Current Trends in Clinical Development of Gene and Cellular Therapeutic Products for Cancer in Japan

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ABSTRACT

Purpose: In Japan, gene therapy and cellular therapy are categorized as regenerative medicine products based on the Pharmaceuticals and Medical Devices Law that was implemented in 2014. In this new law, regenerative medicine products were newly defined, and a conditional and term-limited approval system for regenerative medicine products was instituted. In addition, the Ministry of Health, Labour and Welfare instituted the SAKIGAKE (meaning pioneer or forerunner in Japanese) designation system in 2015. This designation is similar to the breakthrough therapy designation in the United States. These new regulatory frameworks have stimulated clinical development of new gene and cellular products in Japan. In fact, oncolytic virus therapy for glioblastoma and NY-ESO-1 (T-cell receptor) T-cell therapy for synovial sarcoma were granted SAKIGAKE designation in 2016 and 2018, respectively. Oncolytic virus therapy and genetically engineered T-cell therapy for cancer are being actively developed and examined in investigator-initiated trials.

Methods: This review analyzes the domestic and international clinical trial registries to comprehensively collect information on clinical trials of gene and cellular therapeutic products for cancer in Japan.

Implications: Current trends in clinical development of gene and cellular therapeutic products for cancer in Japan are discussed. (*Clin Ther*. 2019;41:174–184)

Keywords: CAR, chimeric antigen receptor, oncolytic virus, T-cell receptor, TCR.

INTRODUCTION

There are 2 pathways for clinical development of investigational medical products in Japan: registration trials and clinical research. Registration trials are defined as clinical trials conducted for the purpose of marketing authorization. Clinical research is not intended for marketing authorization. Registration trials are conducted not only by companies but also by academic researchers as investigator-initiated registration trials. In clinical research, physicians administer medical products to patients as research. Registration trials and clinical research are regulated differently.

In terms of registration trials and marketing authorization, the Pharmaceuticals and Medical Devices Agency (PMDA) reviews investigational new drug notifications of registration trials and marketing authorization applications, and the Ministry of Health, Labour and Welfare (MHLW) approves marketing authorization of drugs, medical devices, and regenerative medicine products. In terms of clinical research, the MHLW is primarily responsible for regulations, and the PMDA deals with investigation of cell-processing facilities only.[1,2]

The present review comprehensively describes current trends in clinical development of regenerative medicine products for cancer in Japan.

REGULATION OF REGISTRATION TRIALS

The MHLW revised the Pharmaceutical Affairs Law and implemented the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (PMD) Act in

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November 2014.[1,3,4] The conditional and term-limited approval system was instituted for regenerative medicine products in this PMD Act. This approval system is similar to the accelerated approval system in the United States and the conditional approval system only for initial marketing authorization in the European Union. Early approval with conditional and term-limited licensing is granted if efficacy can be assumed and safety is confirmed in an early-phase clinical trial. Confirmation of efficacy and further verification of safety after marketing are required.[1] In the PMD Act, cellular medical products, ex vivo gene medical products, and in vivo gene medical products are newly defined as "regenerative medicine products."[1,3,4]

After implementation of the PMD Act, 3 regenerative medicine products were approved as of July 21, 2018, in Japan: a human mesenchymal stem cell–based product* for acute graft-versus-host disease, an autologous skeletal myoblast sheet–based product† for severe ischemic heart failure, and an autologous cultured epidermis product‡ for giant congenital melanocytic nevus. Conditional and term-limited approval was granted to the autologous skeletal myoblast sheet–based product only. There have been no approved regenerative medicine products for cancer as of July 21, 2018.

Moreover, the MHLW instituted the SAKIGAKE (meaning pioneer or forerunner in Japanese) designation system for pharmaceutical drugs in April 2015.[5] In July 2015, the MHLW additionally started the SAKIGAKE designation system for medical devices, in vitro diagnostics, and regenerative medicine products (Table I). Target total review time of 6 months is applied not to SAKIGAKE-designated regenerative medicine products but to SAKIGAKE-designated drugs and medical devices.[6] In general, the target total review time for gene and cellular products is 9 months; the review time excludes the period for companies to prepare responses to PMDA's queries.[7] This SAKIGAKE designation is similar to the breakthrough therapy designation in the United States and PRIME (Priority Medicines) in the European Union.[1] Two regenerative medicine products for cancer have been granted SAKIGAKE designation. In February 2016, the MHLW granted SAKIGAKE designation to oncolytic virus G47 delta for glioblastoma, which is being developed by the University of Tokyo and Daiichi Sankyo (Table II). G47 delta is a genetically engineered herpes simplex virus-1 with triple mutations that realized augmented viral replication in tumor cells and strong induction of antitumor immunity.[8] In March 2018, the MHLW additionally granted SAKIGAKE designation to NY-ESO-1 T-cell receptor (TCR) T-cell therapy (TBI-1301) for synovial sarcoma, which is being developed by Takara Bio Inc (Table III).

