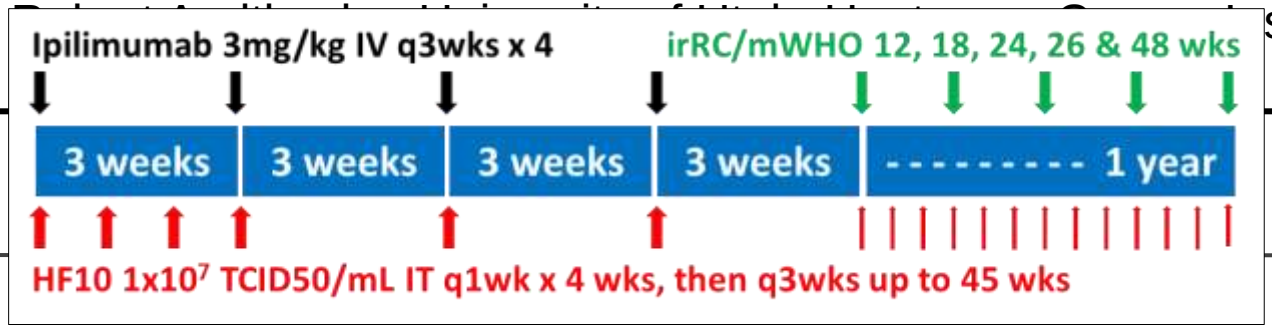
HF10 Clinical Development

To date, a total of ≥**100 patients** have been treated with HF10.

	Phase	Mono or Combo	Tumor type	Status
US	Phase I	monotherapy	Solid tumor	completed
	Phase II	Combo with Ipilimumab	Melanoma	ongoing (enrollment completed)
Japan	Phase I	monotherapy	Solid tumor	ongoing
	Phase II	Combo with Ipilimumab	Melanoma	Planned
	Phase I/II	Combo with Gemcitabine etc.	Pancreatic cancer	Planned
	Investigators' initiated clinical study	Combo with Gemcitabine+Erlotinib	Pancreatic cancer	completed
		monotherapy	Breast, H/N and Pancreatic cancer	completed

Phase 2 trial T14-10682 (US)

Title of the study	A Phase II Study of Combination Treatment with HF10, a Replication-competent HSV-1 Oncolytic Virus, and Ipilimumab in Patients with Stage IIIB, Stage IIIC, or Stage IV Unresected or Metastatic Malignant Melanoma
Objectives	To assess efficacy and safety with repeated administration of intratumoral injections of HF10 at $1x10^7$ $TCID_{50}$/mL in combination with intravenous infusions of 3mg/kg ipilimumab and evaluate the following objectives: **Primary Objective:** Best overall response rate (BORR) at Week 24 **Secondary Objectives:** Safety and tolerability, ORR, PFS, DRR, 1-year survival rate, Evaluation of correlative studies
# of patients	It is planned that at least 43 patients will be enrolled in the study
Methodology	a single arm, open label Phase II trial
Principal Investigator	stitute



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Phase 2 trial T14-10682 (US) - Patient Demographics and Safety

Presented at ASCO 2016

Table 1: Patient Demographics

Characteristics	N (%)	Characteristics	N (%)
Age (Years)		Sex	
Median	67	Male	27 (59%)
Range	29-92	Female	19 (41%)
ECOG Status	N (%)	Disease Stage	N (%)
0	34 (74%)	IIIB	9 (20%)
1	12 (26%)	IIIC	20 (43%)
2	0 (0%)	IV	17 (37%)
HSV-1 antibody	N (%)	Prior Cancer Therapy ≥ 1	N (%)
(+)	30 (65%)	Yes	21 (46%)
(-)	16 (35%)	No	25 (54%)

