Dec 22, 2021
5th India -Japan Medical Products Regulatory Symposium
3. REGENERATIVE MEDICINES SESSION

Updates of Regulations & recent trends in Regenerative Medical Products (Japan)

Masaki Kasai Ph.D.
Deputy Review Director,
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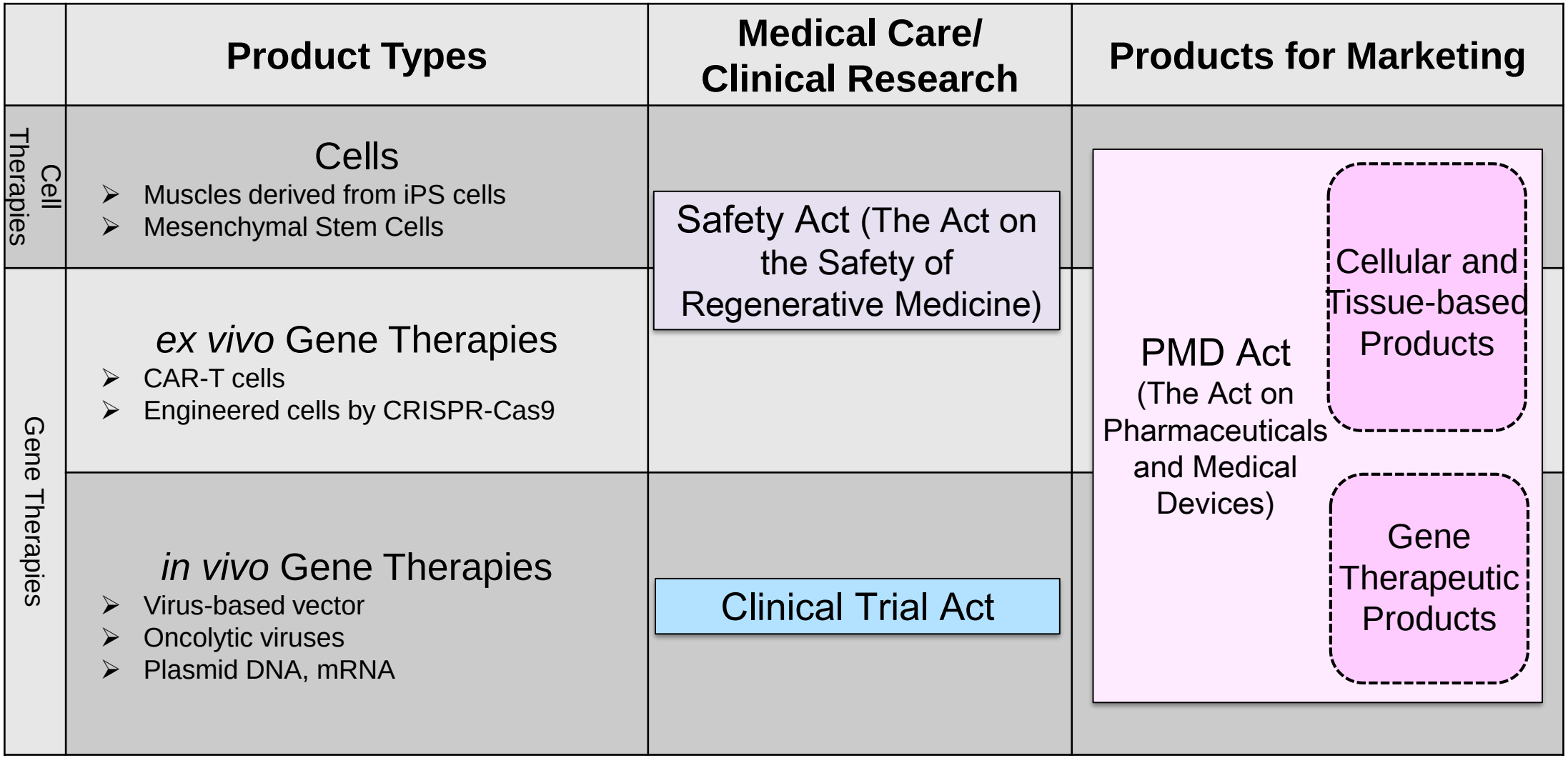
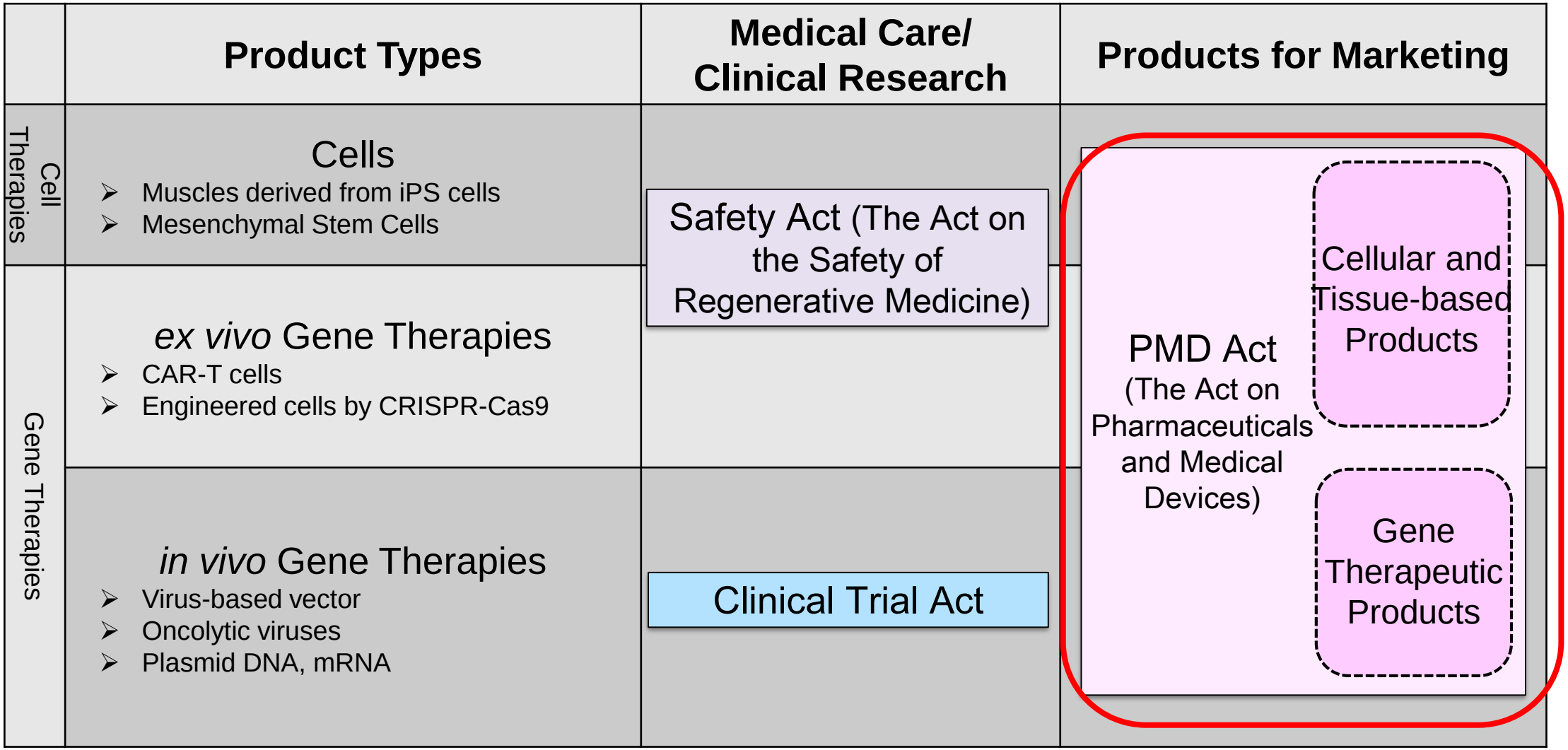
PMDA, Japan