In addition, the MHLW commenced the Project for Enhanced Practical Application of Innovative Drugs, Medical Devices and Regenerative Medicine Products in 2012. The main purpose of this project is cooperation in drafting regulatory guidance documents on evaluation of innovative medical products between the PMDA and academic institutes. The project was completed on March 31, 2017, as

Table I. SAKIGAKE designation.*

Requirements	1. Mode of action is innovative
	2. Target disease is serious
	3. Prominent effectiveness can be expected
	4. The medical product has been developed in Japan, and a sponsor is planning to submit a marketing authorization application in Japan first
Benefits	1. Prioritized consultation (reduced waiting time)
	2. Substantial preapplication consultation
	3. Priority review
	4. Assignment of a PMDA manager as a concierge

PMDA = Pharmaceuticals and Medical Devices Agency.
* Meaning pioneer or forerunner in Japanese.

* Trademark: Temcell® HS (JCR Pharmaceuticals Co Ltd, Hyogo, Japan).

† Trademark: HeartSheet® (Terumo Corporation, Tokyo, Japan).

‡ Trademark: JACE® (Japan Tissue Engineering Co., Ltd., Aichi, Japan).

Table II. Clinical trials of in vivo gene therapies for cancer in Japan.

Therapy/Abbreviation	Disease	Main Institute or Company	Other Information
Talimogene laherparepvec (T-VEC)	Melanoma	Amgen Inc	Phase I, company-initiated registration trial, NCT03064763
HSV-1 oncolytic virus (HF10) + ipilimumab	Melanoma	Takara Bio Inc	Phase II, company-initiated registration trial, NCT03153085, JapicCTI-173591
HSV-1 oncolytic virus (HF10)	Cancer	Takara Bio Inc	Phase I, company-initiated registration trial, NCT02428036, JapicCTI-152935
HSV-1 oncolytic virus (HF10) + gemcitabine + nab-paclitaxel or TS-1	Pancreatic cancer	Takara Bio Inc	Phase I, company-initiated registration trial, UMIN000010150, NCT03252808, JapicCTI-173671, JMACCT CTR website[23]
HSV-1 oncolytic therapy (HF10)	Cancer	Mie University	Phase I, UMIN000007263
Telomerase-selective oncolytic adenovirus (OBP-301) + radiation	Esophageal cancer	Oncolys Biopharma Inc	Phase I, company-initiated registration trial, NCT03213054
Telomerase-selective oncolytic adenovirus (OBP-301) + pembrolizumab	Cancer	National Cancer Center	Phase I, investigator-initiated registration trial, NCT03172819
Telomerase-selective oncolytic adenovirus (OBP-301) + radiation	Head and neck cancer, esophageal cancer, non-small-cell lung cancer	Okayama University	Phase I/II, UMIN000010158
Ad-SGE-REIC	Pleural mesothelioma	Kyorin Pharma	Phase I/II, company-initiated registration trial, JapicCTI-152998
Ad-SGE-REIC-GH	Liver cancer	Okayama University	Phase I, UMIN000027770
REIC/Dkk-3 adenovirus therapy	Pleural mesothelioma	Okayama University	Phase I/II, UMIN000013568
REIC/Dkk-3 adenovirus therapy	Prostate cancer	Okayama University	Phase I/II, UMIN000004929, Maude et al[25]
Oncolytic virus G47 delta	Glioblastoma	University of Tokyo (and Daiichi Sankyo)	Phase II, investigator-initiated registration trial, SAKIGAKE designation,* UMIN000015995
Oncolytic virus therapy G47 delta	Olfactory neuroblastoma	University of Tokyo	UMIN000011636

Table II. (*Continued*)

