December 13, 2024
SymBio Pharmaceuticals Limited
Fuminori Yoshida
Representative Director
President and Chief Executive Officer
(Securities Code: 4582)

Research Results on the Antitumor Effects of Intravenous Brincidofovir and its Potential Use as a Therapy in Combination with Immune Checkpoint Inhibitors to be Presented at the 66th Annual Meeting of the American Society of Hematology

TOKYO, Japan, December 13, 2024 – SymBio Pharmaceuticals Limited (Headquarters: Tokyo; hereinafter "SymBio" or the "Company") today announced that the results of the Company's collaborative research with the National Cancer Centre Singapore on the antitumor effects of intravenous brincidofovir (IV BCV) and the potential use of IV BCV in combination with immune checkpoint inhibitors[1] as a therapy for non-Hodgkin lymphoma[2], were presented at the American Society of Hematology (ASH) Annual Meeting held December 7-10, 2024, in San Diego, California.

SymBio is currently conducting a Phase 1b clinical trial targeting NK/T-cell lymphoma[3] and peripheral T-cell lymphoma[4]. The results presented at ASH show that the combination of BCV and immune checkpoint inhibitors significantly increases the immune cells infiltrating the tumor. This suggests that, in addition to BCV's own antitumor effect, use of BCV in combination with cancer immunotherapies such as immune checkpoint inhibitors may further enhance clinical efficacy. SymBio will continue its clinical development of IV BCV for various types of cancer and further explore its use in combination with immune checkpoint inhibitors.

Statement from Dr. Jason Y Chan, Principal Investigator of the study, Consultant in the Division of Medical Oncology, NCCS, and Clinical Assistant Professor at Duke-NUS Medical School: "The findings from this collaborative study, which suggest not only the antitumor activity of BCV but also its potential to activate cancer immunity and the beneficial effects of combination therapy with immunotherapy, greatly enhance the expectations for BCV's potential capabilities."

Statement from Fuminori Yoshida, President and CEO: "The results of our collaborative research, demonstrating the antitumor effects of IV BCV and the potential for its use in combination with immune checkpoint inhibitors, are encouraging for the expansion into both hematologic and solid tumor areas."

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Related news releases

August 19, 2024: SymBio Initiates Phase 1b Clinical Trial of IV Brincidofovir in Patients with Lymphoma as a First in Human Study for Oncology

March 18, 2024: Research results showing anti-proliferative activity of brincidofovir in B-cell lymphoma to be presented at the AACR Annual Meeting 2024

June 12, 2023: Presentation of the Results of Biomarker Research Predicting the Antitumor Effects of Brincidofovir at the 17th ICML

December 13, 2022: Presentation on the Anti-lymphoma Activity of Brincidofovir at the 64th ASH Annual Meeting

Summary of the presentation

Title: 4172 Therapeutic Repurposing of Brincidofovir in Non-Hodgkin Lymphoma - Potential Synergy with Immune Checkpoint Blockade

Program: Oral and Poster Abstracts

Session: 605. Molecular Pharmacology and Drug Resistance: Lymphoid Neoplasms: Poster III

Hematology Disease Topics & Pathways:

Research, Translational Research

Date: Monday, December 9, 2024, 6:00 PM-8:00 PM

Presentation Abstract: https://ash.confex.com/ash/2024/webprogram/Paper202761.html

About This Presentation

In this study, the effects of BCV were evaluated using 44 cell line models, including NK/T-cell lymphoma and B-cell lymphoma, as well as their respective mouse xenograft models[5]. BCV exhibited potent inhibitory effects in most cell lines, achieving clinically feasible human plasma concentrations in 68% (17/25) of NK/T-cell lymphoma cases and 68.4% (13/19) of B-cell lymphoma cases. These are valuable data for planning future clinical trials.

Furthermore, in the mouse xenograft models, BCV administration significantly suppressed tumor growth in all models. In the NK/T-cell lymphoma model, BCV inhibited MYC[6] and MYC target pathways, which is considered one of the mechanisms of BCV's antitumor effects.

Additionally, BCV was found to activate the STING pathway and induce immunogenic cell death[7]. The observed increase in PD-L1[8] indicated that cancer immunity was activated, which likely contributed to the beneficial effects of combination therapy with immune checkpoint inhibitors.

Note 1: Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are drugs that activate and sustain immune responses against cancer cells by inhibiting immune checkpoints, which are pathways that normally suppress the function of various immune cells.

Note 2: Non-Hodgkin lymphoma

Non-Hodgkin lymphoma is a disease in which lymphocytes undergo malignant transformation. It encompasses B-cell lymphomas, T-cell lymphomas, and NK-cell lymphomas, and accounts for over 90% of all malignant lymphomas.

Note 3: NK/T cell lymphoma

A type of malignant lymphoma that originates from NK or T cells. NK/T-cell lymphomas are classified as low-grade (progressing yearly), intermediate-grade (progressing monthly), or high-grade (progressing weekly), and mainly present as extranodal NK/T-cell lymphomas in the perinasal space or on the skin. This disease is characterized by its relatively high prevalence in Southeast Asia, including China.

Note 4: Peripheral T-cell lymphoma (PTCL)

PTCL is a general term for various lymphoid tumors derived from T cells that have differentiated and matured in the thymus and migrated to peripheral tissues. It is a rare cancer classified as a rapidly progressing aggressive lymphoma, angioimmunoblastic T-cell lymphoma, ALK-positive anaplastic large cell lymphoma, and ALK-negative ALCL are the major types. Primary treatment involves multidrug chemotherapy and radiation, but they are not always effective enough. Although various therapeutic agents have been clinically used for relapsed or refractory PTCL in recent years, no standard treatment has been established, and the development of new therapeutic agents is desired.