Regulations of Regenerative Medicine in Japan



Regulations of Regenerative Medicine in Japan



Approved Regenerative Medical Products in Japan

As of November 2021

Brand Name	Non-proprietary Name	Applicant Company	Approval Date
JACE	Human (autologous) epidermal cell sheet	Japan Tissue Engineering Co., Ltd.	Oct. 29, 2007 (Sep. 29, 2016、Dec. 28, 2018 additional indications)
JACC	Human autologous tissue for transplantation	Japan Tissue Engineering Co., Ltd.	Jul. 27 , 2012
HeartSheet	Human (autologous) skeletal myoblast-derived cell sheet	Terumo Corporation	Sep. 18 , 2015
TEMCELL HS	Human (allogeneic) bone marrow-derived mesenchymal stem cells	JCR Pharmaceuticals Co., Ltd.	Sep. 18 , 2015
STEMIRAC	Human（autologous) bone marrow-derived mesenchymal stem cell	Nipro Corporation	Dec. 28 , 2018
Collategene	Beperminogene perplasmid	AnGes, Inc.	Mar. 26 , 2019
Kymriah	tisagenlecleucel	Novartis Pharma K.K.	Mar. 26, 2019
ZOLGENSMA	onasemnogene abeparvovec	Novartis Pharma K.K.	Mar. 19, 2020
Nepic	human (autologous) corneal limbus-derived corneal epithelial cell sheet	Japan Tissue Engineering Co., Ltd.	Mar. 19, 2020
YESCARTA	Axicabtagene ciloleucel	Daiichi Sankyo Company, Limited	Jan. 22, 2021
Breyanzi	lisocabtagene maraleucel	Celgene Corporation	Mar. 22, 2021
Ocural	human（autologous) oral mucosa-derived epithelial cell sheet	Japan Tissue Engineering Co., Ltd.	Jun. 11, 2021
Delytact	Teserpaturev	Daiichi Sankyo Company, Limited	Jun. 11, 2021
Alofisel	Darvadstrocel	Takeda Pharmaceutical Company Limited	Sep. 27, 2021