Therapy/Abbreviation	Disease	Main Institute or Company	Other Information
Oncolytic virus therapy G47 delta	Prostate cancer	University of Tokyo	Phase I, UMIN000010463
Oncolytic virus therapy G47 delta	Glioblastoma	University of Tokyo	Phase I/II, UMIN000002661
GEN0101 (HVJ-E) + dendritic/tumor fusion cells	Ovarian cancer	Osaka University	Phase I, UMIN000031281
GEN0101 (HVJ-E)	Pleural mesothelioma	Osaka University	Phase I, investigator-initiated registration trial, UMIN000019345
GEN0101 (HVJ-E)	Melanoma	Osaka University	Phase I/II, investigator-initiated registration trial, UMIN000002376
GEN0101 (HVJ-E)	Prostate cancer	Osaka University	Phase I/II, investigator-initiated trial, UMIN000010840, NCT02502994
GEN0101 (HVJ-E)	Prostate cancer	Osaka University	Phase I/II, UMIN000006142, Hirooka et al[26]
Survivin oncolytic adenovirus therapy (Surv.m-CRA-1)	Soft tissue tumor and bone tumor	Kagoshima University	Phase I, investigator-initiated registration trial, UMIN000023120
AdCMV-NK4	Pleural mesothelioma	Chiba University	Phase I, UMIN000015771, Kumon et al[28]
Poliovirus therapy	Glioblastoma	Mie University	Phase I, UMIN000029816

HVJ-E = hemagglutinating virus of Japan envelope; HSV = herpes simplex virus; NCT = trial registration number in the ClinicalTrials.gov database; JapicCTI = trial registration number in the Japan Pharmaceutical Information Center Clinical Trials Information; JMACCT CTR = Center for Clinical Trials, Japan Medical Association, Clinical Trials Registry; UMIN = trial registration number in the UMIN Clinical Trials Registry.
* Meaning pioneer or forerunner in Japanese.

the MHLW had planned. The project included the following subprojects regarding the development of regenerative medicine products for cancer: cancer immunotherapy (Mie University) and oncolytic viruses (University of Tokyo). In fact, several ex vivo gene therapeutic products have been developed by researchers in Mie University, and oncolytic virus G47 delta has been developed by researchers in the University of Tokyo as shown in Tables II and III. In these subprojects, the academic institutes were expected to organize working groups and prepare regulatory guidance documents concerning quality, nonclinical, or clinical parameters of the development of regenerative medicine products in cooperation with the PMDA and MHLW.[2,9] The 2015 Guidance on Cancer Immunotherapy Development in Early-Phase Clinical Studies is one of the results of the cancer immunotherapy subproject between Mie University and the PMDA.[10] The other results are currently available only in Japanese.

REGULATION OF CLINICAL RESEARCH

In November 2014, the MHLW issued the Act on the Safety of Regenerative Medicine (ASRM) for clinical research other than registration trials using cellular medical products. In vivo gene therapy is therefore outside the scope of the ASRM, although regenerative medicine products defined in the PMD Act include in vivo gene therapy.[2,11–13] Ex vivo gene therapy such as adoptive immunotherapy using gene

Table III. Clinical trials of ex vivo gene therapies for cancer in Japan.

Therapy	Disease	Main Institute or Company	Other Information
CD19 CAR T-cell therapy (CTL019) after fludarabine and cyclophosphamide	Diffuse large B-cell lymphoma	Novartis	Phase II, company-initiated registration trial, NCT02445248
CD19 CAR T-cell therapy (CTL019) after fludarabine and cyclophosphamide	Pediatric B-cell acute lymphoblastic leukemia	Novartis	Phase II, company-initiated registration trial, NCT02435849, JapicCTI website[22]
CD19 CAR T-cell therapy (CTL019) after lymphodepleting chemotherapy	Pediatric B-cell acute lymphoblastic leukemia	Novartis	Phase III, expanded protocol, company-initiated registration trial, NCT 03123939, JapicCTI-184039
CD19 CAR T-cell therapy (TBI-1501) after cyclophosphamide	Adult B-cell acute lymphoblastic leukemia	Takara Bio Inc	Phase I/II, company-initiated registration trial, NCT03155191, JapicCTI-173565
CD19 CAR T-cell therapy after cyclophosphamide or bendamustine	B-cell lymphoma	Jichi Medical University	Phase I/II, UMIN000015617, NCT02134262
CD19 CAR T-cell therapy using nonviral vectors (lymphodepleting chemotherapy is not disclosed)	Pediatric B-cell acute lymphoblastic leukemia	Nagoya University	Phase I, UMIN000030984
NY-ESO-1 TCR T-cell therapy (TBI-1301) after cyclophosphamide	Synovial sarcoma	Takara Bio Inc	Phase I/II, company-initiated registration trial, SAKIGAKE designation,* UMIN000029573, NCT03250325, JapicCTI-173514
NY-ESO-1 TCR T-cell therapy (TBI-1301-A) after cyclophosphamide	Adult T-cell leukemia/ lymphoma	Nagasaki University and Mie University	Phase I, investigator-initiated registration trial, UMIN000031853, JapicCTI-183830
NY-ESO-1 TCR T-cell therapy (TBI-1301) +cancer vaccine (CHP:NE1)	Soft tissue sarcoma	Mie University	Phase I/II, investigator-initiated registration trial, JMA-IIA00346
NY-ESO-1 TCR T-cell therapy (TBI-1301) after cyclophosphamide ± fludarabine	Cancer	Mie University	Phase I, investigator-initiated registration trial, NCT02366546, JapicCTI-152896
MAGE-A4 TCR T-cell therapy (TBI-1201) after cyclophosphamide ± fludarabine	Cancer	Mie University	Phase I, investigator-initiated registration trial, UMIN000001063, NCT02096614, JapicCTI-142555