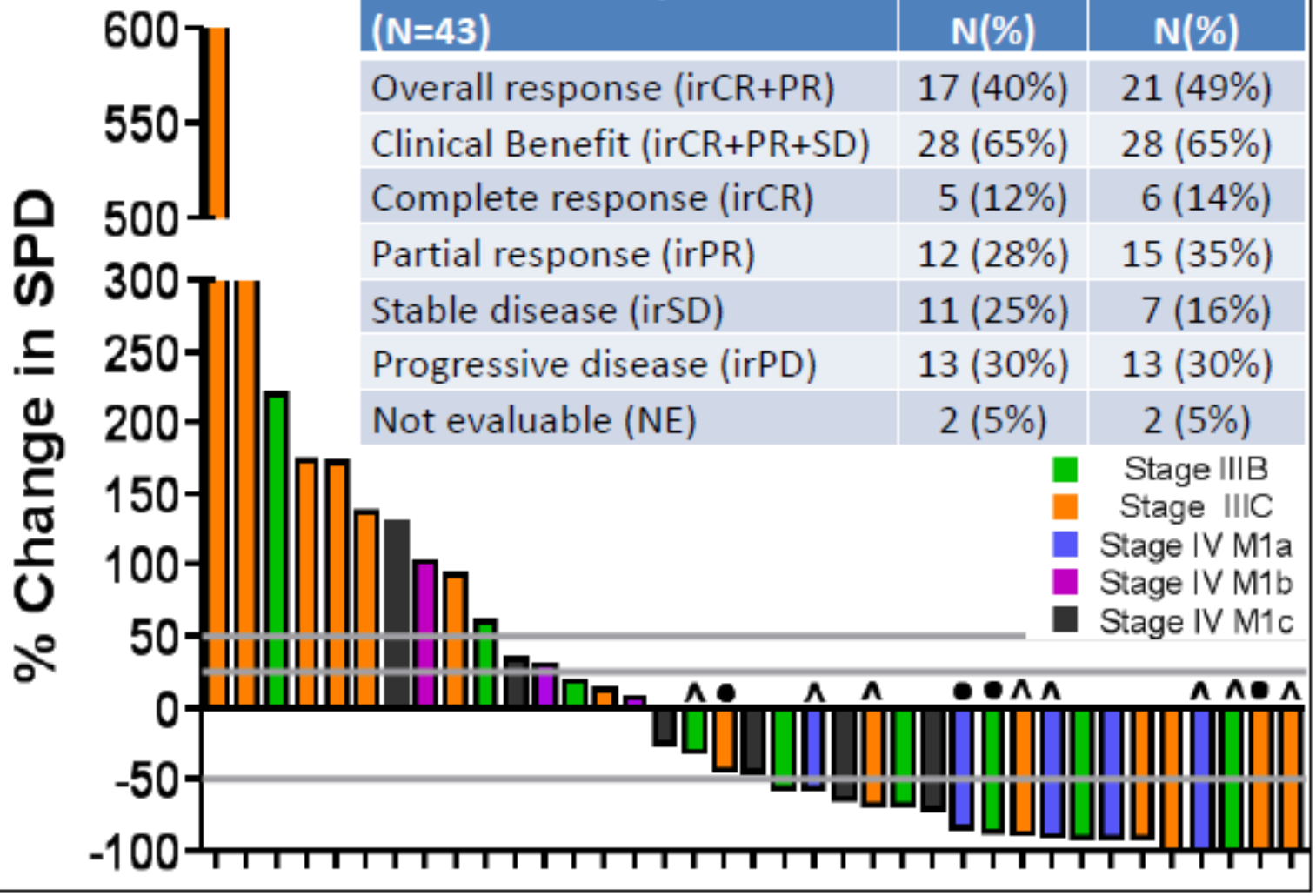
Table 2: Safety Summary

Treatment-Emergent Adverse Events (TEAEs)	Number of Patients (%)
Safety evaluable patients	46
With any TEAEs	46 (100%)
With any TEAEs related to HF10	42 (91%)
With severity ≥ Gr 3 for HF10 related TEAEs	4 (9%)
With any TEAEs related to Ipilimumab	43 (93%)
With severity ≥ Gr 3 for Ipilimumab related TEAEs	10 (22%)
With any serious, HF10 related TEAEs	2 (4%)
With any serious, Ipilimumab related TEAEs	9 (20%)
With any serious, unrelated TEAEs	6 (13%)
Who discontinued drug due to HF10 related TEAEs	0 (0%)

Phase 2 trial T14-10682 (US) – Waterfall plot

Presented at ASCO 2016

Best Overall Response (N=43)	24 wks N(%)	Post 24 wks N(%)
Overall response (irCR+PR)	17 (40%)	21 (49%)
Clinical Benefit (irCR+PR+SD)	28 (65%)	28 (65%)
Complete response (irCR)	5 (12%)	6 (14%)
Partial response (irPR)	12 (28%)	15 (35%)
Stable disease (irSD)	11 (25%)	7 (16%)
Progressive disease (irPD)	13 (30%)	13 (30%)
Not evaluable (NE)	2 (5%)	2 (5%)



• patient has not reached 24 wks of treatment ^patient has not reached 48 weeks of treatment

Phase 2 trial T14-10682 (US)