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Update on Approved Products Jan/2021

Axicabtagene ciloleucel：**YESCARTA（Daiichi Sankyo Company, Limited）**

CD19-directed genetically modified autologous T-cell immunotherapy（CAR-T cell therapy）

Indication:
Relapsed or refractory large B-cell lymphoma（DLBCL, PMBCL, TFL and HGBCL）

Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

Press Release

YESCARTA® Approved in Japan for Treatment of Patients with Relapsed/Refractory Large B-Cell Lymphomas

- Approval based on phase 2 study conducted in Japan and previous pivotal trial data
- Daiichi Sankyo has exclusive rights to YESCARTA in Japan

Tokyo – (January 22, 2021) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today announced the Japan Ministry of Health, Labour and Welfare (MHLW) has approved YESCARTA® (axicabtagene ciloleucel), a chimeric antigen receptor (CAR) T-cell therapy, for the treatment of adult patients with certain relapsed/refractory large B-cell lymphomas.

YESCARTA has been approved in Japan for treatment of patients with relapsed/refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, transformed follicular lymphoma or high-grade B cell lymphoma. The use of YESCARTA is limited to patients not previously treated with a CD-19 CAR-positive T-cell infusion; patients previously treated with two or more lines of treatment including chemotherapy or an autologous stem cell transplant; and, patients not eligible for an autologous stem cell transplant. In January 2017, Daiichi Sankyo received exclusive development, manufacturing and commercialization rights for YESCARTA in Japan from California-based Kite, a Gilead Company.

The approval of YESCARTA in Japan is based on data from the global pivotal trial conducted by Kite (ZUMA-1) and results of a phase 2 study conducted by Daiichi Sankyo in Japan. In the Japanese phase 2, open-label, single-arm study, the same dose (2.0×10^6 cell/kg) of YESCARTA as used in the ZUMA-1 study was administered to assess efficacy and safety in 16 Japanese patients with relapsed or refractory large B-cell lymphoma, including diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, transformed follicular lymphoma or high-grade B-cell lymphoma. An objective response rate, the primary endpoint of the study, was 86.7% (95% CI: 59.5 – 98.3%).

"With the approval of YESCARTA in Japan, we now can offer this innovative one-time cell-based immune therapy to patients in Japan who need new options for B-cell lymphomas that continue to progress on currently available treatments," said Wataru Takasaki, PhD, Executive Officer, Head of R&D Division in Japan, Daiichi Sankyo. "We are grateful to have the opportunity to collaborate with Japanese government agencies and Kite, as well as the trial investigators and patients, all of whom have contributed to this significant treatment advancement in Japan."

Ref. Daiichi Sankyo Company, Limited website
https://www.daiichisankyo.com/files/news/pressrelease/pdf/202101/20210122_E2.pdf

Ref. Daiichi Sankyo Company, Limited website
https://www.medicallibrary-dsc.info/di/yescarta/

Update on Approved Products　Mar/2021

lisocabtagene maraleucel：**Breyanzi（Bristol Myers Squibb Company）**

Bristol Myers Squibb

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Japan's Ministry of Health, Labour and Welfare Approves Breyanzi, a New CAR T Cell Therapy

03/25/2021

CATEGORY: Corporate/Financial News

TOKYO, March 25, 2021 -- Bristol Myers Squibb K.K. this week announced that Japan's Ministry of Health, Labour and Welfare (MHLW) approved *Breyanzi* (lisocabtagene maraleucel: liso-cel), a CD19-directed chimeric antigen receptor (CAR) T cell therapy for the treatment of patients with relapsed or refractory (R/R) large B-cell lymphoma[1] and R/R follicular lymphoma.[2]

The approval is based on efficacy and safety from the TRANSCEND NHL 001 trial in patients with R/R B-cell non-Hodgkin lymphoma (NHL) and the TRANSCEND WORLD trial in patients with R/R aggressive B-cell NHL.