Table III. (*Continued*)

Therapy	Disease	Main Institute or Company	Other Information
MAGE-A4 TCR T-cell therapy after cyclophosphamide	Esophageal cancer	Mie University	Phase I, UMIN000010729
MAGE-A4 TCR T-cell therapy + MAGE-A4 peptide	Esophageal cancer	Mie University	Phase I, UMIN000002395, Fujita et al[29]
MS3-WT1-siTCR T-cell therapy + WT1 peptide	Acute myeloid leukemia and myelodysplastic syndrome	Mie University	UMIN000011519, Tawara et al[16]
HSV-tk T-cell therapy (TBI-0301)	Hematological malignancy	Takara Bio Inc	Phase I, company-initiated registration trial, UMIN000002502, JapicCTI-090932
aAVC-WT1 therapy	Acute myeloid leukemia	University of Tokyo and Riken	Phase I, investigator-initiated registration trial, UMIN000028083

CAR = chimeric antigen receptor; NCT = trial registration number in the ClinicalTrials.gov database; JapicCTI = trial registration number in the Japan Pharmaceutical Information Center Clinical Trials Information; JMA = trial registration number in the Center for Clinical Trials, Japan Medical Association, clinical trials registry; TCR = T-cell receptor; UMIN = trial registration number in the UMIN Clinical Trials Registry.
* Meaning pioneer or forerunner in Japanese.

transfer is within the scope of the ASRM. In cases of clinical research involving in vivo gene therapy, physicians must follow "the Guideline on Clinical Research Using In Vivo Gene Therapy."[2,14] Some (although not all) registration trials and clinical studies involving in vivo or ex vivo gene therapy in Japan are listed on the website of the National Institute of Health Science.[15]

Under the ASRM, clinical research using processed cells are categorized into class I (high risk), II (medium risk), or III (low risk). The use of embryonic stem cells, induced pluripotent stem cells, genetically modified cells, animal cells, or allogeneic human cells is classified as class I. Administering autologous cells to organs similar to the administered cells (homologous use) is classified as class III. The use of autologous cells for other purposes is categorized as class II.[2,11–13]

Currently, any class I and II medical treatment or clinical research involving ex vivo gene transfer is subject to review by the Certified Special Committee for Regenerative Medicine at Osaka University.[2,11–13] This committee can only review applications of clinical research involving ex vivo gene transfer conducted in any Japanese hospital. The following 3 clinical research cases of cancer immunotherapy involving ex vivo gene transfer were discussed in the Certified Special Committee for Regenerative Medicine at Osaka University: CD19 chimeric antigen receptor (CAR) T-cell therapy for B-cell lymphoma (Jichi Medical University); MS3-WT1-siTCR T-cell therapy for acute myeloid leukemia and myelodysplastic syndrome (Mie University); and CD19 CAR T-cell therapy using nonviral vectors for acute lymphoblastic leukemia (Nagoya University) (Table III). MS3-WT1-siTCR T cells are T cells to which the WT1-specific TCR gene was transduced by using a retroviral vector encoding small interfering RNAs for endogenous TCR genes.[16]

In Japan, the Clinical Trials Act has been in effect since April 2018. This act establishes procedures for the conduct of "specified clinical trials," measures for appropriate operations of the certified review board, and publication of information on funds or other

benefits for clinical trials. Specified clinical trials are categorized into the following: clinical trials conducted receiving research funds or other benefits provided by companies; and clinical trials in which unapproved drugs, medical devices, or regenerative medicine products as well as unapproved indications or dosage of approved drugs, medical devices, or regenerative medicine products are examined.[17] The ASRM will be revised to ensure consistency with the Clinical Trials Act.[18]

In addition, the Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms regulates clinical research of gene therapy in Japan. The purpose of this act is to ensure the implementation of the Cartagena Protocol on Biosafety to the Convention on Biological Diversity. The Type 1 Use Regulations are applied to in vivo gene therapy. The Type 2 Use Regulations are applied to ex vivo gene therapy in cases in which remaining viral vectors are not detected.[19]

