



Kyowa Kirin Co., Ltd.

R&D Day

December 11, 2023

Event Summary

[Company Name] Kyowa Kirin Co., Ltd.

[Event Name] R&D Day

[Date] December 11, 2023

[Number of Speakers] 2
Takeyoshi Yamashita Director of the Board, Senior Managing
Executive Officer, Chief Medical Officer
Yoshifumi Torii Executive Officer, Vice President, Head of
R&D Division

Presentation

Moderator: We will now begin the R&D Meeting for FY2023 of Kyowa Kirin Co., Ltd.

Please note the following prior to the start of the meeting. Please be advised that we will keep the names and company names of all participants today for a certain period of time as a list of participants. Please also note that the content of this presentation will be available on our website as an on-demand video stream and transcript. We would appreciate your understanding in this regard before making any comments. The information presented today contains forward-looking statements. Please note that there is uncertainty due to various risks.

Today's speaker is Takeyoshi Yamashita, Director of the Board, Senior Managing Executive Officer, Chief Medical Officer. Yoshifumi Torii, Executive Officer, Vice President, Head of R&D Division. After the presentation, we will be happy to answer any questions you may have. The entire briefing is scheduled to last for approximately 90 minutes. The documents can be downloaded from our IR website, so please make use of them as needed.

Vision

Our Vision toward 2030

Kyowa Kirin will realize the successful creation and delivery of life-changing value that ultimately makes people smile, as a Japan-based Global Specialty Pharmaceutical company built on the diverse team of experts with shared passion for innovation.

* Make patients smile through dramatic improvements in quality of life by identifying the unmet medical needs of people battling with medical conditions and by creating and supplying new drugs or services that help them overcome those challenges.

Provide pharmaceuticals for unmet medical needs

We are focused on developing medicines for diseases where there is a clear patient need for new options. We make full use of multiple therapeutic modalities, including biotechnology such as antibody technology, and beyond, building on our Kyowa Kirin established strengths.

Address patient-centric healthcare needs

We will meet the needs of patients and society by providing value across the entire patient care pathway, delivering cutting-edge science and technology, grounded in our in-depth pharmaceutical knowledge and expertise.

Retain the trust of society

We pursue world-class product quality and operational excellence to grow our business in ways which build long-term trust with our stakeholders.

Who We Are

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Yamashita: I am Yamashita, Chief Medical Officer. Thank you very much for taking time out of your busy schedule to participate in our R&D Day for FY2023 today. To begin the meeting, we will first explain our vision. We had a thorough discussion about what our company aims to be in 2020, soon after entering the global market with our own products. And here is the vision that we formulated.

This means that we create our own value and bring smiles not only to patients suffering from illnesses, but also to their families and healthcare professionals. It is about making such a contribution to society and also making ourselves smile. We were particularly concerned with the keyword life-changing value. Here is our mission and desire to make our patients smile. To achieve this vision, we have established the three Core strategies shown to the right and are vigorously pursuing them on a daily basis.

Research & Development Concept Technology x Biology x OI

The Kyowa Kirin Group is aiming to build a competitive technology platform by enhancing and combining its drug discovery technologies and its drug discovery modalities.
By matching that technology platform with disease-oriented science and by harnessing open innovation with partners that have specific strengths, we aim to develop completely new technologies or select efficient drug discovery targets to create life-changing value.

Technology

We will continue to evolve our antibody technology, while also pursuing the possibilities of other modalities and building a platform that leads to innovative new therapies.

Disease Biology

Continue to provide “Only-one value drug” for UMN, while utilizing the disease science* cultivated to date within KKC

* Nephrology, Oncology, Immunology & allergy, CNS

Open Innovation (OI)

Continue to work on collaborative research activities* with academia, startups and other partners, combine this with rapid access to start up information gained from investment in VC funds and CVC funds, and tap into external innovation through advanced OI activities

* Reenergize the San Diego research base

Create Life-changing value with clear competitive advantages

Kyowa Kirin's Strengths

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Our R&D is characterized by incorporating cutting-edge technologies and scientifically delving into diseases for which adequate medical care has not yet been provided, in order to formulate and implement drug discovery strategies that lead to innovative drugs. And it is a combination of open innovation, which is not limited to a principle of self-sufficiency, but takes advantage of all opportunities outside the Company.

The key drivers of our future growth



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Here are the key products that drive our global business and the development pipelines we expect to be the drivers of future growth.

Biopharmaceuticals, many of which are based on antibody technology, make up our lineup. All of these drugs have different mechanisms of action from existing drugs, which may provide life-changing value, and have been researched and developed in-house. The products and development pipelines of Orchard Therapeutics, which we recently announced its acquisition of shares, will be added to this list.

Today, we would like to provide information on our own development pipelines marked with an asterisk here, as well as on Orchard Therapeutics' hematopoietic stem cell gene therapy technology and its products, for your information.

Today's agenda

- **Development Pipeline using REGULGENT™ - Our bispecific antibody technology**
 - About REGULGENT™
 - KK2260
 - KK2269

- **Toward the Successful Creation and Delivery of Life-changing Value**
 - KHK4951 (Ph1 study results and Ph2 studies overview)
 - Orchard Therapeutics plc (HSC-GT)

Here is today's agenda. First, Torii will introduce our simultaneous bispecific technology, REGULGENT technology, and two projects using this technology, KK2260 and KK2269, for which we will soon be able to report the start of clinical trials.

We will then present the Phase I study results for KHK4951 and an overview of the Phase II study. Finally, I would like to introduce Orchard Therapeutics' technologies and products.

Dr. Torii, please go ahead.

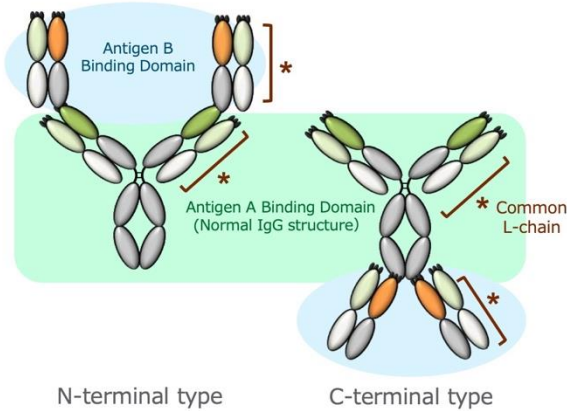
Development Pipeline using REGULGENT™ Our bispecific antibody technology

- About REGULGENT™
- KK2260
- KK2269

Torii: I am Torii, Head of R&D Division. From here, we will introduce individual development pipelines. First, we would like to introduce our simultaneous bispecific antibody technology, REGULGENT, and our development pipelines based on this technology.

About REGULGENT™

- General characteristics of bispecific antibodies
- Able to perform actions that IgG cannot by acting on two types of antigens*
 - Composed of a combination of non-common L-chain antibodies or by utilizing antibody-like molecules
- * e.g., cross-linking of two types of cells or molecules



Characteristics of REGULGENT™

Simple structure, minimized immunogenicity

- Use of common L-chain (*), only natural IgG sequence
- Uniformity with no combination of different molecules
- Physical properties and pharmacokinetics equivalent to IgG

Bivalent-bivalent binding, N&C-terminal type

- Can be expanded to a variety of mechanisms of action

Stable production process, easy handling

- High productivity equivalent to IgG
- Can be adapted to the conventional antibody manufacturing process

Proprietary bispecific antibody technology created from our antibody R&D experience

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First, let me introduce REGULGENT. The first characteristic of bispecific antibodies in general is that they act on two types of antigens, allowing them to act in a way that IgG cannot. In many cases, the light chains, L-chains are combined in a non-common manner, or the pattern consists of so-called antibody-like or antibody-like molecules that are not immunoglobulins.

In contrast, REGULGENT has a simple structure consisting of a common L-chains and a natural IgG sequence. This is expected to minimize immunogenicity, and also allows for the production of uniform molecules, since different combinations of molecules do not arise in the structure. In addition, the physical properties and pharmacokinetics are equivalent to those of IgG.

In addition, REGULGENT not only acts on two antigens, but also features bivalent-bivalent binding, binding at two sites for each antigen.

As shown in the figure on the left, there are two patterns, N-terminus type and C-terminus type, and we believe that these characteristics will enable us to develop a variety of mechanisms of action. In addition, the productivity of this molecule is equivalent to that of IgG, and since the conventional antibody production process can be used, we believe that it is an easy-to-handle molecule for which a stable production process can be expected to be established.

REGULGENT, with these properties, is our proprietary antibody technology that is the result of Kyowa Kirin's long experience in research and development of antibodies. We will continue to utilize this technology for the creation of new drugs in the future.

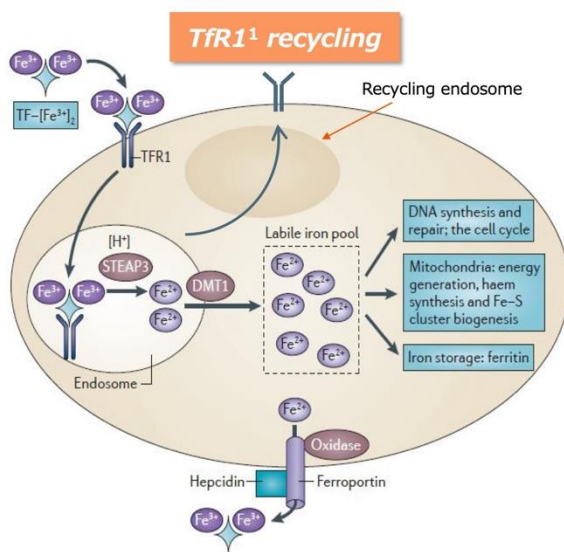
Development Pipeline using REGULGENT™ Our bispecific antibody technology

- About REGULGENT™
- **KK2260**
- KK2269

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Let me now introduce the first of the two development projects using this bispecific antibody technology, KK2260.

Relationship between cells and iron



Iron is an important element for cell growth and survival

- DNA synthesis
Ribonucleotide reductase - requires iron ions in the active center
- Energy generation
Iron ion is required for ATP production via TCA cycle² in mitochondria

TfR1 contributes to cellular uptake of iron

- Iron ions bind to transferrin, which binds to TFR1 and is taken up into the cell
- TFR1 is recycled after intracellular iron supply and is again involved in iron uptake

1. Transferrin receptor 1; 2. Tricarboxylic acid cycle = Citric acid cycle

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Modified from: Torti, S. V. et al., Nat Rev Cancer, 2013

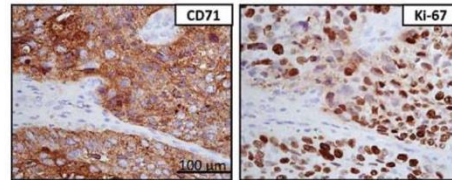
Before going into the explanation of the product itself, I will first explain the relationship between cells and iron, which is important for understanding KK2260. Iron is an essential element for cell survival and proliferation and is known to be involved in DNA synthesis and energy production. In the body, iron ions are taken up into cells by binding to a protein called transferrin and then to the transferrin receptor. It has also been shown that transferrin receptor 1 is recycled back to function after iron is supplied to the cell.