Large B-cell lymphoma comprises several disease types including diffuse large B-cell lymphoma (DLBCL). DLBCL is the most common form of non-Hodgkin lymphoma in Japan, accounting for 30-40% of all B-cell cases diagnosed,[3] and is especially prevalent among people in their 60's.[4] There is currently no established standard-of-care treatment for patients with R/R large B-cell lymphoma,[5] which underscores the need for new treatments for in this disease area. Follicular lymphoma accounts for 10-20% of all B-cell NHL cases in Japan. Patients initially respond to chemotherapy, but relapse is common, especially in advanced-stage patients.[5] There is also no established standard-of-care treatment for patients with follicular lymphoma grade 3B.[5]

Jean-Christophe Barland, President and CEO of Bristol-Myers Squibb K.K. and Celgene K.K., said, "I am pleased that we have received regulatory approval in Japan for Breyanzi, our first CAR T cell therapy, which will allow us to provide a new treatment option for patients fighting relapsed or refractory large B-cell lymphoma and relapsed or refractory follicular lymphoma. In addition, we are filing an application for a further CAR T cell therapy to address more unmet medical needs. As a game-changer committed to 'innovation with heart', Bristol Myers Squibb will continue on its journey to help patients prevail over serious diseases."

Breyanzi is a chimeric antigen receptor T cell therapy designed to target CD19, which is expressed on the cell during normal B-cell development and maintained even after malignant transformation of B cells. Breyanzi aims to target CD19-expressing cells and is administered in a one-time infusion as a defined, purified composition to reduce variability of the CD8 and CD4 component dose. Breyanzi will be manufactured at Bristol Myers Squibb's cellular immunotherapy manufacturing facility in Bothell, Washington and at a partner company facility in Japan.

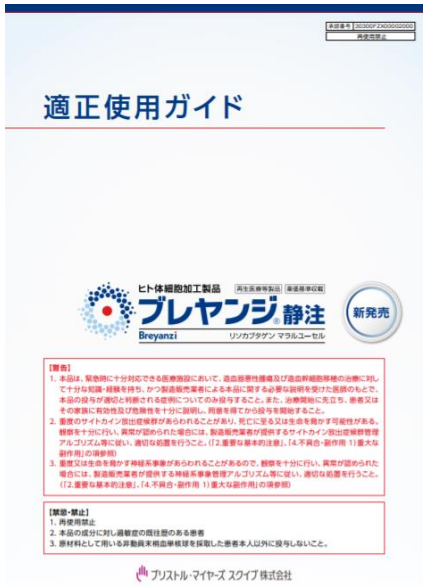
Breyanzi was approved by the U.S. Food and Drug Administration on February 5, 2021 for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. Breyanzi is not indicated for the treatment of patients with primary central nervous system lymphoma. Breyanzi has been granted Priority Medicines (PRIME) designation for relapsed or refractory DLBCL in the European Union and a Marketing Authorization Application is currently under review by the European Medicines Agency.

Ref. Bristol Myers Squibb Company website
https://news.bms.com/news/corporate-financial/2021/Japans-Ministry-of-Health-Labour-and-Welfare-Approves-Breyanzi-a-New-CAR-T-Cell-Therapy/default.aspx

CD19-directed genetically modified autologous T-cell immunotherapy（CAR-T cell therapy）

Indication:

- Relapsed or refractory large B-cell lymphoma（DLBCL, PMBCL, transformed low-grade NHL and HGBCL）
- Relapsed or refractory FL


適正使用ガイド

ヒト体細胞加工製品
ブレヤンジ静注
Breyanzi
リソカブタゲン マラルユーセル
新発売

【警告】
1. 本品は、緊急時に十分対応できる医療施設において、造血器悪性腫瘍及び造血幹細胞移植の治療に対して十分な知識・経験を持ち、かつ製造販売業者による本品に関する必要な説明を受けた医師のもとで、本品の投与が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分に説明し、同意を得てから投与を開始すること。
2. 重度のサイトカイン放出症候群があらわれることがあり、死亡に至る又は生命を脅かす可能性がある。観察を十分に行い、異常が認められた場合には、製造販売業者が提供するサイトカイン放出症候群管理アルゴリズム等に従い、適切な処置を行うこと。（「2.重要な基本的注意」、「4.不具合・副作用 1)重大な副作用」の項参照）
3. 重度又は生命を脅かす神経系事象があらわれることがあるので、観察を十分に行い、異常が認められた場合には、製造販売業者が提供する神経系事象管理アルゴリズム等に従い、適切な処置を行うこと。（「2.重要な基本的注意」、「4.不具合・副作用 1)重大な副作用」の項参照）

【禁忌・禁止】
1. 再使用禁止
2. 本品の成分に対し過敏症の既往歴のある患者
3. 原材料として用いる非動員末梢血単核球を採取した患者本人以外に投与しないこと。

ブリストル・マイヤーズ スクイブ株式会社

Ref. Bristol Myers Squibb Company website
https://file.bmshealthcare.jp/bmshealthcare/pdf/guide/BRE-guide-2107.pdf

Update on Approved Products Jun/2021

human（autologous) oral mucosa-derived epithelial cell sheet
：**Ocural（Japan Tissue Engineering Co., Ltd.）**

Indication:
Limbal Stem Cell Deficiency

J-TEC

June 11, 2021
Japan Tissue Engineering Co., Ltd.