JAPAN AGENCY FOR MEDICAL RESEARCH AND DEVELOPMENT

Japan Agency for Medical Research and Development (AMED) was established in April 2015. AMED funds medical studies and research facilities to promote the practical application of beneficial research outcomes. Before the establishment of AMED, researchers were required to request funding from several ministries, depending on the phase of their studies. Now, AMED provides streamlined, consistent support from initial investigations to practical application of new medicines and treatments in the real world. AMED is responsible for a budget of approximately 139 billion Japanese Yen (JPY) in 2018. AMED's major grant projects are as follows: project for drug discovery and development (20.9 billion JPY), Japan cancer research project (16.0 billion JPY), Japan regenerative medicine project (15.7 billion JPY), project for medical device development (12.9 billion JPY), rare/intractable disease project of Japan (12.4 billion JPY), Japan genomic medicine program (10.4 billion JPY), and the project of translational and clinical research core centers (8.6 billion JPY), as well as others.[20]

In particular, the Practical Research for Innovative Cancer Control program of the Japan cancer research project and The Translational Research Program; Strategic Promotion for Practical Application of Innovative Medical Technology (TR-SPRINT) of the project of translational and clinical research core centers have funded many clinical trials of gene and cellular therapies for cancer, including the following: oncolytic virus G47 delta (University of Tokyo); hemagglutinating virus of Japan envelope (HVJ-E) (Osaka University); survivin-responsive conditionally replicating adenoviruses regulated with multiple factors (Surv.m-CRA-1; Kagoshima University); NY-ESO-1 TCR T-cell therapy (Nagasaki University and Mie University); aAVC-WT1 therapy (University of Tokyo and Riken); MS3-WT1-siTCR T-cell therapy (Mie University); and CAR T-cell therapy using nonviral vectors (Nagoya University) (Tables II and III). In addition, these 2 AMED programs have funded preclinical research projects of gene and cellular therapies for cancer, which are listed in Table IV; as shown, many oncolytic virus therapies and CAR T-cell therapies have been funded.

CLINICAL TRIALS IN JAPAN

To comprehensively describe clinical trials of gene and cellular therapies for cancer that were or are currently being conducted in Japan, we examined the UMIN Clinical Trials Registry,[21] Japan Pharmaceutical Information Center Clinical Trials Information,[22] the Center for Clinical Trials, Japan Medical Association, Clinical Trials Registry,[23] and ClinicalTrials.gov.[24] The UMIN Clinical Trials Registry, Japan Pharmaceutical Information Center Clinical Trials Information, and the Center for Clinical Trials, Japan Medical Association, Clinical Trials Registry are the Japanese clinical trial registries.

Clinical trials of in vivo gene therapies, ex vivo gene therapies, and other cellular therapies for cancer that were or are currently being conducted in Japan and were listed in the 3 Japanese clinical trial registries and ClinicalTrials.gov as of July 21, 2018, are described in Tables II and III and the Supplemental Table (see the online version at https://doi.org/10.1016/j.clinthera.2018.11.003), respectively. These tables present information on the therapeutic product, target disease, sponsor (company- or investigator-initiated), registration trial or clinical research, trial registration number, and reference document in which clinical trial results were shown. In total, data on 24 in vivo gene therapy trials, 16 ex vivo gene therapy trials, and 55 other cellular

Table IV. Preclinical research projects of gene and cellular therapies for cancer in Japan supported by the 2 Japan Agency for Medical Research and Development projects.

Therapy	Disease	Institute
In vivo gene therapy		
CXCL2 HVJ-E	Cancer	Osaka University
SOCS-3 adenovirus therapy (AdSOCS-3)	Pleural mesothelioma	Kochi University
Interleukin-12 oncolytic virus therapy	Melanoma	Shinshu University
p53 virus therapy	Cancer	Okayama University
Oncolytic measles virus therapy	Cancer	University of Tokyo
Oncolytic coxsackievirus therapy	Cancer	Kyushu University and University of Tokyo
Oncolytic vaccinia virus therapy	Cancer	Tottori University
Genome-editing vector	Cancer	Some medical institutes
Cellular therapy		
GITR CAR T-cell therapy	Cancer	Mie University
EPHB4 CAR T-cell therapy	Soft tissue sarcoma	Kyoto Prefectural University of Medicine
CAR T-cell therapy	B-cell lymphoma	Yamaguchi University
CD116 CAR T-cell therapy using nonviral vectors	Myeloid malignancies	Shinshu University
CAR T-cell therapy	Multiple myeloma	Osaka University
iPS-derived CAR T-cell therapy	Cancer	Kyoto University
iPS-derived T-cell therapy	Cancer	Kumamoto University
NK T-cell therapy	Cancer	Keio University and Riken
NK cell therapy	Cancer	Kyushu University
Dendritic cell therapy (Vaccell®) tella, Inc., Tokyo, Japan	Cancer	Kyushu University

