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CHUGAI PHARMACEUTICAL CO., LTD.

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CHUGAI PHARMACEUTICAL CO., LTD.

R&D Meeting

December 17, 2024

Event Summary

[Company Name]	CHUGAI PHARMACEUTICAL CO., LTD.
[Company ID]	4519-QCODE
[Event Language]	JPN
[Event Type]	Analyst Meeting
[Event Name]	R&D Meeting
[Fiscal Period]	
[Date]	December 17, 2024
[Number of Pages]	61
[Time]	15:00 – 16:54 (Total: 114 minutes, Presentation: 75 minutes, Q&A: 39 minutes)
[Venue]	Webcast
[Venue Size]	
[Participants]	

[Number of Speakers]	6	
	Tsukasa Kusano	Executive Vice President, Head of Project & Lifecycle Management Unit
	Dr. Misato Hashizume	Franchise Lead for Hematological Malignancies
	Yuji Habara	Giredestrant & Inavolisib & HER2 Franchise Lifecycle Leader Divarasib Lifecycle Leader
	Dr. Shunichiro Iwasawa	Avutometinib Lifecyle Leader
	Kae Miyata	Head of Corporate Communications Dept.
[Analyst Names]*	Kazuaki Hashiguchi	Daiwa Securities
	Seiji Wakao	JPMorgan Securities
	Koichi Mamegano	BofA Securities
	Hiroshi Wada	SMBC Nikko Securities
	Miki Sogi	Sanford C. Bernstein

Fumiyoshi Sakai	UBS Securities
Yo Mizuno	Tokio Marine Asset Management

*Analysts that SCRIPTS Asia was able to identify from the audio who spoke during Q&A or whose questions were read by moderator/company representatives.

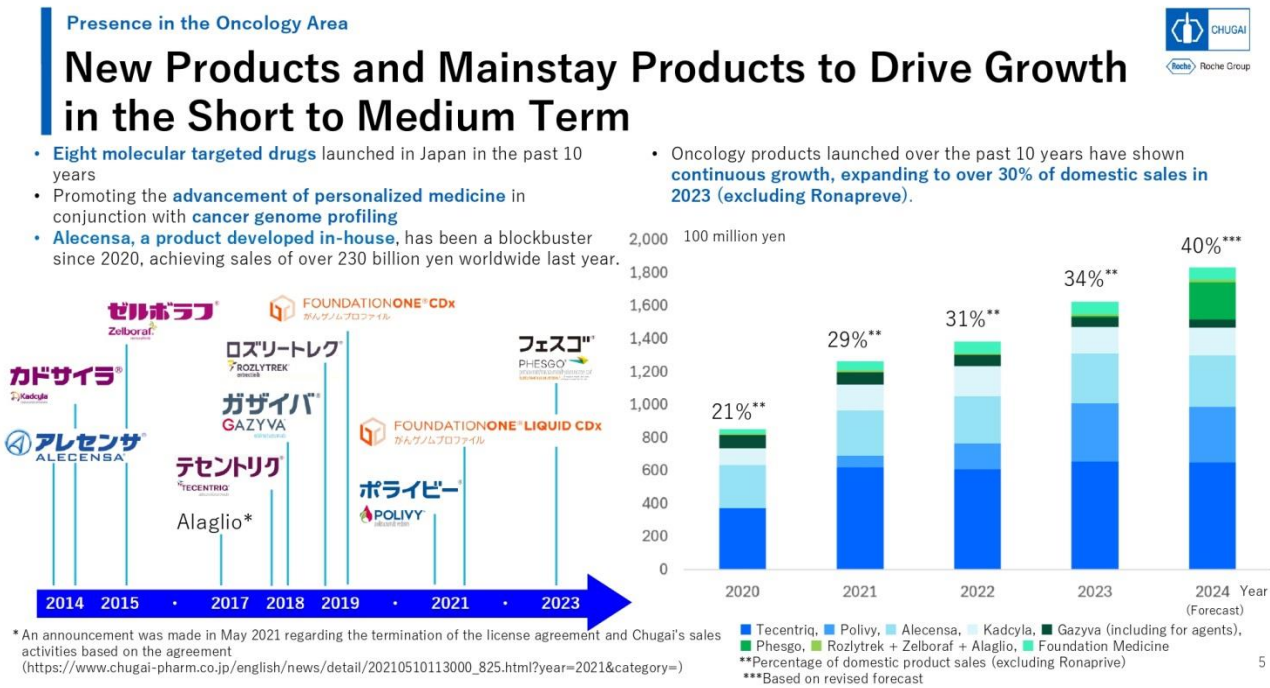
Presentation

Miyata: Thank you very much for attending the CHUGAI R&D Meeting today. I am Miyata, Head of Corporation Communications Department, and I will be facilitating today's session. Thank you for your cooperation.