Relationship between cancers and iron

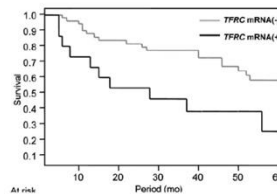
- Many cancer types have an association with iron
- High expression of TfR1 in many cancer types which affects cancer growth and prognosis

Type of cancer	Type of evidence
Non-small-cell lung cancer	Cell culture, animal models and epidemiological
Breast cancer	Cell culture, animal models, human tissue studies and epidemiological
Renal cell carcinoma	Cell culture and animal models
Hepatocellular cancer	Cell culture, animal models and epidemiological
Oesophageal, stomach, aerodigestive and gastric cancer	Human tissue studies, animal models and epidemiological
Colorectal cancer	Cell culture, human tissue studies, animal models and epidemiological
Prostate cancer	Cell culture and epidemiological
Haematological cancers (leukaemias, lymphomas and myeloma)	Cell culture, animal models, epidemiological and clinical case study
Melanoma	Cell culture and animal model
Pancreatic cancer	Cell culture, animal models and clinical trial
Bladder cancer	Cell culture

Torti, S. V. et al., Nat Rev Cancer, 2013



TfR1 expression of ESCC patient: Chan et al., ONCOLOGY REPORTS, 2014



Survival after surgery of ESCC patients: Wada et al., Ann. Surg. Oncol., 2006

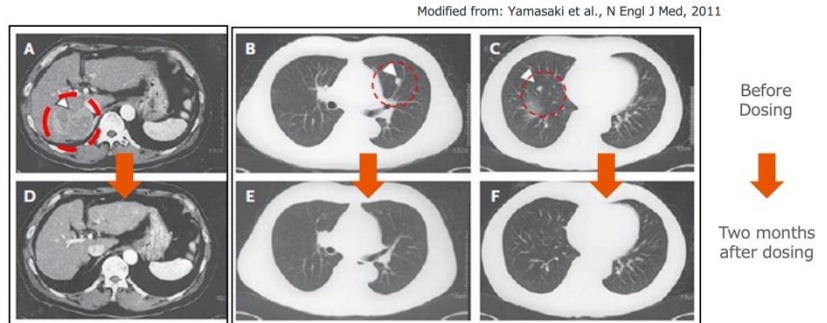
TfR1 = CD71: Transferrin receptor 1, Ki-67: One of the cell growth marker protein, ESCC: Esophageal squamous cell carcinoma

Since iron is essential for cell survival and proliferation, iron has also been implicated in the survival and proliferation of many cancer types, as reported in the paper shown at left. It has also been reported that transferrin receptor 1 is highly expressed in many cancer types and that gene expression of transferrin receptors is a predictor of cancer prognosis, as shown on the right.

Anticancer effects and systemic side effects of iron depletion

- Efficacy of Deferoxiamine, an Iron Chelator, in Hepatocellular Carcinoma

Anticancer effect observed by iron depletion in cancer cells



- However, systemic iron depletion raises a safety concern (e.g. severe anemia) because iron plays an important function in all cells

Need to find a way to suppress systemic side effects and exert only anticancer effects

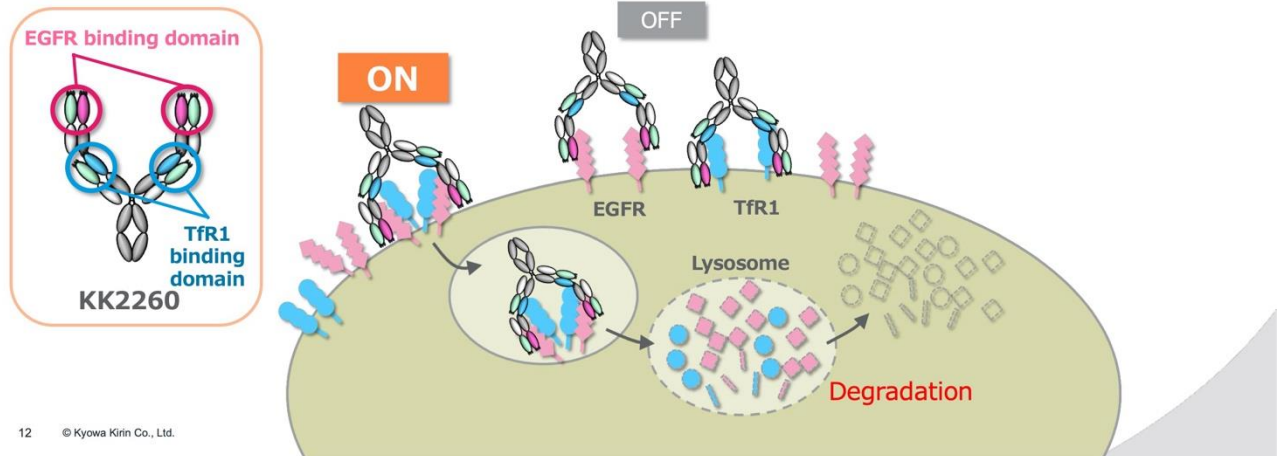
There are also reports that this property is used to lead an anticancer effect by depleting iron. As shown in the figure here, anticancer effects have been reported when iron chelators are administered to patients with hepatocellular carcinoma.

However, as we have explained, iron plays an important function in all cells, and systemic iron depletion has been reported to be a safety concern, e.g., severe anemia. For this reason, it is necessary to devise ways to exert only anticancer effects while suppressing anemia and other systemic side effects.

KK2260: EGFR-TfR1 bispecific antibody

To avoid systemic side effects = selective iron depletion in cancer cells

- No neutralizing activity when bound to TfR1 only or EGFR only
- Cross-links TfR1 and EGFR to induce TfR1 degradation in lysosomes



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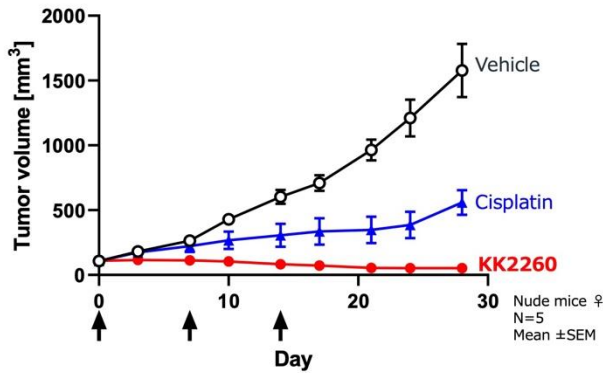
Therefore, in order to avoid systemic side effects, in other words, to realize selective iron depletion in cancer cells, we have created KK2260, a bispecific antibody against EGF receptor and transferrin receptor 1, which are molecules highly expressed in cancer, using REGULGENT technology.

By cross-linking transferrin receptor 1 and EGF receptor, we considered to achieve selective iron depletion by inducing transferrin receptor 1 to lysosomes and promoting degradation of transferrin receptor 1.

Since REGULGENT is in a bivalent and divalent bondable format, we believe that it is able to cross-link both molecules in the vicinity and promote the degradation of transferrin receptor 1. To minimize side effects, we also selected antibodies that do not show activity when bound to only one of the antibodies.

KK2260: Drug Efficacy and Safety in Nonclinical Studies

■ Efficacy: ESCC¹ PDX² model (EGFR+/TfR1+)



High efficacy was shown in all three models evaluated

1. Esophageal squamous cell carcinoma.
2. Patient-derived xenograft. ESCC PDX tumors were obtained from In-Vivo Science Inc.
3. Known as the side effect of EGFR neutralization

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■ Safety

- 200 mg/kg of KK2260 was administered to cynomolgus monkeys once a week x 4 times
→ No serious toxicity, including skin toxicity³, was observed. Mild and transient anemia was observed.

In nonclinical studies, we found that KK2260 was able to exert its effects while suppressing systemic side effects.

Development for EGFR-high expressing cancers are planned.

Here are the efficacy in non-clinical studies and the safety data.

PDX model mice, in which patient-derived samples were transplanted into mice, were evaluated for efficacy against ESCC, esophageal squamous cell carcinoma, and all three models evaluated showed strong efficacy.

In terms of safety, a high safety profile was confirmed in the GLP study in crab-eating macaques up to a maximum dose of 200 mg/kg, and no serious toxicity was observed, including skin toxicity, a known side effect of EGF receptor-neutralizing activity. Anemia was observed at the highest dose but was minor and recoverable.

Thus, we found that KK2260 is able to exert its medicinal effects while suppressing systemic side effects in nonclinical studies. KK2260 will be developed for the treatment of cancers that highly express the EGF receptor.

Development Pipeline using REGULGENT™ Our bispecific antibody technology

- About REGULGENT™
- KK2260
- KK2269

Next, we introduce KK2269. Before going into the explanation of the product itself, I will first explain the expectations and issues of CD40 agonist antibodies.

About CD40 agonistic antibody

■ Expectations

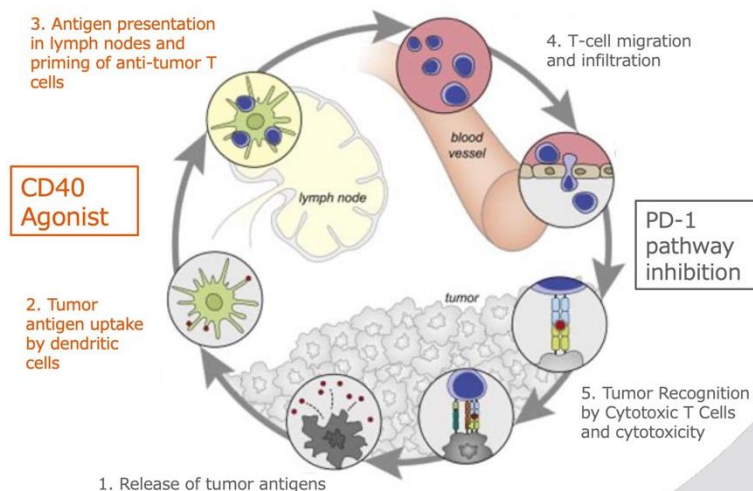
To cure cancer by inducing de novo anti-tumor immunity in patients that are not sufficiently acquired anti-tumor immunity and/or that are refractory to existing immunotherapy

■ Issues

Over-activation of the systemic immune system, resulting in a narrow therapeutic window

Cancer Immunity Cycle

Modified from: *Immunity*, Volume 39, Issue 1, 2013, 1-10



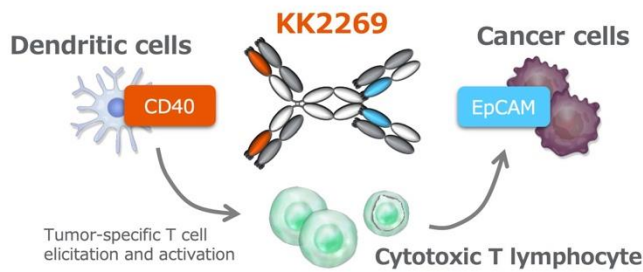
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The cancer immune cycle is shown on the right; for example, PD-1 inhibitors, which are currently highly effective in clinical practice, are involved in tumor cell damage by cytotoxic T cells as you can see in number five on the lower right of this cycle. Therefore, it is also believed that PD-1 inhibitors will not be effective if the patient's body does not generate sufficient amounts of these anti-tumor T cells in the first place.

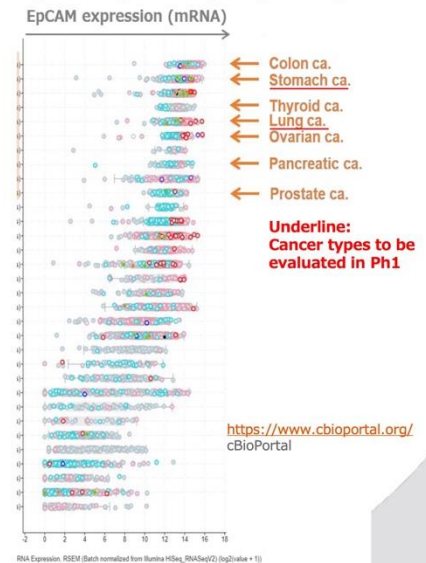
On the other hand, CD40 agonists are involved in the uptake of tumor antigens by dendritic cells, as you can see in numbers two and three in the figure on the right, and antigen presentation in lymph nodes to elicit anti-tumor T cells. Therefore, CD40 agonists are expected to induce anti-tumor immunity against so-called cold tumors, which are tumors for which cancer immunity has not been sufficiently induced or tumors that are refractory to existing immunotherapy, and convert them into hot tumors, thereby curing cancer.

However, this CD40 agonist antibody also causes excessive activation of the systemic immune system, resulting in side effects, and is generally known to have a narrow safety margin.