CAR = chimeric antigen receptor; HVJ-E = hemagglutinating virus of Japan envelope; iPS = induced pluripotent stem; NK = natural killer.

therapy trials were collected (Table V). We compared the number of clinical trials of oncolytic virus, CAR T-cell therapy, and TCR T-cell therapy in Japan versus that in the United States, the European Union, and China. The number of clinical trials in the United States, the European Union, and China listed in ClinicalTrials.gov[24] as of July 21, 2018, were examined. As shown in Table VI, oncolytic virus therapy has been actively developed in Japan, whereas CAR T-cell therapy has been much more actively developed in China and the United States.

Regarding in vivo gene therapeutic products, 6 and 18 trials were or are conducted by companies and academic institutes, respectively (Table II). Regarding ex vivo gene therapeutic products, 6 and 10 trials were or are conducted by companies and academic institutes (Table III). Talimogene laherparepvec and CD19 CAR T-cell therapy (CTL019) are being developed by foreign pharmaceutical companies and are already approved in the United States.[25] However, these therapeutic products had not yet been approved in Japan as of July 21, 2018. All the other therapeutic products are being developed by Japanese pharmaceutical companies or Japanese academic institutes. None of these products has been approved in Japan.

Brief descriptions regarding the Japanese in vivo gene therapeutic products are as follows. HF10 is a spontaneously mutated oncolytic virus derived from a herpes simplex virus-1.[26] OBP-301 is an oncolytic virus in which the *hTERT* (human telomerase reverse transcriptase) promoter drives the expression of the *E1A* and *E1B* genes linked to an internal ribosome entry site.[27] Ad-REIC is an adenovirus vector

Table V. The number of clinical trials of gene and cellular therapies for cancer in Japan.

Therapy	No. of Clinical Trials
In vivo gene therapy	24 (oncolytic virus: 24)
Ex vivo gene therapy	16 (CAR T cell, 6; TCR T cell, 8; other, 2)
Other cellular therapy	55

CAR = chimeric antigen receptor; TCR = T-cell receptor.

carrying the human *REIC* (reduced expression in immortalized cell)/*Dkk-3* gene.[28] Inactivated Sendai virus particles are labeled as HVJ-E, which, fused to prostate cancer cells via cell surface receptors, cause apoptosis of prostate cancer cells in vitro and in vivo. HVJ-E also induces antitumor immunity by activating natural killer (NK) cells and cytotoxic T cells and suppressing regulatory T cells in vivo.[29] Survivin-responsive conditionally replicating adenoviruses regulated with multiple factors (Surv.m-CRAs) selectively replicate in and kill a broad range of cancer cell types.[30] Ad-NK4 is a type 5 adenovirus containing the expression cassette of the cytomegalovirus promoter-linked full-length of NK4 cDNA followed by the SV40 T antigen-derived poly A additional signal.[31] Oncolytic virus G47 delta was mentioned earlier.

Table VI. The number of clinical trials of gene and cellular therapies for cancer in Japan, China, the United States, and the European Union.

Therapy	No. of Clinical Trials			
	Japan	China	United States	European Union
Oncolytic virus	24	0	43	24
CAR T cell	6	93	47	9
TCR T cell	8	11	68	12

CAR = chimeric antigen receptor; TCR = T-cell receptor.

Brief descriptions regarding the Japanese ex vivo gene therapeutic products are as follows. NY-ESO-1 and MAGE-A4 TCR T-cell therapy use TCR gene-engineered T cells with retroviral transduction of NY-ESO-1 and MAGE-A4–specific TCR genes, respectively.[32] Lymphocytes expressing the herpes simplex virus thymidine kinase suicide gene (HSV-tk T cells) are widely applicable to a variety of hematologic malignancies. These cells can be promptly eliminated by administration of ganciclovir, which allows graft-versus-host disease to be safely managed.[33] aAVC-WT1 therapy uses allogeneic fibroblasts loaded with alpha-GalCer and transfected with WT1-encoding mRNA.[34] MS3-WT1-siTCR T-cell therapy was mentioned earlier.

As shown in Tables II and III, it is noteworthy that several oncolytic virus products and TCR T-cell products in combination with chemotherapy, peptides, or radiation are examined in the Japanese clinical trials.