Note 5: Mouse Xenograft Model

Xenograft models using highly immunocompromised mice have been used to transplant human cancer cell lines for the evaluation of anticancer drugs targeting cancer cells.

Note 6: MYC

Also known as c-MYC, is one of the oldest oncogenes, and abnormalities of this family of genes have been found in a wide range of cancer types, including translocations, mutations, and amplifications in hematopoietic tumors. It functions as a nuclear transcriptional regulator and is known to be a very important factor that controls the balance of proliferation and differentiation of hematopoietic cells by regulating the expression of dominant genes.

Note 7: Immunogenic Cell Death (ICD)

Certain anticancer drugs, radiation therapy, and oncolytic viruses can increase endoplasmic reticulum stress within cancer cells, leading to the release of DAMPs (damage-associated molecular patterns) such as calreticulin. This process activates the adaptive immune system against cancer cells.

Note 8: PD-L1

PD-L1 is highly expressed in many cancer cells and binds to PD-1 expressed on immune cells. This interaction promotes the inactivation and suppression of immune cells, leading to immune tolerance and enabling cancer cells to evade immune attack. Currently, multiple immune checkpoint inhibitors targeting PD-L1 have been launched.

About brincidofovir

Brincidofovir (BCV) has a new mechanism of action as a lipid conjugate of cidofovir (CDV). CDV is an antiviral drug already approved and marketed in the United States, but unapproved in Japan. BCV is expected to be an effective treatment against a wide spectrum of dsDNA virus infections (herpesvirus such as cytomegalovirus and Epstein-Barr virus (EBV), adenovirus, BK virus, papillomavirus and smallpox virus including mpox, etc.), with superior features such as high activity antiviral effect in comparison with CDV and other antiviral drugs. Due to the breakthrough nature of the BCV molecule, in which a specific length of lipid chain is attached to the CDV, BCV is converted into a molecule that acts directly within the cell, thereby dramatically increasing the efficiency of cellular uptake and showing a high antiviral activity.

Clinical trials

The Company initiated a Phase 2a clinical trial in patients with adenovirus infection after hematopoietic stem cell transplantation (March 2021) and received Fast Track designation from the FDA (April 2021). Proof of Concept (POC) of antiviral efficacy established based on data up to cohort 3 (May 2023). A use patent that SymBio applied for based on the results of this study has been granted by the Japan Patent Office (January 2024). The preliminary result was presented in major conferences: ASH 2023, 2024 Tandem Meetings, and ID Week 2024.

The Company initiated a Phase 2a clinical trial in patients with CMV infection after Hematopoietic Stem Cell Transplantation in June 2024.

The Company submitted a Clinical Trial Notification in Japan and initiated a global Phase 1b/2 clinical trial for malignant lymphoma in June 2024.

Based on the establishment of POC data, SymBio will continue to build a clinical development platform and move forward with clinical development for other indications.

Preclinical trials

Collaborations with prominent research institutions include:

- A number of recent studies have demonstrated that EBV is a risk factor for MS. SymBio entered into CRADA with the NINDS in March 2023 to establish a new antiviral treatment method for MS and has been conducting collaborative research to develop a clinical trial.

- CRADA with the National Institute of Allergy and Infectious Diseases (NIAID), affiliated with the 3 NIH, to evaluate the efficacy of BCV for EB virus-associated lymphoproliferative diseases (April 2023).
- Research on the involvement of infection by reactivation of latent viruses in various neurological severity diseases of the brain, including Alzheimer's disease, has been ongoing for the past several years, and a simple three-dimensional mimicry of human neural stem cell cultures and brain tissue established by Tufts University in the United States, the A Sponsored Research Agreement was signed (December 2022) to examine the effect of BCV on HSV infection using a herpes simplex virus (HSV) infection/reactivation model established by Tufts University in the U.S., which uses human neural stem cells cultured to mimic brain tissue in three dimensions.
- We are currently conducting collaborative studies with the National Cancer Centre Singapore, the University of California, San Francisco, and other institutions to confirm its anti-cancer activity and to identify synergistic effects when combined with its antiviral activity. Research results were presented in several congresses: ASH in December 2022, ICML in June 2023 and EHA in June 2024.
- Initiated a non-clinical trial at the University of California, San Francisco Neurosurgery Brain Tumor Center to evaluate the anti-tumor effect of BCV on refractory brain tumors (September 2021).
- SymBio entered into a Material Transfer Agreement (MTA) with the School of Medicine at Pennsylvania State University in the U.S. to conduct a preclinical study to verify the antiviral activity of BCV in a mouse model of poliomyelitis virus infection. In November 2022, we concluded Material Transfer Agreement (MTA) with Penn State College of Medicine in the U.S. to conduct a preclinical study to verify the antiviral activity of BCV in a mouse model of poliomavirus infection (November 2022). In July 2024, new findings from the research were published in journal *mBio®*.

License Agreement

In September 2019, SymBio entered into a license agreement with Chimerix Inc. for the exclusive worldwide rights to develop, market, and manufacture BCV for all diseases except orthopoxviruses (such as smallpox and mpox). In June 2021, brincidofovir tablets and oral suspension (oral formulation) were approved in the United States for the treatment of smallpox in adults and pediatric patients, including neonates. In September 2022, Chimerix's brincidofovir business was acquired by Emergent BioSolutions Inc.

About SymBio Pharmaceuticals Limited

SymBio Pharmaceuticals Limited was established in March 2005 by Fuminori Yoshida who previously

served concurrently as Corporate VP of Amgen Inc. and founding President of Amgen Japan.
The Company's underlying corporate mission is to "deliver hope to patients in need" as it aspires to be a leading global specialty biopharmaceutical company dedicated to addressing underserved medical needs.