KK2269: CD40-EpCAM* bispecific antibody



Examples of EpCAM-high expressing tumors

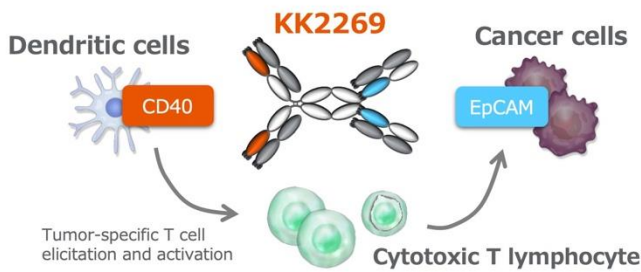


- **Targets CD40 and EpCAM simultaneously, exerting CD40 agonist activity against dendritic cells in close proximity to the tumor**
- **Successfully separated the induction of anti-tumor immunity from its side effects (systemic immune hyperactivation)**

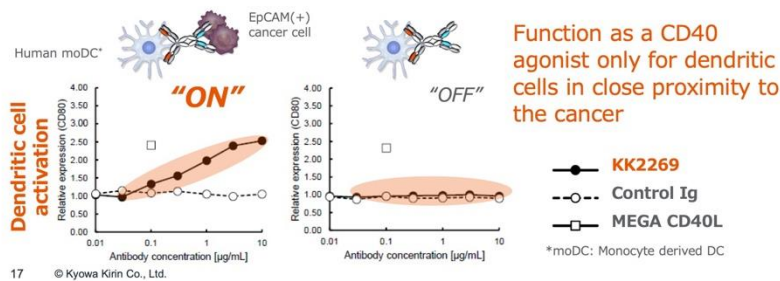
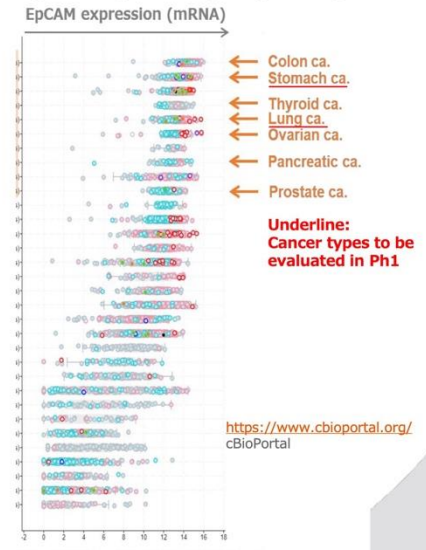
*EpCAM: Epithelial Cell Adhesion Molecule, marker molecules for epithelial tumors

Therefore, we sought to target tumors and have CD40 agonists function only in the major periphery. As a result, we have created a molecule that combines our proprietary CD40 antibody with binding to EpCAM, an epithelial cell adhesion molecule that is highly expressed in various types of tumors. We aimed to achieve CD40 agonist activity against dendritic cells in the vicinity of tumor cells to achieve the induction of anti-tumor immunity, and to isolate systemic immune hyperactivation. The result of these considerations is KK2269.

KK2269: CD40-EpCAM* bispecific antibody



Examples of EpCAM-high expressing tumors



See the two graphs on the lower of the page. The graph on the left clearly shows the activation of dendritic cells by KK2269, where both human dendritic cells and cancer cells expressing EpCAM are present. On the other hand, in the graph on the right, the absence of cancer cells and the binding of KK2269 to dendritic cells alone does not result in the activation of dendritic cells.

These results indicate that KK2269 functions as a CD40 agonist only against dendritic cells in the vicinity of the tumor.

On the right, data on the expression level of EpCAM in each tumor is shown and described for reference.

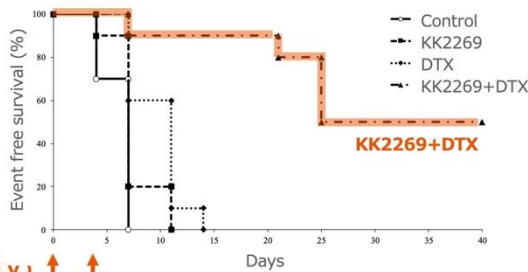
KK2269: Efficacy and safety confirmed in non-clinical studies

Survival rate



- Human CD40-expressing Tg mice
- PD1-resistant tumor model
- DTX: Docetaxel

KK2269 (i.v.) ↑ ↑



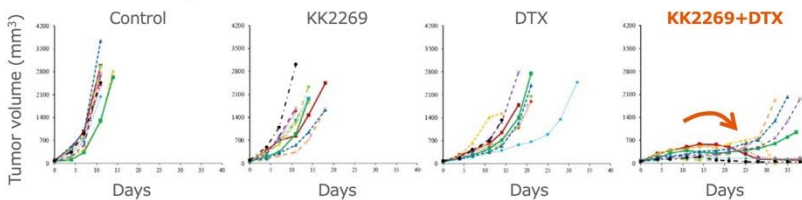
■ Efficacy

- KK2269 showed remarkable synergy with certain chemotherapy
- Characteristic delayed tumor regression suggesting the induction of de novo anti-tumor immunity (see below).

■ Safety

- High safety profile observed in cynomolgus monkeys up to 200 mg/kg (the highest dose in the GLP study)

Tumor volume by individual



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Non-clinical studies demonstrated the concept: anti-tumor efficacy with high safety

Next, we present the results of an in vivo study of this drug. Using human CD40-expressing transgenic mice, we have created a tumor model that is resistant to PD-1 antibodies and tested KK2269 as a single agent and in combination with docetaxel.

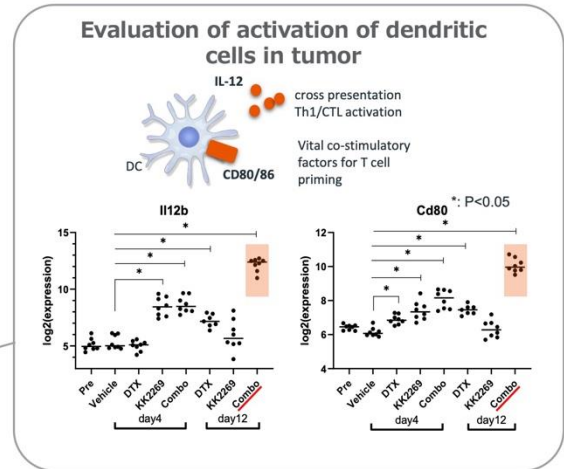
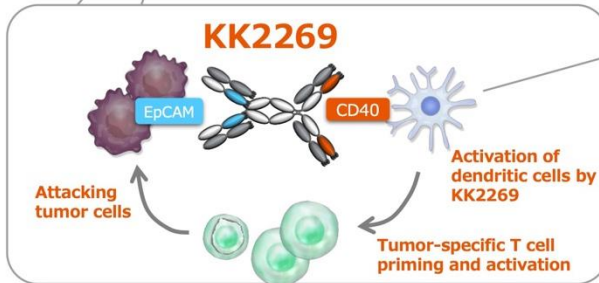
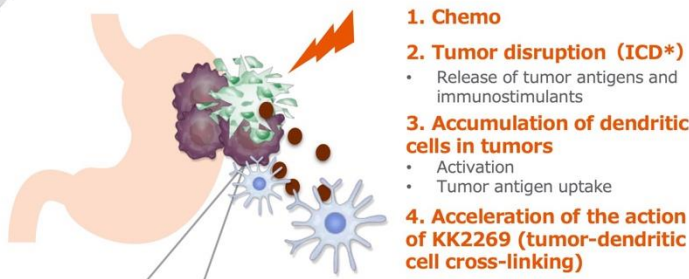
As shown in the graph, KK2269 exhibited remarkable synergy with docetaxel, resulting in such a prolonged survival of mice in the combination group.

The graph below shows the tumor volume by individual model, and characteristic delayed tumor regression was observed approximately two weeks after the first dose in the docetaxel combination group. We believe that this data shows tumor regression due to the induction of anti-tumor immunity, so to speak, like a vaccine.

As for the safety, on the other hand, the GLP study in cynomolgus monkeys showed a high safety profile up to the highest dose of 200 mg/kg.

Thus, in nonclinical studies, KK2269 was confirmed to have both anti-tumor effects and safety.

Full value of KK2269 in chemo combination



Synergy of Chemo+KK2269 was confirmed. POC to be obtained in clinical trials

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*: Immunogenic cell death

I've just introduced the synergy with docetaxel combination, and I will explain the mechanism of synergy.

First, certain types of chemotherapy produce ICD, or immunogenic cell death, in cancer cells, causing tumor cells to release tumor antigens as well as immunostimulants. This facilitates the accumulation of dendritic cells in the tumor.

As I mentioned earlier, KK2269 is a CD40 agonist that is driven by cross-linking between tumors and dendritic cells, so we believe that as a result of its combination with chemotherapy, cross-linking between tumors and dendritic cells will be more efficient and promote KK2269's action.

In fact, this mechanism has been suggested experimentally, and as shown in the figure on the right, a remarkable activation of dendritic cells in the tumor was observed when KK2269 was used in combination with chemotherapy.

We will confirm the synergy between chemotherapy and KK2269 demonstrated in these nonclinical studies in clinical trials to be initiated in the future.

This is the end of the introduction of REGULGENT technology and bispecific antibodies using this technology.

Toward the Successful Creation and Delivery of Life-changing Value

- KHK4951 (Ph1 study results and Ph2 studies overview)
- HSC-GT (Orchard Therapeutics plc)

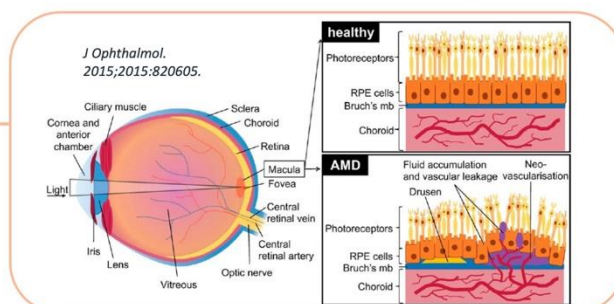
Next, as one of our efforts to continuously create life-changing value, we would like to introduce the progress of KHK4951 to date.

KHK4951: tivozanib eyedrop

- Active ingredient - tivozanib: A small molecule VEGFR inhibitor discovered by Kyowa Kirin with high selectivity and potent activity
- Completed Ph1 study in patients with exudative neovascular age-related macular degeneration (nAMD)

- Abnormal angiogenesis results in macular damage and significant vision impairment
- Caused by VEGF*1 production from retinal pigment epithelial cells
- Drug-treated patient number
Japan: approx. 200,000 Global: approx. 1.6 million

*1: Vascular endothelial Growth Factor



- Standard of Care: Intravitreal injection of anti-VEGF drugs
Due to invasive administration route and treatment burden (e.g. hospital visit) of the SOC, there is clear medical needs for non-invasive treatment option.



Lancet 2012; 379: 1728-38

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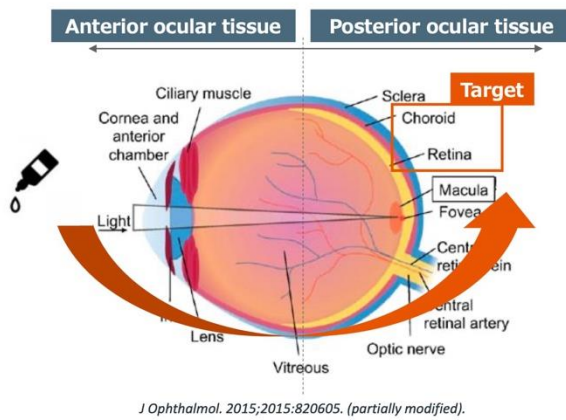
Here is another overview of KHK4951, which we reported on last year.

This product is an eye drop formulation with tivozanib as the active ingredient. Tivozanib is a small molecule VEGF receptor inhibitor that we have created with high kinase selectivity and potent inhibitory activity. Last year, we completed a Phase I study for neovascular age-related macular degeneration and nAMD.