Marketing approval obtained for
Autologous Cultured Oral Mucosal Epithelium "Ocural"
— World's first regenerative medical product using oral mucosal epithelial cells for the treatment of limbal stem cell deficiency —

Japan Tissue Engineering Co., Ltd. ("J-TEC", headquarters in Gamagori, Aichi, Japan; President & CEO Ken-ichiro Hata) is pleased to announce that marketing approval was obtained for Autologous Cultured Oral Mucosal Epithelium "Ocural" on June 11, 2021.

"Ocural" is a product for the treatment of limbal stem cell deficiency,[*1] and it is the world's first regenerative medical product using oral mucosal epithelial cells to treat this disease. This product will be manufactured in Japan and was developed through the practical application of technology developed by Prof. Kohji Nishida of the Department of Ophthalmology, Osaka University Graduate School of Medicine. It will be Japan's second regenerative medical product in the ophthalmology field, following Autologous Cultured Corneal Epithelium "Nepic",[*2] for which marketing approval was obtained in March 2020.

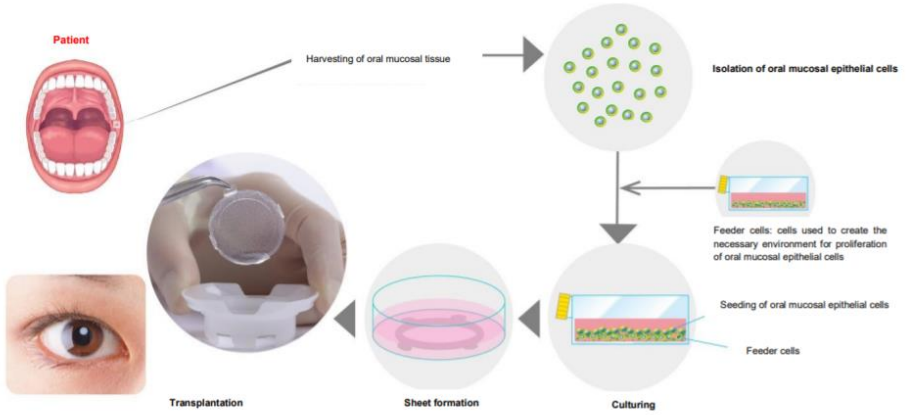
"Ocural", the product for which marketing approval was obtained this time, is a sheet of epithelial cells derived from human (autologous) oral mucosa that is manufactured by harvesting the patient's own oral mucosal tissue and culturing the cells isolated from it. The purpose of the product is to repair damaged corneal epithelium, and when this product is transplanted onto the surface of the patient's eyes, the patient's own oral mucosal epithelial cells become engrafted and epithelialize. "Ocural" is a promising new treatment method for patients who have extensive damage to the cornea of both eyes from limbal stem cell deficiency and have markedly reduced visual acuity. "Ocural" was designated a regenerative medical product for the treatment of rare diseases[*3] in 2020, with the indication of limbal stem cell deficiency.

As the top runner in regenerative medicine in Japan, J-TEC obtained marketing approval for Autologous Cultured Epidermis "JACE", which became Japan's first regenerative medical product, in 2007, and began marketing it in 2009. J-TEC went on to obtain marketing approval for Autologous Cultured Cartilage "JACC" in 2013 and Autologous Cultured Corneal Epithelium "Nepic" in March of 2020. "JACC" and "Nepic" were Japan's first regenerative medical products in the orthopedic surgery and ophthalmology fields, respectively.

Through the practical application of "Ocural" in addition to "Nepic", J-TEC has made it possible to provide therapies for corneal epithelial diseases, for which curative treatment methods previously did not exist. J-Tec is promoting the industrialization of regenerative medicine and contributing to the improvement of patients' quality of life (QOL) by further strengthening sales of its existing products and accelerating the development of new regenerative medical products.

Ref. Japan Tissue Engineering Co., Ltd. Website
https://www.jpte.co.jp/customers/medical/Ocural/index.html

Transplantation of autologous cultured oral mucosal epithelium "Ocural"



Ref. Japan Tissue Engineering Co., Ltd. website
https://www.jpte.co.jp/sys/upload/save/84257614460cb0241d5650.pdf

Update on Approved Products Jun/2021

Teserpaturev：**Delytact（Daiichi Sankyo Company, Limited）**

Indication:
Malignant Glioma

Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

Press Release

DELYTACT® Oncolytic Virus G47Δ Approved in Japan for Treatment of Patients with Malignant Glioma

- First oncolytic virus ever approved for treatment of malignant glioma or any primary brain cancer
- Fourth innovative oncology medicine approved in Japan over the past two years for Daiichi Sankyo

Tokyo – (June 11, 2021) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today announced that it has received conditional and time-limited approval from the Japan Ministry of Health, Labour and Welfare (MHLW) for DELYTACT® (teserpaturev/G47Δ), an oncolytic virus, for the treatment of patients with malignant glioma.