Regarding other cellular therapies for cancer, many clinical trials in which dendritic cells, NK cells, alpha beta T cells, or gamma delta T cells were administered were conducted as clinical research in academic institutes or clinics in Japan (see the Supplemental Table in the online version at https://doi.org/10.1016/j.clinthera.2018.11.003). Results of several clinical research projects have been described in international journals.[35,36] Tax-targeting dendritic cell vaccine therapy with mogamulizumab for adult T-cell leukemia (Kyushu Cancer Center) has been funded by AMED and is being conducted as an investigator-initiated registration trial.

DISCUSSION AND CONCLUSIONS

The current review collected information on 95 clinical trials of gene and cellular therapeutic products that were or are being conducted in Japan. We believe that the tables in this review could be useful for understanding current trends in clinical development of regenerative medicine products for cancer in Japan. Although no gene and cellular therapies for cancer have been approved in Japan, much clinical research and many investigator-initiated registration trials of gene and cellular therapies for cancer (especially cellular therapies) were or are being conducted by academic researchers. As mentioned earlier, there are some promising original oncolytic virus products, CAR T-cell products, and TCR T-cell

products in Japan. Although some clinical trials are currently being conducted by pharmaceutical companies in Japan as shown in Tables II and III, clinical development of gene and cellular therapies for cancer in Japan by pharmaceutical companies is not active. Marketing authorization of talimogene laherparepvec and CD19 CAR T-cell therapies in the United States and the new Japanese regulatory frameworks such as the conditional and term-limited approval system and the SAKIGAKE designation are stimulating academic researchers and pharmaceutical companies to actively pursue clinical development of gene and cellular therapies for cancer in Japan.

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CONFLICTS OF INTEREST

Dr. Nagai was paid for consulting or an advisory role by Takara Bio Inc. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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APPENDIX A. SUPPLEMENTARY DATA

Supplemental Table 1. Clinical trials of cellular therapies other than ex vivo gene therapies in Japan

Therapy	Disease	Institute	Other Information
Tax-targeting dendritic cell vaccine therapy + mogamulizumab	adult T-cell leukemia	Kyushu Cancer Center	Phase I, investigator-initiated registration trial, UMIN000016683
WT1/MUC pulsed dendritic cell therapy	Pancreatic cancer, Biliary tract cancer	Nagasaki University	Phase I/II, UMIN000010388
RNF43 peptide pulse dendritic cell therapy + activated lymphocytes	Cancer	Kyushu University	Phase I, UMIN000003945
Dendritic cell therapy	Pancreatic cancer	Fukushima Medical University	Phase I/II, NCT00795977
dendritic cell therapy	Thymic carcinoma	Fukushima Medical University	UMIN000023543
WT-1 pulsed Dendritic cell therapy	Acute myeloid leukemia	Kyoto University	UMIN000000796
alpha-GalCer pulsed dendritic cell therapy	salivary grand tumor	Chiba University	Phase I/II, UMIN000024669
alpha-GalCer pulsed dendritic cell therapy	Non-small cell lung cancer	Kyusyu Cancer Center	Phase II, UMIN000010386
alpha-GalCer pulsed dendritic cell therapy	Non-small cell lung cancer	Chiba University	Phase II, UMIN000007321
alpha-GalCer pulsed dendritic cell therapy + activated CTL	Head and neck cancer	Chiba University	Phase I, UMIN000009431
alpha-GalCer pulsed dendritic cell therapy	Head and neck cancer	Chiba University	UMIN000001933
alpha-GalCer pulsed dendritic cell therapy + NKT cell	Head and neck cancer	Chiba University	Phase II, UMIN000000852
alpha-GalCer pulsed dendritic cell therapy + NKT cell	Head and neck cancer	Chiba University	Phase I/II, UMIN000000722
alpha-GalCer pulsed dendritic cell therapy	Lung Cancer	Chiba University	Phase I, UMIN000005208
alpha-GalCer pulsed dendritic cell therapy	Lung Cancer	Chiba University	Phase I/II, UMIN000001184
alpha-GalCer pulsed dendritic cell therapy	Lung Cancer	Chiba University	Phase I/II, UMIN000000948
alpha-GalCer pulsed dendritic cell therapy	melanoma	Chiba University	Phase I/II, UMIN000001930
Dendritic cell therapy +cyclophosphamide +docetaxel	Head and neck cancer	University of Yamanashi	Phase I, UMIN000003725 NCT01149902

(*continued on next page*)

Supplemental Table 1. (*Continued*)