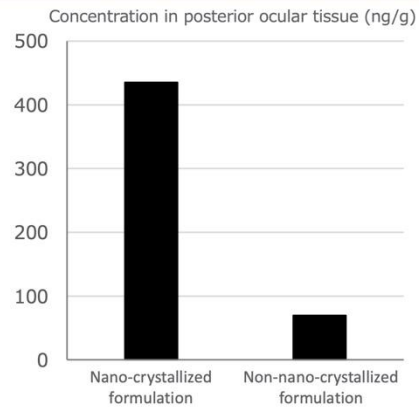
nAMD is a disease in which the macula of the posterior eye is affected by abnormal angiogenesis, resulting in significant vision impairment. The cause is VEGF production from retinal cells, and the number of patients treated with drugs is estimated to be approximately 200,000 in Japan and 1.6 million globally.

The current standard of care is intravitreal injection of anti-VEGF drugs, which is a highly invasive treatment, and the establishment of a non-invasive treatment is desired.

Nano-crystallized formulation for delivery of active ingredients to the posterior ocular tissues



Drug concentration in the posterior ocular tissue after topical instillation of tivozanib eye-drop to rats



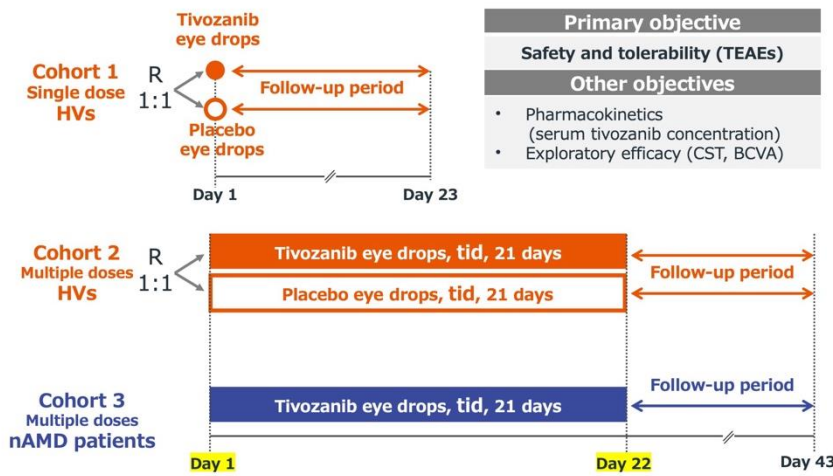
The nano-crystallized formulation we developed enabled efficient delivery of the active ingredients to the posterior ocular tissues.

22 © Kyowa Kirin Co., Ltd.

KHK4951 will be a nanocrystal eye drop formulation of the active ingredient tivozanib. As shown in the graph on the right, when tivozanib was administered to rats by ophthalmic injection, the nano-crystallized KHK4951 on the left was found to deliver the active ingredient tivozanib more efficiently to the posterior ocular region than the standard suspension formulation on the right, which had not been nano-crystallized.

KHK4951 is a nanocrystalline ophthalmic formulation of tivozanib, which has potent VEGF receptor inhibitory activity and high VEGF receptor selectivity and is expected to be an effective product for nAMD due to its high drug delivery to the posterior ocular region.

Ph1 study



Primary objective
Safety and tolerability (TEAEs)
Other objectives
<ul style="list-style-type: none"> Pharmacokinetics (serum tivozanib concentration) Exploratory efficacy (CST, BCVA)

Healthy volunteers in cohorts 1 and 2
Inclusion criteria
<ul style="list-style-type: none"> Age ≥ 20 to < 50 years Visual acuity ≥ 20/20
Exclusion criteria
<ul style="list-style-type: none"> Current illness requiring treatment Current or history of dry eye

Patients with nAMD* in cohort 3
Inclusion criteria
<ul style="list-style-type: none"> CST ≥ 300 μm BCVA score ≥ 23 letters
Exclusion criteria
<ul style="list-style-type: none"> Glaucoma, ischemic optic neuropathy, retinitis pigmentosa

* Both treatment-naïve and previously anti-VEGF treated patients were enrolled.

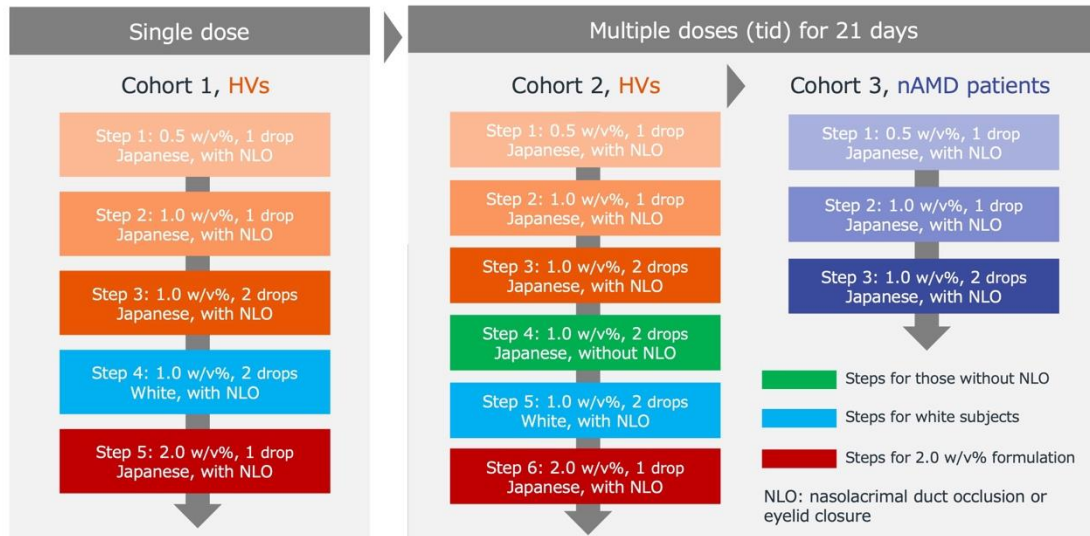
BCVA: best corrected visual acuity; CST: central subfield thickness; HVs: healthy volunteers; R: randomization; TEAE: treatment-emergent adverse event; tid: three times a day.

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Here we introduce some of the results of the Phase I study, excerpted from the presentation at the 77th Annual Meeting of the Japanese Society of Clinical Ophthalmology held in October of this year.

The study consisted of three cohorts, from the upper left side: single dose in healthy adults, repeated dose in healthy adults, and repeated dose in Japanese patients with nAMD. The repeated-dose group was administered three times daily for 21 days. The primary endpoints are safety and tolerability.

Ph1 study: Dosage regimen



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As shown here, in each cohort, Japanese and Caucasians, the concentration of the drug administered, and the dosage, one drop and two drops, were grouped together and each group was referred to as a Step in the evaluation.

In this study, to reduce systemic exposure after ophthalmic administration of KHK4951, NLO, which is to apply pressure to the lacrimal sac, and eyelid closure, which is to close the eyelid, were performed after ophthalmic administration. We assumed that some patients in the repeated-dose group would not be able to fully perform these procedures in real-world clinical practice, we also evaluated Step 1 without NLO or eyelid-closing procedures as mentioned earlier, in order to evaluate the maximum safety risk.

Ph1 study: Safety

Any TEAE or ocular AE in the study eye	Placebo (tid), HVs (n = 12)	Tivozanib (tid), HVs							Tivozanib (tid), nAMD patients			
		Step 1 Jpn with* 0.5 w/v% 1 drop (n = 6)	Step 2 Jpn with* 1.0 w/v% 1 drop (n = 6)	Step 3 Jpn with* 1.0 w/v% 2 drops (n = 6)	Step 4 Jpn without† 1.0 w/v% 2 drops (n = 6)	Step 5 White with* 1.0 w/v% 2 drops (n = 6)	Step 6 Jpn with* 2.0 w/v% 1 drop (n = 6)	HVs Total (n = 36)	Step 1 Jpn with* 0.5 w/v% 1 drop (n = 7)	Step 2 Jpn with* 1.0 w/v% 1 drop (n = 10)	Step 3 Jpn with* 1.0 w/v% 2 drops (n = 11)	nAMD patients Total (n = 28)
Any TEAE, n (%)	2 (16.7)	3 (50.0)	4 (66.7)	6 (100.0)	6 (100.0)	4 (66.7)	5 (83.3)	28 (77.8)	3 (42.9)	4 (40.0)	5 (45.5)	12 (42.9)
Death, other serious, or other significant	0	0	0	0	0	0	0	0	0	0	0	0
Eye disorders, n (%)	1 (8.3)	2 (33.3)	4 (66.7)	2 (33.3)	6 (100.0)	3 (50.0)	5 (83.3)	22 (61.1)	1 (14.3)	4 (40.0)	3 (27.3)	8 (28.6)
Punctate keratitis	1 (8.3)	2 (33.3)	2 (33.3)	1 (16.7)	6 (100.0)	3 (50.0)	3 (50.0)	17 (47.2)	0	1 (10.0)	3 (27.3)	4 (14.3)
Eye irritation	0	0	3 (50.0)	1 (16.7)	4 (66.7)	1 (16.7)	3 (50.0)	12 (33.3)	0	2 (20.0)	0	2 (7.1)
Foreign body sensation in eyes	0	0	0	0	1 (16.7)	0	1 (16.7)	2 (5.6)	0	0	0	0
Vision blurred	0	0	0	0	1 (16.7)	0	0	1 (2.8)	0	0	0	0
Eye pruritus	0	0	0	0	0	1 (16.7)	0	1 (2.8)	0	0	0	0
Eye pain	0	0	0	0	0	0	0	0	0	1 (10.0)	0	1 (3.6)
Lacrimation increased	0	0	0	0	0	0	0	0	0	1 (10.0)	0	1 (3.6)
Pinguecula	0	0	0	0	0	0	0	0	1 (14.3)	0	0	1 (3.6)
Swelling of eyelid	0	0	0	0	0	0	0	0	0	1 (10.0)	0	1 (3.6)

TEAE: any adverse event (AE) that occurred or worsened in the period between the first administration of the study drug and the end of the study; death: any AE with an outcome of 'fatal'; other serious: serious AEs other than death; other significant: non-serious AEs leading to withdrawal of the investigational product. *With nasolacrimal duct occlusion or eyelid closure. † Without nasolacrimal duct occlusion or eyelid closure. Jpn: Japanese.

No serious adverse events leading to study discontinuation were observed in either HVs or Japanese nAMD patients

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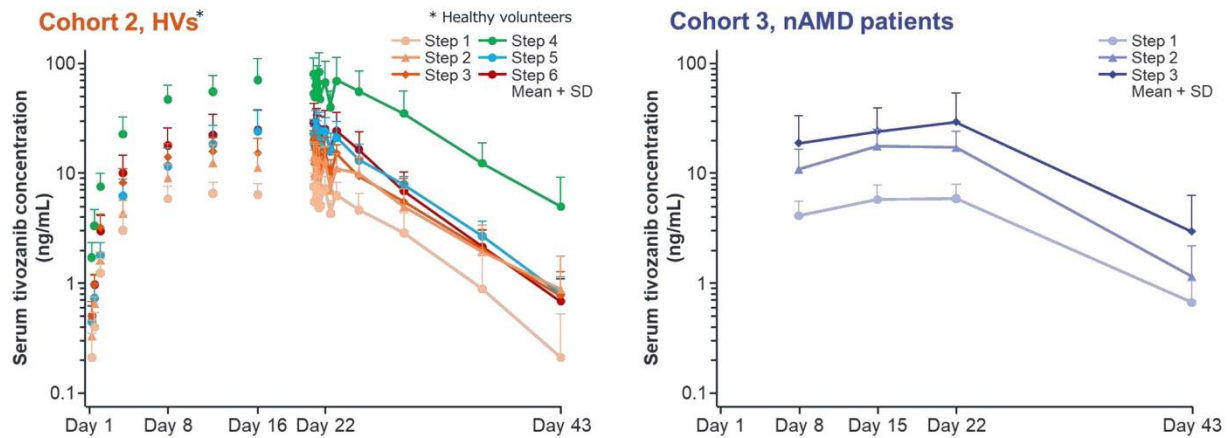
The results of the safety evaluation are shown here.