DELYTACT previously received SAKIGAKE Designation and Orphan Drug Designation from the MHLW for this indication and is now the first oncolytic virus to be approved in any region of the world for treatment of malignant glioma or any type of primary brain cancer. Daiichi Sankyo has been collaboratively developing DELYTACT with Dr. Tomoki Todo of the Institute of Medical Science, The University of Tokyo, and is the Marketing Authorization Holder of DELYTACT in Japan.

The approval of DELYTACT in Japan is based on results of a single-arm phase 2 clinical trial evaluating DELYTACT in patients with residual or recurrent glioblastoma, the most common and aggressive form of malignant glioma.[1] The trial met its primary endpoint for one-year survival rate in an interim analysis. Results of the study will be submitted for publication by Dr. Todo.

"With the approval of DELYTACT in Japan we can now offer the first-ever oncolytic virus therapy option to patients with glioblastoma and other malignant gliomas that are not controlled with currently available treatments," said Wataru Takasaki, PhD, Executive Officer, Head of R&D Division in Japan, Daiichi Sankyo. "DELYTACT is the fourth oncology medicine to be approved in Japan for Daiichi Sankyo over the past two years and we are grateful for the opportunity to collaborate with Dr. Todo to deliver this truly innovative treatment modality to patients and physicians in Japan."

About Malignant Glioma

Glioma, which originates in glial cells in brain tissue, represents almost 80 percent of all malignant primary brain tumors.[2] Glioma is classified from grade I to IV based on the level of malignancy.[2] Grade III and grade IV are called malignant glioma or high grade glioma and characterized by rapid progression, high rate of recurrence and poor prognosis.[3]

1

genetically engineered replication-competent herpes simplex virus type 1（Oncolytic virus）

Conditional and Time-limited approval
Duration of Approval: 7 years

Sakigake-designated product
(Forerunner priority review assignment)

Ref. Daiichi Sankyo Company, Limited website
https://www.medicallibrary-dsc.info/di/delytact/

Ref. Daiichi Sankyo Company, Limited website
https://www.daiichisankyo.com/files/news/pressrelease/pdf/202106/20210611_E_47.pdf

Update on Approved Products　Sep/2021

Darvadstrocel：**Alofisel（Takeda Pharmaceutical Company Limited）**

Human allogeneic adipose-derived mesenchymal stem cell

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Takeda Receives Approval to Manufacture and Market Alofisel®▼ (darvadstrocel) in Japan for Treatment of Complex Perianal Fistulas in Patients with Non-active or Mildly Active Luminal Crohn's Disease

September 27, 2021

- Alofisel (darvadstrocel) is the first expanded human allogeneic adipose-derived mesenchymal stem cell therapy to be approved in Japan
- Alofisel provides a potential cell-mediated closure option for patients with complex perianal fistulas associated with Crohn's disease who have shown an inadequate response to at least one existing medicinal treatment[1,2,3]