– Tumor Response in non-injected visceral lesion

Figure 3: Response of Patient 001-005

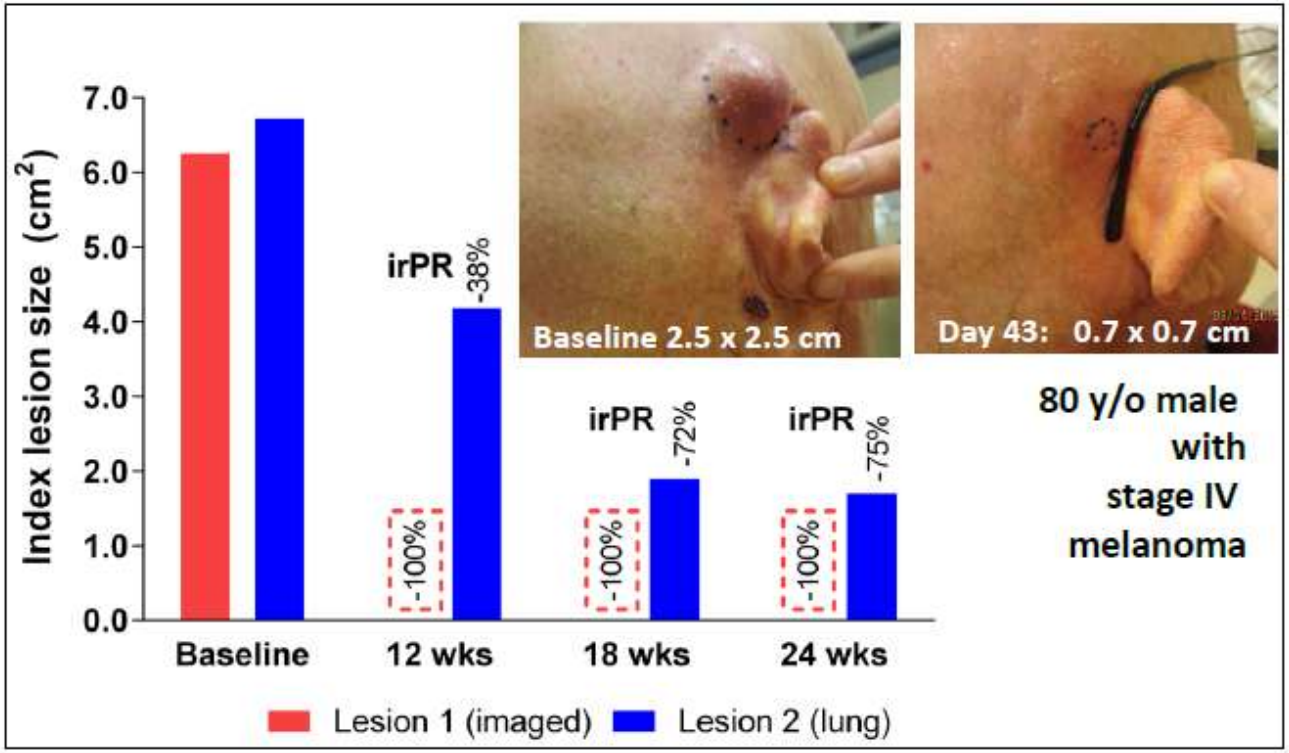
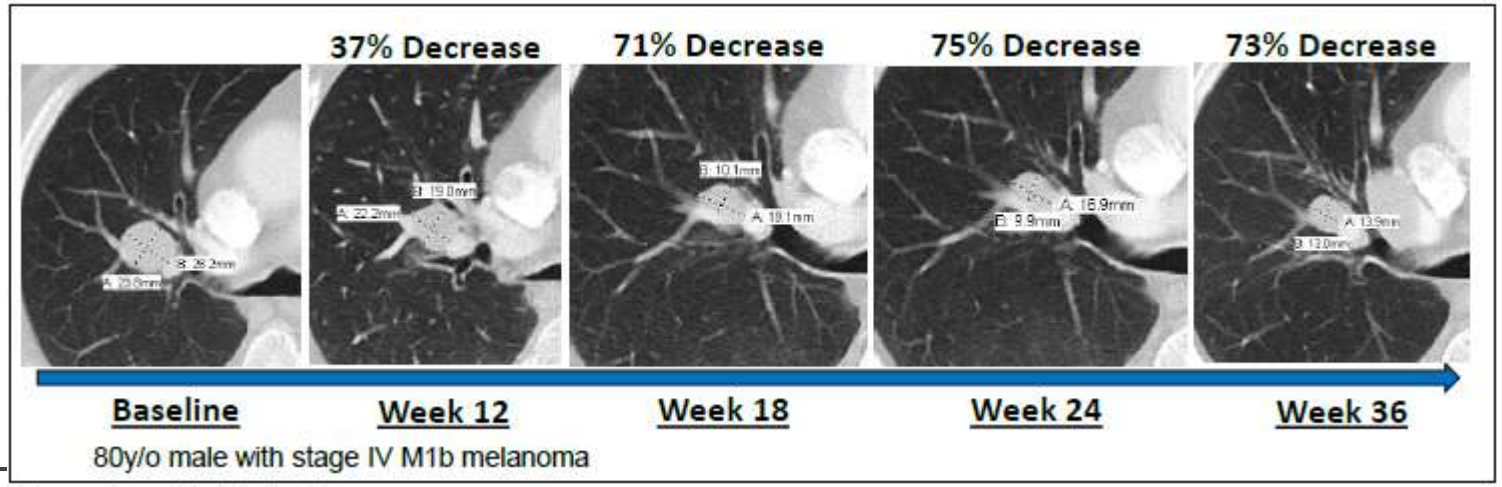