First of all, although treatment-related adverse events were observed as shown in the table, no adverse events leading to discontinuation of the study were observed throughout the study.

Eye adverse events included punctate keratitis and eye irritation, both of which were grade 1 to 2, non-serious, reversible, and did not lead to discontinuation of the drug.

No serious adverse events leading to discontinuation of the study were observed in either healthy adults or Japanese nAMD patients, and there was no significant difference in safety profile between healthy adults and nAMD patients. So we consider that the Phase I study has confirmed that KHK4951 is well tolerated.

Ph1 study: Serum Drug Concentration



- Mean serum concentrations of tivozanib increased in a dose-dependent manner.
- No significant differences in serum pharmacokinetics were observed between HVs and nAMD patients.

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The next step will be the serum drug concentration. Here are the data on serum drug concentrations for two cohorts of subjects, cohort 2 of healthy adults and cohort 3 of nAMD patients, who received repeated doses.

As shown in the graph, serum concentrations of tivozanib, the active ingredient in KHK4951, increased in a dose-dependent manner in both cohorts, and there were no significant differences in serum drug levels between healthy adults and nAMD patients.

KHK4951 Ph1 study summary

Safety

- There were **no serious AEs or AEs leading to discontinuation.**
- **There were no remarkable differences in its safety profiles between Japanese and White, and between HVs and nAMD patients.**

Pharmacokinetics

- Mean serum tivozanib concentration increased in a dose-dependent manner.
- No significant differences in serum concentration were found between HVs and nAMD patients.

+ Exploratory evaluation of efficacy also conducted

Decided to conduct Ph2 study based on the Ph1 study results

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The above results are summarized in this slide.

The Phase I study showed that KHK4951 was well tolerated and no critical safety risks were identified for further development.

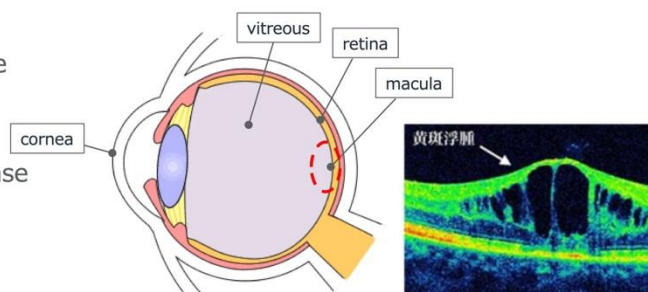
The study also evaluated efficacy, but this was an exploratory evaluation and was not set as the primary endpoint.

We have considered this point within our company, and in light of the fact that we have not set up such a validity evaluation at its root, we are very sorry, but we have decided to refrain from announcing the specifics today. However, although we cannot provide details, the results obtained from this Phase I study were positive, and we have decided to conduct a Phase II study for this product.

Diabetic Macular Edema (DME)

*Target indication for Ph2 study

- As a complication of diabetic retinopathy, high blood sugar causes damage to capillaries in the macula, resulting in edema of the macula and impairment of vision
- VEGF contributes the development of the disease
- Number of patients treated with drugs:
 - Japan: approx. 140K, Global: approx. 1.3M
- Standard of Care:
 - Intravitreal injection of anti-VEGF drugs or steroids, or intraocular implants
 - Ocular surgery (vitrectomy, laser treatment)



References : <https://www.civillink.net/fsozai/eye.html>
<https://www.eye.med.kyushu-u.ac.jp/patient/question/index3.html>

**Current treatment methods are all highly invasive
 A need for less invasive treatment options**

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Here is an introduction to diabetic macular edema, which will begin clinical trials from the Phase II.

This is a complication of diabetic retinopathy, a condition in which high blood sugar damages capillaries in the macula, causing edema of the macula and loss of vision. Like nAMD, VEGF is also involved in this disease.

The number of patients treated with drugs is estimated to be approximately 140,000 in Japan and 1.3 million globally. Current treatment methods are still mainly surgical techniques such as highly invasive intravitreal injections of drugs, intraocular implant surgery, and laser therapy. For this reason, less invasive treatment methods are required.

KHK4951 Ph2 study overview

Locations	<ul style="list-style-type: none"> (For both studies) JP, US, AU, KR
Study Completion (estimated)	<ul style="list-style-type: none"> (For both studies) 2026Q1
Enrollment (estimated)	<ul style="list-style-type: none"> nAMD 180, DME 150
Primary Endpoint	<ul style="list-style-type: none"> Reduction of 15 or more letters in BCVA (Best corrected visual acuity) as measured by ETDRS² visual acuity chart from baseline
Participant Group/Arm	Intervention/Treatment
Experimental: Arm A KHK4951 High dose	<ul style="list-style-type: none"> Drug: KHK4951 KHK4951 eye drop for 44(nAMD)/36(DME) weeks until end of the trial Drug: Aflibercept Injection Intravitreal injection (IVT) of aflibercept will be given as specified in the protocol
Experimental: Arm B KHK4951 Middle dose	
Experimental: Arm C KHK4951 Low dose	

1. Clinical Trials.gov ID: NCT06116890 (nAMD), NCT06116916 (DME); jRCT ID: jRCT2031230401 (nAMD), jRCT2031230400 (DME) 2. Early Treatment Diabetic Retinopathy Study

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Here is an overview of the Phase II study for KHK4951.

Both studies will be conducted in Japan, the United States, South Korea, and Australia, and are scheduled to be completed in Q1 of 2026.

The expected number of subjects is 180 for nAMD and 150 for DME. The primary endpoint is a decrease more than 15 letters in BCVA, best corrected visual acuity, compared to baseline. We expect that the administration of KHK4951 will decrease the percentage of patients whose BCVA drops by 15 letters or more.

In addition, this study is an actual drug group study with three different dose arms, and KHK4951 and Eylea will be administered and evaluated over a defined period of time.

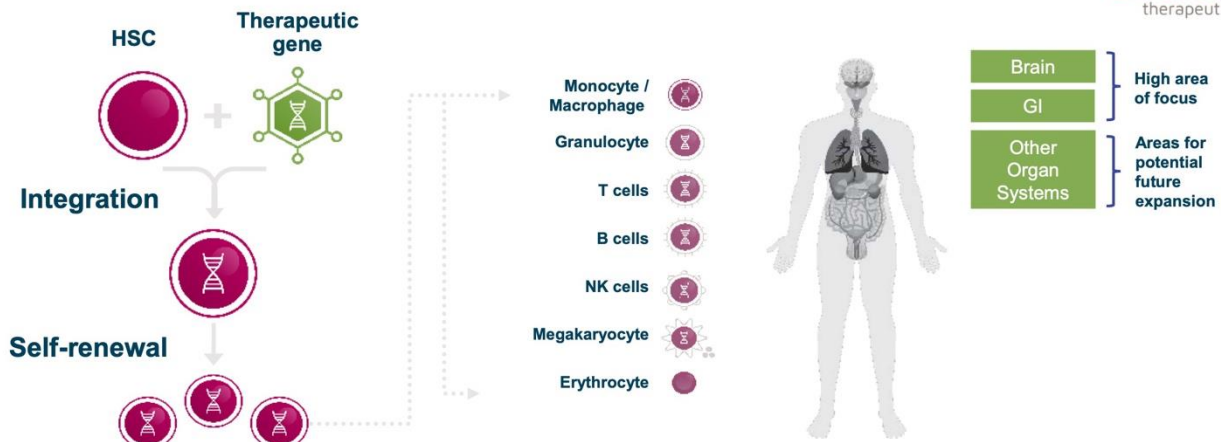
These are the introduction of KHK4951.

Toward the Successful Creation and Delivery of Life-changing Value

- KHK4951 (Ph1 study results and Ph2 studies overview)
- **HSC-GT (Orchard Therapeutics plc)**

Yamashita: Next, Yamashita will introduce Orchard Therapeutics' technologies, hematopoietic stem cell gene therapy technologies and products, which we announced its acquisition on October 5.

Hematopoietic Stem Cell Gene Therapy (HSC-GT)



HSC-GT allows delivery of gene-modified blood/immune cells to any part of the body

Literature references: Alessia Capolongo, Rita Milazzo, Letterio Salvatore Politi, Angelo Quattrini, Alessio Palini, Tiziana Piatì, Stefania Merella, Alessandro Nonis, Clelia di Serio, Eugenio Montini, Luigi Naldini, and Alessandra Biffi, PNAS September 11, 2012 109 (37) 15018-15023; <https://doi.org/10.1073/pnas.1205858109>; Tissue macrophages: heterogeneity and functions, Siamon Gordon and Annette Plüddemann, BMC Biology 2017 15:53, 29 June 2017

First, I'll explain an overview of HSC-GT, the hematopoietic stem cell gene therapy.

Hematopoietic stem cells are cells that reside primarily in the bone marrow and can differentiate into a variety of blood cells. HSC-GT is characterized by taking these hematopoietic stem cells, introducing a gene for a specific therapeutic purpose, and returning them to the body.

These genetically engineered cells differentiate into a variety of blood cell types in the body, including monocytes, macrophages, T cells, and B cells as they are indicated in the center of this slide. These differentiated cells are then distributed throughout the body to express the introduced genes.

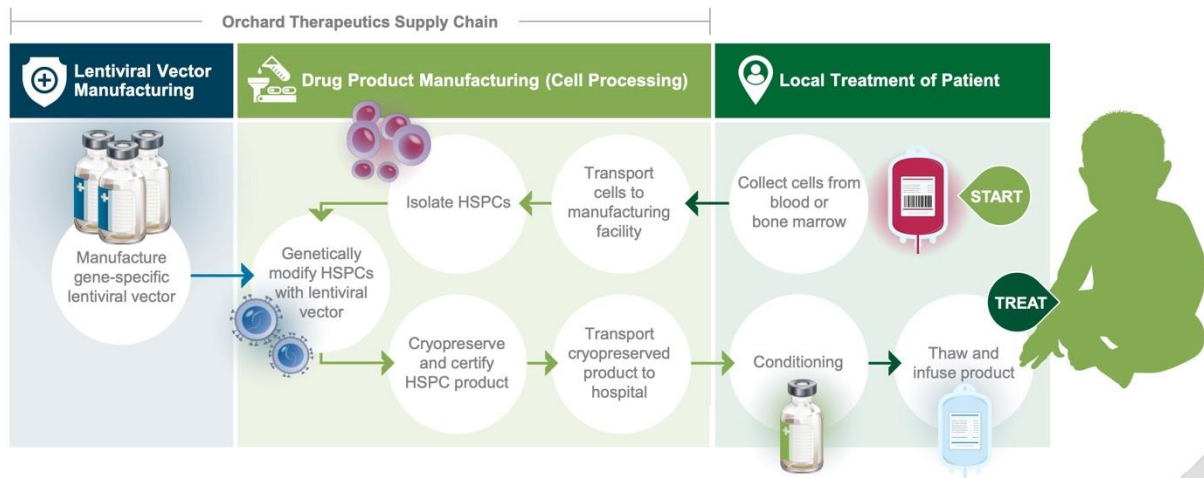
Currently, Orchard Therapeutics is successfully applying this technology to treat patients with a genetic disorder called lysosomal disease, which is an abnormality in the enzyme that breaks down waste products in cells.

Gene Therapy Manufacturing

GMP Cell Product Manufacturing Platform

KYOWA KIRIN

Orchard
therapeutics



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Figure: Created by Orchard Therapeutics plc

This slide shows the process of advancing this hematopoietic stem cell (HSC) gene therapy.