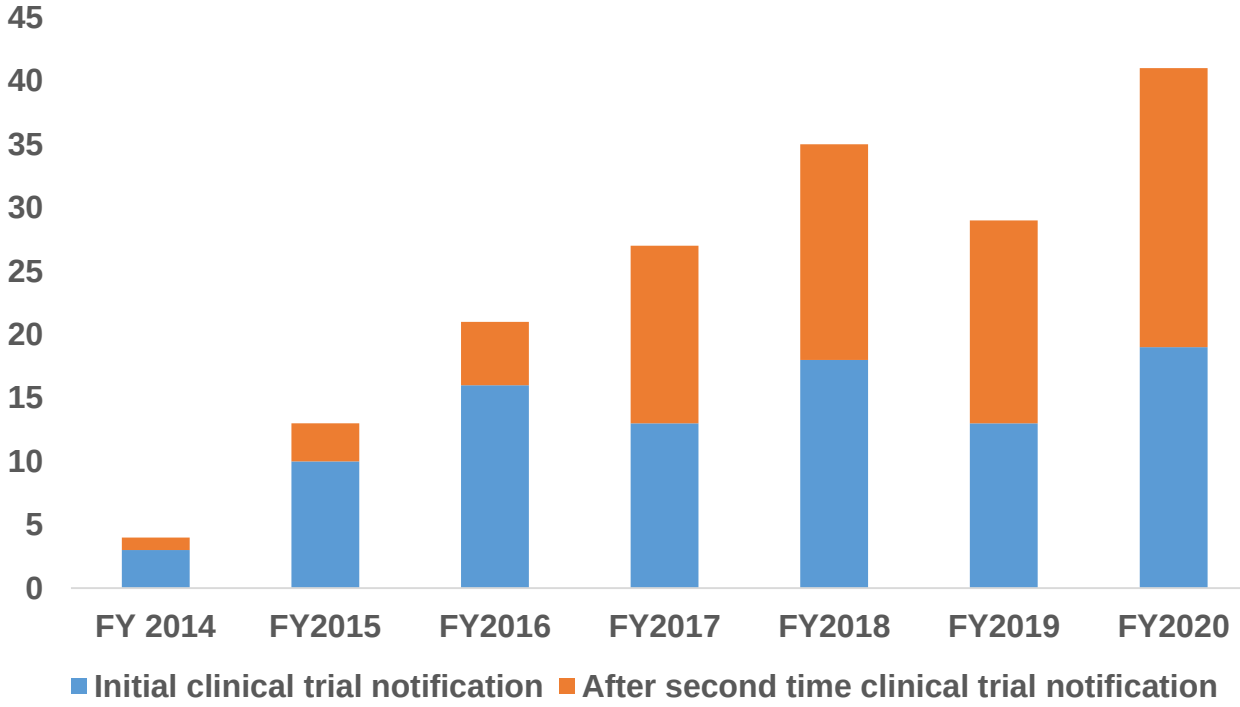
Osaka, Japan, September 27 – Takeda Pharmaceutical Company Limited (TSE:4502/NYSE:TAK) ("Takeda") today announced that it has received approval from the Japan Ministry of Health, Labour and Welfare to manufacture and market Alofisel (darvadstrocel) - development code: Cx601 - for the treatment of complex perianal fistulas in patients with non-active or mildly active luminal Crohn's disease (CD).[3] This product is indicated for the treatment of patients who have shown an inadequate response to at least one existing medicinal treatment.[3]

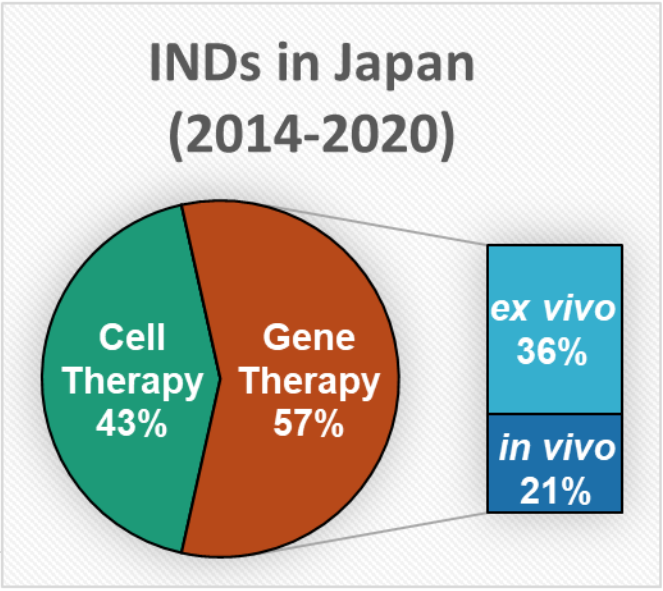
Ref. Takeda Pharmaceutical Company Limited website
https://www.takeda.com/newsroom/newsreleases/2021/takeda-receives-approval-to-manufacture-and-market-alofisel-darvadstrocel-in-japan-for-treatment-of-complex-perianal-fistulas-in-patients-with-non-active-or-mildly-active-luminal-crohns-disease/

Indication:
Complex perianal fistulas in patient with non-active and mildly active Crohn's disease

Ref. Takeda Pharmaceutical Company Limited website
https://www.takedamed.com/medicine/detail/?medicine_id=1242