Figure 3: Patient 001-005 Responses in Non-Injected Lesion (Lung)



*percent change calculated from baseline

Presented at AACR-NCI-EORTC 2015, ASCO 2016

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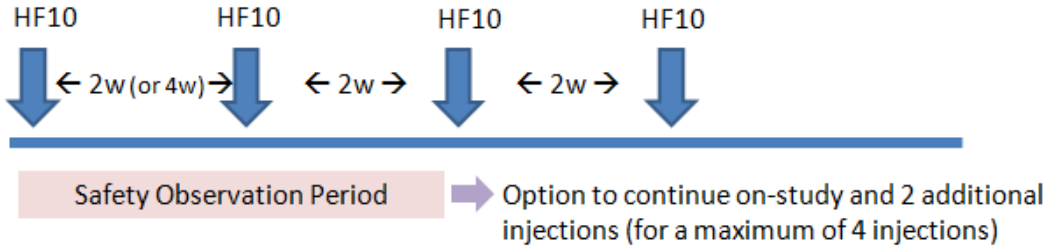
Phase 2 trial T14-10682 (US)
- Comparison with other immunotherapy

Therapy	Grade ≥ 3 AEs, %	Response Rate, %
Monotherapy		
Ipilimumab	27	6–15
Pembrolizumab	13	27–38
Nivolumab	16	34–40
T-VEC	11	26
PV-10	15	51
CVA 21	0	28
Combination therapy		
Nivolumab + ipilimumab	**55**	52
T-VEC + ipilimumab	32	50
T-VEC + pembrolizumab	24	56
HF10 + Ipilimumab	30	49

T-VEC : Treatment naïve patients
HF10 : ≥ 2nd line patients

ASCO 2016 CME symposium
- The Role of Immunotherapy in the Medical Management of Melanoma

Phase 1 trial TBI1401-01 (JP)

Title of the study	Phase I Trial of Intratumoral Administration of TBI-1401(HF10) in Patients with Solid Tumors with Cutaneous and/or Superficial Lesions
Objectives	• To evaluate the safety and tolerability of HF10 at $1x10^6$ and $1x10^7$ $TCID_{50}$/dose in patients with refractory solid tumors with cutaneous and/or superficial lesions (e.g., malignant melanoma, SCC of the skin). • To look for evidence of the overall and local antitumor activity of repeated intratumoral injections of HF10, as well as to investigate the development of anti-HSV antibodies, and antitumor T cell reactivity.
# of patients	6 patients
Methodology	open label, non-randomized, two-stage, dose escalation Phase I study 
Princip Investi	■ 米国第Ⅰ相試験の反復投与コホートと同様の試験デザイン ■ HF10の$1x10^7$ TCID50/日までの日本人における忍容性を確認するとともに、**用量反応性**及び**安全性プロファイル**の国内外差を検討する

Experiences in Regulatory process in the US and Japan

Regulatory status

		Milestones	Date of completion *(italic: target)*
US	Regulatory approvals in the US	Original IND submission (Phase 1 trial)	Mar 31, 2007
		IND amendment#22 submission (Phase 2 trial)	**April 30, 2014**
	Phase 2 study ongoing	Completion of the enrollment	Mar, 2016
		Completion of primary analysis	*End of Sep, 2016*
JP	Regulatory approvals in Japan	Pre-IND meeting with PMDA	Sep 22, 2014
		Clinical Trial Notification (Phase 1 trial)	**Jan 21, 2015**
	Phase 1 study ongoing	Completion of the enrollment	*Aug, 2016*
		Completion of primary analysis	*Nov, 2016*