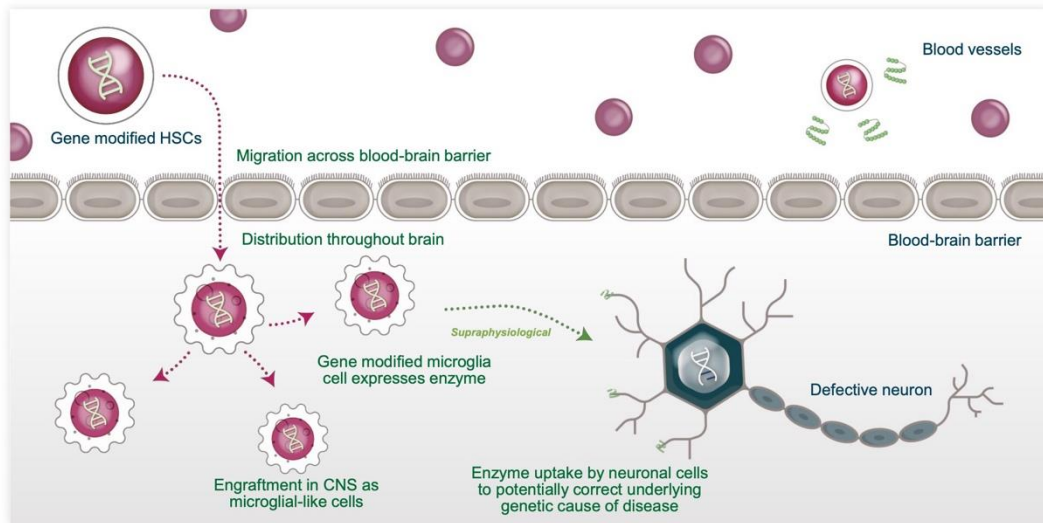
The first step is to collect blood stem cells from the patient, on the right side. The collected cells are transported to a manufacturing facility where the HSCs are isolated and then transfected therapeutic genes using lentiviral vectors. The transfected hematopoietic stem cells are cryopreserved and sent to a medical facility where the patient waits.

The patient, on the other hand, undergoes a pretreatment to accept these modified cells, and after the modified cells delivered, receives a transplant of his or her own hematopoietic stem cells transfected with the gene.

Orchard Therapeutics manufactures quality-controlled lentiviral vectors for gene transfection, as shown in the left. They have established the above series of processes, and they have already received approval in Europe and offered this treatment to patients.

Delivering Proteins to Brain

Potential to Treat Multi-System Neurometabolic Diseases via Cross-Correction



Next, I will explain about the delivery to the brain, which is the characteristics of this HSC-GT.

Treatment for abnormal enzymes that break down cellular waste products includes enzyme replacement therapy, in which normally functioning enzymes are administered as proteins. However, the brain has a cerebrovascular barrier, which restricts the transfer of substances from the blood to the brain, and even if enzyme proteins are administered into the bloodstream, there is a problem that they do not fully reach the brain. Therefore, there is unfortunately a problem that enzyme replacement therapy cannot adequately treat CNS disorders, and the patient's quality of life still leaves significant room for improvement.

On the other hand, microglia are cells in the brain that are derived from hematopoietic stem cells, and their progenitor cells can pass through the cerebrovascular barrier, the blood-brain barrier, and enter the brain. In other words, if a gene is transfected into hematopoietic stem cells, the differentiated cells from them can enter the brain and continue to supply the brain with the desired enzymes normally as cells in the brain called microglia.

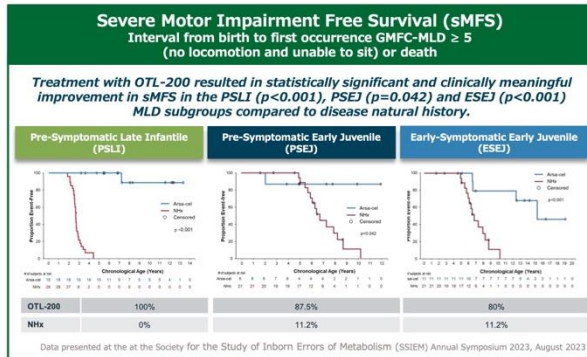
This allows HSC gene therapy to improve central function, which has been a problem in the past.

Libmeldy® (OTL-200, atidarsagene autotemcel)



- MLD (Metachromatic Leukodystrophy)
 - Fatal genetic CNS disorder
 - Rapid and irreversible loss of motor and cognitive function
 - In its most severe form, most children pass away within five years of symptom onset¹

Status	Next Catalyst	Expected timing of Catalyst
Launched in Europe Filed in US	FDA approval	PDUFA: March 18, 2024



Ref.) Orchard Therapeutics plc, Q2 2023 Financial Results and Webcast
<https://ir.orchard-tx.com/static-files/9fed8b65-2fd9-491a-97c0-69bf6595c0c3>



Potential annual market opportunity for Libmeldy® across all patient segments assuming an average per patient net price of \$2.5M and universal newborn screening²

1. van Rappard DF, Boelens JJ, Wolf NI. Metachromatic leukodystrophy: disease spectrum and approaches for treatment. *Best Pract Res Clin Endocrinol Metab* 2015; 29: 261-73.
2. The sale price of Libmeldy® will vary from jurisdiction to jurisdiction and could vary for a variety of reasons, some of which are outside of the company's control. The net price utilized on this slide is for illustrative purposes only and is not an estimate or prediction of the average net price of Libmeldy® globally.

Orchard Therapeutics has already received approval in Europe for this technology. This is what we call Libmeldy. This is a treatment for a lysosomal disease called metachromatic leukodystrophy.

In this disease, glycolipid-degrading enzymes do not function, resulting in intracellular accumulation of unwanted glycolipids, which leads to impaired motor function and cognitive decline due to central nervous system dysfunction, as mentioned earlier. The timing of onset is variable, but the prognosis is poor for those who develop the disease from infancy to about six years of age, and they die before reaching adulthood. Libmeldy is a transplant of hematopoietic stem cells with normal gene for such patients.

In the graph on the left, the red line shows the incidence of the disease in untreated cases, and the blue line shows that Libmeldy suppresses the incidence of disease. Its effectiveness varies slightly at the point of initiation of treatment, with the onset of symptoms expected to be avoided if treatment is initiated before the onset of symptoms.

The drug was approved in Europe in 2020 and the results of the US FDA review will be known in March of next year. We can expect Libmeldy to grow in the coming years by promoting the widespread use of this treatment, identifying patients early in the process, and expanding the geographic area covered.

Development Pipelines: OTL-203, OTL-201

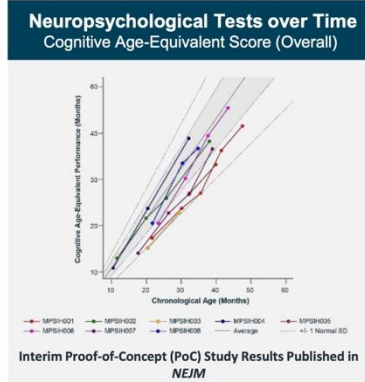
OTL-203

■ Indication: MPS-IH¹

- Multisystemic neurometabolic condition affecting cognition, growth and skeletal function
- ~1:100,000 live births; NBS² established in some geographies, incl. U.S.

■ Current Status

- Interim PoC results published in NEJM³
- Moving into a Pivotal (Ph3) study in 2H 2023



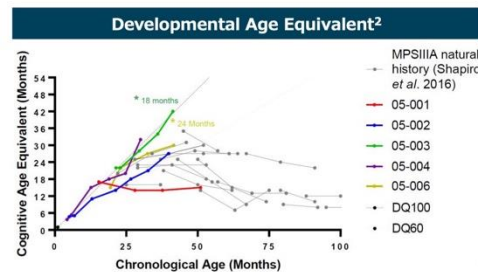
OTL-201

■ Indication: MPS-III A⁴

- Accumulation of substrate heparan sulfate leading to severe CNS degeneration w/ somatic manifestations
- Development slows from 3 years of age, followed by cognitive decline, behavioral disturbances, loss of skills and eventual death, No successful treatment options

■ Current Status

- PoC study (Ph1/2) is ongoing
- Biochemical/clinical data reported in 2023 ASGCT meeting



© Kyowa Kirin Co., Ltd. 1. Mucopolysaccharidosis type I, Hurler syndrome; 2. Newborn Screening; 3. Engl J Med 2021; 385:1929-1940 DOI: 10.1056/NEJMoa2106596; 4. Mucopolysaccharidosis type IIIA (Sanfilippo Syndrome type A)

Following Libmeldy, development of two more drugs is underway. Both target the same lysosomal diseases as Libmeldy, and although the therapeutic target enzymes are different, the therapeutic concepts and processes are common with those of Libmeldy.

OTL-203 is intended for mucopolysaccharidosis type I, that called Hurler's disease. The disease manifests itself in significant cognitive, growth, and skeletal dysfunction. This product has already obtained POC in clinical trials and the results have been published in a paper. One example is the improvement of cognitive function shown here. In addition, improvements in growth, skeletal abnormalities, and motor function have also been observed.

Based on these results, the FDA has granted Fast Track designation and Orchard Therapeutics has announced that it will begin pivotal trials this year.

The other, OTL-201, is for mucopolysaccharidosis Type IIIA. This is an extremely serious disease with onset of symptoms around age 3, resulting in cognitive decline, behavioral disturbances, loss of skills, and death.

The POC study is currently underway, and it was announced at the American Society for Gene and Cell Therapy meeting in May of this year that five patients who received the drug showed sustained improvement in objective enzyme function, with four of the five patients achieving cognitive function comparable to that of healthy children.

Expected Synergy

Further Development as a Japan-Based Global Specialty Pharmaceutical Company

- To be a Japan-based Global Specialty Pharmaceutical Company providing life-changing value to high unmet medical needs in concert with our existing business through Crysvida and Poteligeo

Reinforcement of Innovative New Drug Discovery & Development

Kyowa Kirin

- Experience and expertise of R&D and commercialization in Biologics and Antibody Drugs
- Proprietary next-generation antibody technology
- Continuous efforts on new modalities

Orchard Therapeutics

- Experience and know-how in the marketing HSC-GT¹ in EU
- High technology in HSC-GT¹ (Research, CMC, SCM, etc.)
- Patient access and collaboration with medical institutions
- Efforts and experience in new modalities

- A key step toward delivering advanced value to patients
 - Pursuing the potential for “One-time treatment in life”
 - Challenge to correct the underlying cause of a genetic disease
 - Personalized medicine / Precision medicine
 - Providing treatment beyond the existing drugs
- Address a broader range of UMNs

1. Hematopoietic Stem Cell Gene Therapy

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Here are some of the synergies we expect with Orchard Therapeutics.

We have already mentioned the enhancement of the pipeline. First, we are building a foundation as a global specialty pharma through the development of global products such as Crysvida and Poteligeo, and we believe that the products and developments of Orchard, which I have just introduced, will make a significant contribution to the development of our business.

I think you will agree that this fits very well with our vision of bringing smiles to people's faces by continuously creating and providing life-changing value, as I explained at the beginning of this presentation.

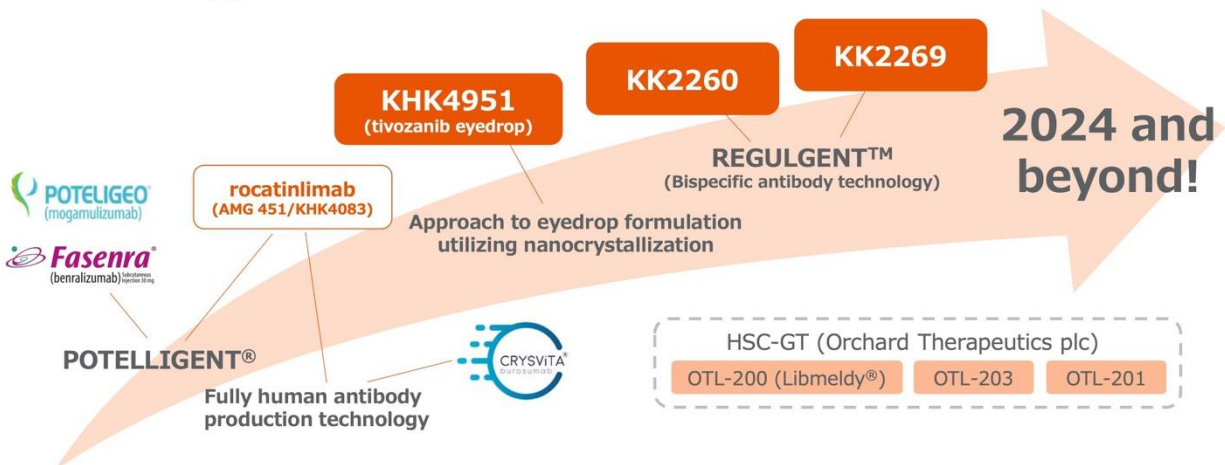
Second, Orchard Therapeutics' technology and know-how and our various capabilities will complement each other and enhance our research and development.