Number of clinical trial notifications for regenerative medical products



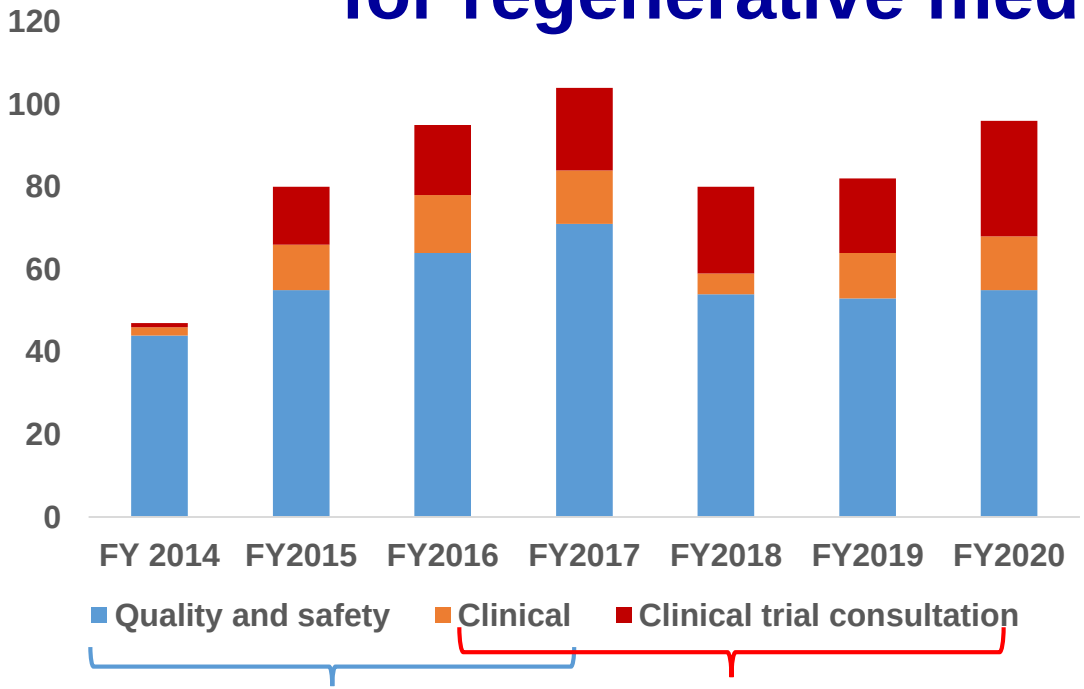


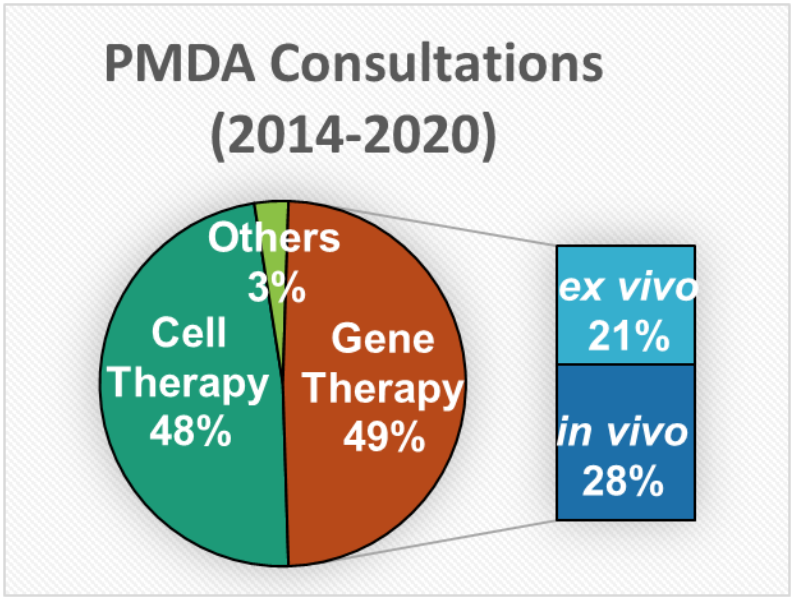
	FY 2014	FY2015	FY2016	FY2017	FY2018	FY2019	FY2020
Initial clinical trial notification	3(1)	10(2)	16(7)	13(8)	18(8)	13(7)	19(9)
After second time clinical trial notification	1(1)	3(2)	5(0)	14(10)	17(3)	16(7)	22(5)
Protocol change notification	2	19	52	93	151	206	215

The table in brackets in parentheses indicate the number of notifications of investigator-initiated clinical trials.
The number within brackets is included in the number outside the bracket.

https://www.pmda.go.jp/files/000238173.pdf
Cell & Gene Therapy Insights 2020; 7: 131-40

Number of consultations for regenerative medical products





Regulatory Science strategy consultation: (consultation for starting clinical trial)

Consultation for clinical trial (total)

	FY 2014	FY2015	FY2016	FY2017	FY2018	FY2019	FY2020
RS consultations (total)	46	66	78	84	59	64	68
Quality and safety	18(44)	29(55)	26(64)	29(71)	25(54)	29(53)	25(55)
Clinical	2	11	14	13	5	11	13
Clinical trial consultation	1	14	17	20	21	18	28

This consultation category includes consultations conducted as Pharmaceutical Affairs Consultation on R&D strategy on and before November 24, 2014. Some consultations were divided into multiple sessions over several days to confirm the quality and safety of the relevant products before submission of clinical trial notifications. The tables in brackets indicate the total number of these sessions.

https://www.pmda.go.jp/files/000238173.pdf
https://www.pmda.go.jp/files/000241289.pdf
Cell & Gene Therapy Insights 2020; 7: 131-40

Summary

- Research and development of Regenerative Medical Products for practical use is very active, especially gene therapy products.
- The number of the approved products using data from foreign clinical studies and/or multi-regional clinical trials is also increasing.
- We continue to provide the effective advices and strategies to enhance the development of Regenerative Medical Products.