Therapy	Disease	Institute	Other Information
Cytotoxic T-cell therapy	leukemia	Aichi cancer center	Phase I/II, C000000162 C000000161
NKT cell therapy	Head and neck cancer	Chiba University	Phase II, UMIN000009607
Naïve rich T-cell therapy	Hepatocellular carcinoma	Kyoto Prefectural University of Medicine	Phase II, UMIN000003861
Naïve rich T-cell therapy	Digestive cancer, lung cancer	Kyoto Prefectural University of Medicine	Phase I, UMIN000001835 Reference 32
NK cell therapy	Digestive cancer	Kyoto Prefectural University of Medicine	Phase I, UMIN000007527 Reference 33
alpha beta T-cell therapy + temozolomide	high-grade glioma	Juntendo University	Phase I/II, UMIN00032147
alpha beta T-cell therapy + nivolumab	Cancer	Seta Clinic	UMIN000028756
alpha beta T-cell, CTL, gamma delta T-cell, NK cell, or dendritic cell therapy	Cancer	Seta Clinic	UMIN000019030
alpha beta T-cell therapy + oxaliplatin +bevacizumab +capecitabine	Colorectal cancer	Fukuoka University	Phase I, UMIN000010908
alpha beta T-cell or dendritic cell therapy + chemoradiotherapy	esophageal cancer	Gunma University	UMIN000017350, UMIN000014099
alpha beta T-cell therapy + chemoradiotherapy	pancreatic cancer	Gunma University	UMIN000013426
alpha beta T-cell therapy + proton therapy	pancreatic cancer	Hyogo Ion Beam Medical Center	UMIN000012201
alpha beta T-cell therapy	Cancer	Kyushu University	UMIN000009420
gamma delta T-cell therapy	Cancer	Kyushu University	UMIN000009422
NK cell and gamma delta T-cell therapy	Cancer	Ibaraki Children's Hospital	Phase II, UMIN000028370
gamma delta T-cell therapy	Bladder cancer	Tokyo Women's Medical University	Phase I/II, UMIN000010942
gamma delta T-cell therapy	renal cell carcinoma	Tokyo Women's Medical University	UMIN000016793
gamma delta T-cell therapy + zoledronic acid	ovarian cancer	Tokyo Women's Medical University	Phase I/II, UMIN000015233

Supplemental Table 1. (*Continued*)

Therapy	Disease	Institute	Other Information
gamma delta T-cell therapy + zoledronic acid + IL-2	Renal cell carcinoma	Tokyo Women's Medical University	Phase I/II, UMIN000004482 NCT00588913
gamma delta T-cell therapy	Prostate cancer	Tokyo Women's Medical University	Phase I/II, UMIN000006617
WT-1 pulsed gamma delta T-cell therapy	Cancer	Seta Clinic	UMIN000015410
gamma delta T-cell therapy + zoledronic acid	Hepatocellular carcinoma	University of Tokyo	UMIN000011184
gamma delta T-cell therapy + docetaxel + cisplatin+5-FU	esophageal cancer	University of Tokyo	Phase I, UMIN000008097
gamma delta T-cell therapy	esophageal cancer	University of Tokyo	UMIN000002839
gamma delta T-cell therapy	esophageal cancer	University of Tokyo	UMIN000001419
gamma delta T-cell therapy	Multiple myeloma	Japanese Red Cross Medical Center	Phase II, UMIN000007878
gamma delta T-cell therapy	Multiple myeloma	Japanese Red Cross Medical Center	UMIN000000554 C000000343
gamma delta T-cell therapy	Non-small cell lung cancer	University of Tokyo	Phase II, UMIN000006128
gamma delta T-cell therapy	Non-small cell lung cancer	University of Tokyo	Phase I/II, C000000336
gamma delta T-cell therapy + radiofrequency ablation therapy	Hepatocellular carcinoma	Tokyo Medical University	UMIN000004583
gamma delta T-cell therapy + zoledronic acid	Gastric cancer	University of Tokyo	UMIN000004130
gamma delta T-cell therapy + rituximab	B-cell lymphoma	Japanese Red Cross Medical Center	UMIN000003641
gamma delta T-cell therapy	Hepatocellular carcinoma	University of Tokyo	UMIN000001418
gamma delta T-cell therapy + gemcitabine	Biliary tract cancer	University of Tokyo	UMIN000001417
gamma delta T-cell therapy + gemcitabine	Pancreatic cancer	University of Tokyo	UMIN000000931
gamma delta T-cell therapy	Colorectal cancer	University of Tokyo	UMIN000000854
gamma delta T-cell therapy + radiation + zoledronic acid	Bone metastasis	University of Tokyo	UMIN000000628

NCT: trial registration number in the ClinicalTrials.gov database. UMIN and C: trial registration number in the UMIN clinical trials registry (UMIN-CTR).