As explained today, Orchard Therapeutics achieves its therapy by gene transfection of enzymes into hematopoietic stem cells. We are looking to combine the technologies we possess. For example, instead of enzymes, other proteins with therapeutic effects could be combined with this platform. We believe that the combination of biopharmaceutical or antibody technologies developed by Kyowa Kirin will open up the possibility of realizing new treatments.

We also believe that the need for medical care will continue to grow in sophistication into the future. In this context, the possibility of being able to treat diseases from the root, and the possibility of only needing one treatment in one's lifetime, is something we would like to continue to pursue.

Libmeldy has already realized personalized medicine, in which gene therapy is performed using the patient's own cells. We intend to continue to focus on these as therapeutic agents that go beyond existing drugs. We hope to develop our research and development to meet a wider range of unmet medical needs.

Innovative New Drug Creation by Kyowa Kirin Drug Discovery Technology



Kyowa Kirin will realize the successful creation and delivery of life-changing value that ultimately makes people smile

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Today, I explained about KK2260 and KK2269 using our proprietary bispecific antibody technology, REGULGENT, and KHK4951 which is an approach to eyedrop formulation utilizing nanocrystallization, and Orchard's HSC-GT.

Under our vision of successful creation and delivery of life-changing value that ultimately makes people smiles, we are striving to challenge new technologies and deepen our understanding of disease, even under the surface, and we are also working on research and development in collaboration and cooperation with external parties. And we will do our utmost to develop as a global specialty pharmaceutical company that embodies our vision.

That's all for my presentation. Thank you for your attention.

Question & Answer

Moderator [M]: We would like to start the question-and-answer session.

Yamaguchi [Q]: This is Yamaguchi from Citigroup Global Markets. Thank you. First of all, I would like to ask about KK2260. In essence, this antibody degrades TfR, but its antibody function is EGFR, so what differentiates it from ordinary EGFR antibodies is that it degrades this TfR more and more, so in the end it becomes stronger?

I couldn't figure out the point of differentiation from existing drugs at the moment, but is my understanding correct? Is the concept of TfR degradation to drop more and more cancer cells?

Torii [A]: As you mentioned, the EGF receptor is used only as a scaffold, and the anti-tumor, cell-killing mechanism involves bringing transferrin receptor 1 to the lysosome and degrading it. Thereby depleting iron. This is the main MOA.

Yamaguchi [Q]: So by depleting iron, those cells die?

Torii [A]: Yes. They will die. They will die by apoptosis.

Yamaguchi [Q]: So you are saying that the TfR is what is more important, and in a sense, EGFR does not have to be this one, but any other one would be fine if there a lot of them.

Torii [A]: Yes, that's right. We are using it as a scaffold, as a tool to guide the transferrin receptor to the lysosome.

Yamaguchi [Q]: I understand. Another question is about CD40, cold tumor to hot, I think it was indeed a hot area, but what I didn't understand was what is called EpCAM. The cancers you are targeting now include stomach cancer and lung cancer, which are areas where PDX and PD-1 antibodies are effective.

My understanding is that cold means breast or colon at the top of the list, but PDX and PDLX are already quite effective in this area, so I wasn't sure if this CD40 would be able to differentiate itself from existing products.

Torii [A]: As you mentioned, looking at the overall results, there are some areas that are generally effective, but if we look at the details, there are segments where checkpoint inhibitors do not work well. We would like to proceed with the selection of actual cancer types for which EpCAM is indicated, while taking into consideration the actual expression level of EpCAM and its expected effects.

Yamaguchi [Q]: So, you are going to focus on cold, which is a cancer type that the existing ones don't work and make it hot with this. It has to be cold because it uses chemo from the beginning and it is difficult to differentiate from existing products in areas where chemo is used from the beginning. Will you be finding a cancer in the concept of making cold tumor hot with this, and then using chemo to beat it?

Torii [A]: Yes. As you understand.

Yamaguchi [Q]: I understand. Specifically, what sort of cancer are they? After all, is it quite common in stomach or lungs, too, depending on the cases?

Torii [A]: In Phase I, we are going to conduct it for all patients, but we will discuss this part with the clinical doctors and decide which cancer types we will actually target to the later stages of development, while looking at the safety data obtained from Phase I.

Yamaguchi [M]: Thank you very much. That's all.

Muraoka [Q]: Hello. This is Muraoka from Morgan Stanley MUFG Securities. Thank you. I would like to ask about KHK4951; there were some nuances like there are some things that cannot be released yet in the data.

I'm talking about the part where the eye drop is nano-crystallized to reach the posterior ocular area properly. You showed us some data from OCT one year ago. Today, the data was back to the data with rat, but if you have anything that will show us that you can do better, please share it with us. I'm sure there are things you can't say today though.

And also for KHK4951, I think the does was three times daily in the Phase I, and the number of times of eye drops. As for the daily does, is it going to be the same? And what was the background behind the slight difference in the 36-week, 44-week, and evaluation timeframes between DME and AMD?

Sorry, I know it was a lot in one question, but please explain KHK4951.

Torii [A]: Regarding the first point, we had originally hoped to be able to present more clinical data, but due to the Pharmaceutical Affairs Law and promotion codes, there is a risk that it might fall under the category of pre-promotion. As for the data from the Phase I, I would like to apologize for not being able to show you all of it.

Regarding the first question, data that shows whether the drug is being delivered to the posterior eye area, clinical data would be most convincing, but it is not practical to measure that much in humans, so we must use data from animals. We are also working on some other animal species, but we will check if we can disclose them and if so, we will introduce them later.

Regarding your second question, I would like to ask for your understanding that we are refraining from disclosing more information on the number of doses than is currently available on ClinicalTrials.gov. As for the administration period, we have set the evaluation period for each of the two indications, taking into consideration the differences in treatment with standard therapy.

That is all for the explanation from me.

Muraoka [Q]: I understand. Thank you very much. The second question was simple, KK2260, anemia is a risk factor, and I thought a KK2260 type probably means that anemia should always be a concern when targeting other points with this TfR1.

I'm a bit of a layman, but I'm wondering if we could inject EPO or NESP together to avoid the risk of anemia, but isn't that what you are talking about?

Torii [A]: Is the background of your question now about anemia risk with our bispecific or about the introduction of treatment with transferrin receptor antibodies?

Muraoka [Q]: I'm sorry I don't understand properly. I simply thought that for anemia, administering EPO would solve that problem; I didn't think it so carefully.

Torii [A]: I think it is possible in logic. On the other hand, I believe that the most desirable profile for patients is to prevent the drug itself from causing anemia, which is what we should aim for.

As I explained earlier, minor anemia has been observed at the highest dose in non-clinical trials, but we will carefully monitor the safety of this part of the drug in clinical trials and discuss how to avoid or treat it with clinical doctors as we proceed with development.

Muraoka [M]: All right, that's all. Thank you.

Wakao [Q]: This is Wakao from JPMorgan, thank you very much. Thank you. I would like to ask about page seven. Have you compared your company's bispecific antibodies with those of ordinary bispecific that have different right and left hands, with such as KK2260 and KK2269, which you introduced today, say, in animals?

I have a feeling that conceptually it looks better than the normal one, but I would like to know how much of an impact it would actually have in real-world clinical practice.

Torii [A]: Naturally, we have internally examined several format patterns, including the standard monovalent and monovalent portion, and compared it to the standard monovalent and bivalent, or bivalent and bivalent, and other patterns. We have confirmed that the best combination is the bivalent and bivalent, at least for the indication of cancer types we are currently targeting.

Wakao [Q]: I understand. Are you saying that KK2260 and KK2269 have been found to be superior to the usual bispecific in your company's basic research?

Torii [A]: Against this antigen. Other companies are doing bispecific against other antigens, so this is not a comparison with them.

Wakao [Q]: I understand. So then, depending on the antigen, is it necessary to consider which is better?

Torii [A]: It depends on antigen expression in the target cells or turnover of the antigen. It varies considerably depending on such circumstances, we have been considering the optimal format on a case-by-case basis.

Wakao [Q]: I understand. On page seven, in terms of the manufacturing process, what is the approximate yield of your product? I have often heard that the yield rate is low for ordinary bispecific, and I have heard stories of 1 gram to 2 grams per liter, but what about your company?

Torii [A]: I can't give you specific numbers, but we are developing and launching regular antibodies with other pipelines, and compared to the past, the titers of the recent antibodies have been improved. We have been able to obtain the same level of titers as our own non-bispecific antibodies. I cannot tell you more than that.

Wakao [Q]: Okay, thank you very much. Second, can you just tell us about the competitive situation? Conceptually, the antibody [inaudible] is not that complicated, so I think there are people who are thinking along the same lines.

I believe that there are other companies that are targeting the same type of target with regard to KK2269, which is the C-terminus type. Can you tell us about the competitive landscape and what, if any, clear advantages your company has? Especially about KK2269.

Torii [A]: Thank you very much for the question. So we have two perspectives on KK2269. First of all, as for the development of single CD40 antibody, the most advanced CD40 antibody is APX-005M. The Phase II trial has been completed, but unfortunately the endpoint has not been reached, and the Company has not yet received information on whether or not it will go on to Phase III. Several other Phase I and Phase II products are also in development for a single CD40 antibody product.

On the other hand, with regard to bispecific antibodies, ABBV-427 (Note: ABBV-428 is the correct number), for example, is done by AbbVie. This is a bispecific antibody against CD40 and mesothelin. However, this is an antibody-like bispecific with artificial sequences, unlike our natural products, which are based on natural sequences.

Roche, on the other hand, is now developing a bispecific against CD40 and FAP in Phase I. We have information that this is a combination of monovalent and bivalent drugs, with monovalent against FAP and bivalent against CD40. We will continue to monitor the efficacy and safety to compare our products with these drugs specifically. That is all from me.

Wakao [M]: Thank you. That's all.

Hashiguchi [Q]: My name is Hashiguchi from Daiwa Securities. Thank you very much for the explanation. The first is about KK2260. What were your reasons for choosing EGFR as a target or rather a scaffold? If this works to some extent, what about the possibility of expanding on antibodies using other targets as scaffolds?

Torii [A]: As I mentioned earlier, we have selected this EGF receptor as a scaffold antigen based on a comprehensive consideration of several factors, including the protein expression level in the target cells and the ease of cross-linking.

As for future development, since this is a highly applicable format, we are considering changing the scaffold, or changing the transferrin receptor 1 to another MOA that has the potent cytotoxicity.

Hashiguchi [Q]: How advanced is your preclinical research on the combination of other targets with the transferrin receptor as a scaffold? And if you find that this is a promising approach, when can we expect to see the next pipeline in the clinical study?

Torii [A]: I would like to refrain from providing information on this area because it is also related to research strategies. I apologize.

Hashiguchi [Q]: I understand. The second point, about KK2269. The tumor volume data by individual on the bottom of the slide on page 18 shows that some individuals in the combination group seem to have developed resistance to the drug even though it was effective at first.

Do you know what kind of individuals are more likely to develop resistance to the drug, and which individuals are more likely to sustain its effects?

Torii [A]: Although the mice in this study are of a near-neighborly lineage, the genes are not completely identical, so there are some differences in the immune responses of the hosts. This difference might have influenced some individuals to be almost cured while others showed signs of proliferation. However, regarding the exact cause of these differences, we are currently conducting investigations, but we have not yet been able to clearly identify the underlying factors.