日米の規制の違い – 事例①

＜薬事＞

- 腫瘍溶解性ウイルスは、米国では医薬品、日本では再生医療等製品に分類
  - 薬事法改正（2014年11月25日施行）により、それまでの医薬品としての開発から再生医療等製品としての開発に変更
  - 条件及び期限付承認制度の適応対象となる

＜再生医療等製品の範囲＞
(1) 人又は動物の細胞に培養等の加工を施したものであって、
イ　身体の構造・機能の再建・修復・形成するもの
ロ　疾病の治療・予防を目的として使用するもの

(2) 遺伝子治療を目的として、人の細胞に導入して使用するもの

第21回GLP研修会 PMDA公開資料より抜粋
http://www.pmda.go.jp/files/000208000.pdf

日米の規制の違い－事例②

＜非臨床＞

- 2005年当時の日本では、第Ⅰ相試験開始の条件として、サルの毒性試験が必要とされた。一方、米国ではマウスの毒性試験データにより充足

- 製造工程由来不純物（日本）：
  原材料について、供給業者から成分及び分量の情報を入手し、最終製品中に含まれる個々の不純物の安全性評価が必要　（ウイルス・細胞加工製品で必要）

POINT

＜CMC（製造・品質）＞

- 生物由来原料基準への対応（日本）
  - 一部原材料については、原材料の原材料の情報まで必要
    （例えば、培地に含まれる生物由来成分の製造に用いた原材料、それらのCOO/COAの入手、メーカーへの問合せ）

POINT

日米の規制の違い – 事例③

腫瘍溶解性ウイルスの開発においては、ウイルス排出（viral shedding）*1 の評価が推奨される （ICH見解「腫瘍溶解性ウイルス」）

＊1 患者の分泌物／排泄物を介した腫瘍溶解性ウイルスの拡散

＜臨床＞

- 米国ではウイルス投与の外来治療が可能。日本の第Ⅰ相試験では、ウイルス投与後1日は入院管理が必要。
  - 過去のHF10の臨床試験の結果から、ウイルス活性化による全身反応、第三者への伝播の可能性を完全に否定できない
  - 一方、海外第Ⅰ相試験で第三者への感染報告がないことから、入院の翌日以降は在宅管理を認める
- 第三者へのウイルス感染防止策*2： 米国では患者にウイルス投与後1週間の順守を求めるところ、日本では2週間の順守を求める。

＊2 マスクの着用、他者への不必要な接触の制限等

POINT

→ 臨床および非臨床データから より安全性に配慮した観察検査スケジュールの構築

→ 規制当局と適宜適切に相談しながら計画立案

HF10 日米臨床開発のまとめ

To date, a total of ≥**100 patients** have been treated with HF10.

	Phase	Mono or Combo	Tumor type	Status
US	Phase I	monotherapy	Solid tumor	completed
	Phase II	Combo with Ipilimumab	Melanoma	ongoing (enrollment completed)
Japan	Phase I	monotherapy	Solid tumor	ongoing
	Phase II	Combo with Ipilimumab	Melanoma	Planned
	Phase I/II	Combo with Gemcitabine etc.	Pancreatic cancer	Planned
				eted
			Pancreatic cancer	eted

米国臨床データおよび開発経験を有効活用し
日本での早期承認取得

日本遺伝子細胞治療学会
タカラバイオ共催セミナー

第22回日本遺伝子細胞治療学会学術集会
- 2016年7月28日(木)～30日(土)，虎ノ門ヒルズ

- 日時：**7月29日(金)12時～13時**
- 共催セミナー
  Cutting edge of Oncolytic Virus Immunotherapy

- 演者：Robert H.I. Andtbacka, MD, CM
  Surgical Oncology Department of Surgery University of Utah, Huntsman Cancer Institute
- 座長：小澤 敬也 先生
  東京大学医科学研究所 附属病院長、先端医療研究センター・遺伝子治療開発分野、教授

JSGCT
日本遺伝子細胞治療学会

第54回日本癌治療学会学術集会

シンポジウム「**日米の腫瘍溶解性ウイルス療法（Oncolytic Virus Immunotherapy）最前線**」

- 日時：**10月21日（金）**
  10時10分～12時10分
- 座長：
  山崎直也先生（国立がんセンター中央病院），
  藤原俊義先生（岡山大学）
- 演者：
  - Robert Andtbacka, MD (University of Utah)
  - Sanjiv Agarwala, MD (St. Lukes)
  - Merrick Ross, MD (MD Anderson)
  - **藤原俊義先生、粕谷英樹先生**
- 共催：タカラバイオ、オンコリスバイオファーマ