Hashiguchi [M]: Thank you very much. That's all.

Mamegano [Q]: Hello. I'm Mamegano from BofA Securities. I too have a question regarding REGULGENT technology. I understand that KK2269 that you explained now is effective when used in combination with chemotherapy, but can you tell me what you think about the reasons why it is not effective as a single agent?

I think KK2260 worked well as a single agent, but is this a REGULGENT feature of the C-terminus or a specific problem with KK2269?

Torii [A]: Regarding your question, the first step is to induce ICD, which, as you can see on the upper left side on page 19, induces immunogenic cell death and releases various tumor antigens or immunostimulants. This is where the combination with docetaxel, an anticancer drug with a strong ICD effect, becomes very important.

So, in the case of KK2269 alone, it is difficult to expect it to act alone, since the ICD here is not that strong.

Mamegano [Q]: I understand. I was wondering if by cross-linking both of these, it would work cold to hot by cytotoxicity cells, but now I see that this part of chemotherapy is important.

Torii [A]: Yes. Guidance to ICDs here is very important.

Mamegano [M]: Okay, thank you very much. That's all.

Tsuzuki [Q]: I'm Tsuzuki, Mizuho Securities. Thank you. I was wondering if I could ask you a few things about the technology on page seven. I know that your company has reached the point of bivalent and bivalent, but is there any progress in the request to reduce it to bivalent and monovalent, or rather, making it trivalent, as other companies have done?

Also, I think your company is doing VHH antibodies quite strongly in Japan, but in that sense, is there any difference in convenience with VHH antibodies? Can you comment on this area?

Torii [A]: We are also considering patterns other than the bivalent and bivalent pattern as you mentioned and examining not only antibodies but also antibody-like structures, or even VHH. We are considering various options, but the actual information we are obtaining is also related to our research strategy, so I am sorry, but we will not be disclosing this information.

Tsuzuki [M]: I understand. Thank you.

Wada [Q]: I am Wada, SMBC Nikko Securities. I also have a question about the perspectives you mentioned on page 12 in the REGULGENT section. The first point is that I would like to know the mechanism where it does not show neutralizing activity when bound to only one of them.

The other point is whether it is necessary to make them bispecific, both KK2260 and KK2269. For example, for KK2260, do you have comparative data with antibodies that inhibit EGFR, and for CD40, do you have comparative data with antibodies that inhibit CD40 or only CD40 in non-clinical studies? What do you think?

Torii [A]: Regarding this aspect, naturally, EGF receptor antibodies or single antibodies targeting CD40 have been leading the way as developmental products. For EGFR, CD40, and our KK2260, the MOA (Mechanism of Action) is transferrin receptor 1 antibody, the development of those antibodies is also progressing. However, there are still concerns regarding their safety, which has caused some challenges.

In contrast, our product exhibits its effects when the two components are combined, and we are currently advancing its development with the aim of differentiation in that area.

As to why it is necessary to combine both, we are still studying the details, including structural analysis, etc., and will disclose the information at the appropriate time when it becomes clear. That is all from me.

Wada [M]: Thank you very much.

Yamaguchi [Q]: Thank you. I would like to ask you about Orchard, first of all, Libmeldy, the gene therapy. Do you know the duration of the effect? Please let us know how many years it takes for the effect to gradually diminish, or if there are any information you know this now. This is my first question.

Yamashita [A]: Yamashita will answer the question. In this hematopoietic stem cell gene therapy, a gene is completely incorporated in the hematopoietic stem cell with a lentivirus. And on the theoretical point of view, that these hematopoietic stem cells will continue to self-renew properly in the body, thus providing a continuous supply of differentiated cells for a long time, and this effect will last forever.

In fact, the cases currently reported with Libmeldy, once treated, have been very close to normal since then, and I wonder how old the patients are now. I think some of them were 10 years old or something.

So, basically, it is something that will pretty much, hopefully, only need to be treated once in a lifetime.

Yamaguchi [Q]: I understand. Also, there are already existing products for ordinary enzyme replacement therapy, of course not for this metachromatic leukodystrophy, but I think there are quite a few other ones. Also, as you know, JCR is using JBC to deliver to the brain with transferrin, although it is used in a different way.

There are currently no existing drugs for the treatment of metachromatic leukodystrophy, and bone marrow transplantation has been the only available option. I believe that your company's future strategy involves addressing this situation. Although there is an existing enzyme replacement therapy, it does not effectively reach the brain, leading to various issues. However, there is the option such as JBC, and I wonder if it is part of your company's medium- to long-term strategy to gradually replace each existing therapy with such a product as a competitor.

Please tell us how you view this JBC and existing enzyme replacement therapies, including beyond the pipeline you have now.

Yamashita [A]: The products and developments that are currently underway at Orchard, which are so-called monogenic, single gene disorders of lysosomal disease, and they normalize them. Or they introduce a gene that would restore that function, which is where the once-in-a-lifetime treatment I mentioned earlier comes in.

As you asked, enzyme replacement therapy is also currently used as a treatment for some of these diseases. Though as you pointed out, regarding Libmeldy, there is no other treatment, and as I explained earlier, enzyme replacement therapy is difficult to use for this disease, as central nervous system disorders can have a very subsequent prognostic impact. We are now focusing on these areas.

Of course, any other company that tries to carry enzymes there with technology that would pass the blood brain barrier will be a potential competitor. As I mentioned in the case of Libmeldy, for example, this is a disease that must be treated very early in life, or once the degeneration of the central nervous system has progressed, it will not return no matter how many enzymes are introduced afterward. Therefore, we believe that finding the disease early and treating the root cause will continue to be a very promising treatment.

Therefore, when considering where to begin with the current technology, we are currently taking into account various factors such as whether the target site is within the central nervous system and determining the optimal timing for treatment.

On the other hand, some of the areas may be put off, as was the case earlier, where treatment that approaches the brain with other techniques may be a threat as a competitor. I would like to discuss this with Orchard in the future.

I think there is a possibility of using hematopoietic stem cells as a vehicle to deliver proteins or antibodies with therapeutic effects to the central nervous system, in addition to the current enzyme function defects. We are considering the possibility of expanding this to other diseases as well, and we would like to continue our consideration on such possibilities. That's all.

Yamaguchi [M]: Thank you very much.

Wakao [Q]: I'm Wakao from JPMorgan. This is the second time. I too would like to know about Orchard. Since you are using a lentivirus, my understanding is that it will be randomly inserted into the genome, but I wonder if that is correct and what the safety concerns are due to the random insertion.

For example, I know you are waiting for FDA approval, but is there any situation or possibility that this could be an issue when the FDA approves the product in March?

Yamashita [A]: Thank you for your questions. First of all, you are correct about gene transfer using lentivirus. The thing about this is that it is where the virus inserts its genes at the genome, which is not something it has complete control over.

In fact, there is a concern about the safety of lentiviruses because of the possibility that the inserted genes may alter the functions of other internal genes, and there have been reports of cases in which lentiviruses have been used in hematopoietic stem cells, causing cells to proliferate abnormally or to differentiate and grow differently from their original state.

Orchard's technology is being applied to this type of product using a genetic structure that reduces such concerns as much as possible, and the possible risks have been minimized as much as possible.

As for the impact on the approval of FDA, considering that there is no cure for MLD, and that it is a very serious disease, the balance of benefits and risks will probably not be a major issue for FDA approval. That is all.

Wakao [Q]: Could this be a subject for discussion in the future as you do so and expand horizontally?

Yamashita [A]: As I said before, we need to always consider the balance between benefits and risks, and whether this is an appropriate option compared to other options. Safety is an irreplaceable factor in the development of these products depending on the disease, so this is something we will carefully consider and think about.

Wakao [Q]: I understand. Also, is it the baby that is the target of development using this technology? So I wonder if it would be OK to do a hematopoietic stem cell transplant, so they can drop the hematopoietic stem cells after adulthood and then transplant them again. On the other hand, looking at the Orchard pipeline, I thought that they are conducting clinical trials that are targeted more towards babies, so how would you define the age of the target patients?

Yamashita [A]: Thank you very much for the question. I showed you three graphs earlier. These three graphs show the effects of the three types of treatment: Pre-Symptomatic Infantile, Pre-Symptomatic Early Juvenile, and Early-Symptomatic Early Juvenile. The effect of the treatment varies slightly depending on the age of the child from birth and whether or not symptoms appear.

This disease, MLD, is caused by nerve damage in the brain as a result of the accumulation of what is normally degraded in the brain. Once impaired, supplementation with enzymes that later remove the unwanted substances will not restore the impaired brain function. That is why it is very important to give this treatment during this pre-symptomatic period, before the symptoms appear.

As you can see on the far right, the treatment is effective to a certain extent when the patient is Early-Symptomatic and the signs of the disease have appeared, but in the case of a bone marrow transplantation as an adult with the symptoms you mentioned earlier, this treatment is not feasible.

Wakao [Q]: Is this the same for OTL-203?

Yamashita [A]: Yes, that's right. Basically, the mechanism of central effects this time is similar, and the focus is still on identifying patients with this disease early and treating them.

Wakao [Q]: So then it doesn't necessarily compete with enzyme replacement therapy, or there are some aspects of the timing of treatment that are not completely identical?

Yamashita [A]: I think there is a certain amount of lysosomal disease where enzyme replacement therapy has been successful, but I believe that for these diseases, this drug is the treatment of choice where early central damage occurs.

Wakao [M]: I understand. Thank you, that's all.

Hashiguchi [Q]: I would like to ask this question to gain a better understanding of the uniqueness of REGULGENT technology. You have just introduced KK2269's competitors and potential competitors. I think you introduced the clinical stage, but if we expand our attention to the preclinical stage, the concept of cross-linking CD40 and cell adhesion molecules may also be done by a Swedish company called Alligator.

If you look at this company's website, you will see almost the same picture as the one you presented today, but I wonder if you could comment on what is the difference between their Neo-X-Prime technology and your REGULGENT technology.

Torii [A]: It is difficult to make comparisons without sufficient information yet. Also, as I showed you earlier, each company has different conditions, so it is difficult to have a scientific discussion unless we compare two companies under the same conditions in the same system.

As of yet, we do not have information on clear differentiation.

Hashiguchi [M]: I understand. Thank you. That's all.

Yamaguchi [Q]: First, I think your company has developed various hematologic cancers globally, but I don't think you have done much in solid tumors. The competition for development is quite fierce, so I would like to ask you about some ideas to increase the speed of development, or something like that, although it has nothing to do with research. If the concept is interesting, development will proceed, but if you have any ideas for how to speed up the development of solid tumors, please let us know. This is my first question.

Torii [A]: It may not be only for solid cancers, but as you know, the FDA has also recently recommended through Project Optimus that recommends not the usual way of doing cancer up to now.

If we were to collect clinical data in the usual way, it would take a considerable amount of time and cost. In this regard, we will make maximum use of modeling and simulation, or what FDA calls MIDD, to efficiently utilize animal models and other non-clinical data and obtain highly predictive data with the fewest number of patients possible in actual clinical trials. We are now in the process of proceeding development while taking on such challenges.

On the other hand, there is still a part of the management side that is considering how to maximize the value of this drug, so will we continue to do this in-house until the end, or will we work with partners who have this kind of experience to further accelerate the process? We are in a situation where we are continuing to consider various options to maximize the value of the drug.

Yamaguchi [Q]: Thank you very much. Also, I think there were several bispecific candidate patents, and two of them came up this time, but will these two be used for the time being? Or, for example CD40, there are many other things besides EpCAM, as I recall, but would you like to add more? Or is this where you promote these two drugs for now and maximize this?

Like how the pipeline will be connected in the future, since it is a modality technology. What do you think about?

Torii [A]: We are actually running a research-level project using the bispecific antibody technology, and we will explain about it when we are ready to disclose it to you. That's all.

Yamaguchi [M]: Thank you.

Moderator [M]: Thank you very much for attending our R&D briefing today. Thank you for your continued support of Kyowa Kirin.