Today's information session is being held onsite and is also available via Zoom webinar. Today's agenda is shown on the screen of the venue, on the web screen, and on page three of the presentation material. There will be time for screen capture before each presentation.

Questions will be taken in batches after all presentations have been completed. Q&A is expected to last 30 minutes. We welcome your active questions. Please note that your audio will be muted during the presentation.

Mr. Kusano will explain our presence in the oncology area.



Kusano: My name is Kusano from CHUGAI PHARMACEUTICAL CO., LTD. I would like to talk about CHUGAI's presence in the oncology area.

CHUGAI has contributed to patient care and achieved growth through the creation of innovations in cancer treatment and the promotion of personalized medicine.

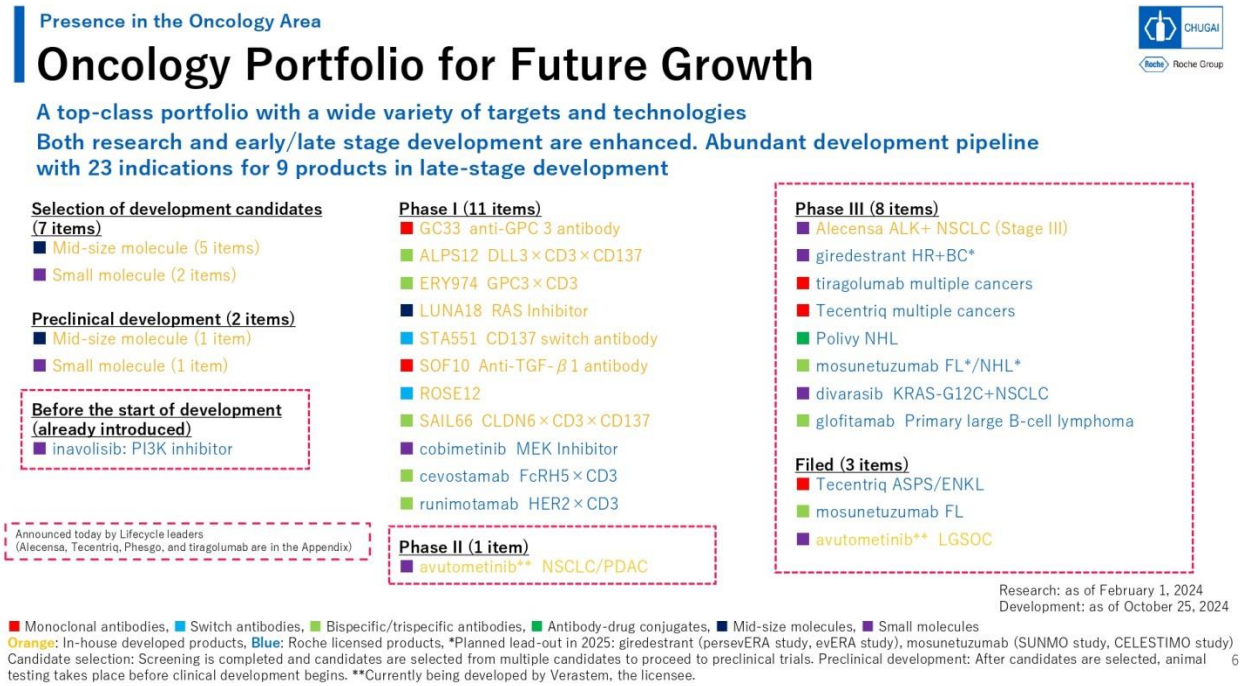
Looking back over the past 10 years, as shown here, we have marketed eight molecular-targeted drugs in Japan. Using multiple modalities, including small molecules, antibodies, and antibody-drug conjugate, we have contributed to patients with lung, breast, liver, colorectal, solid tumors, and hematologic cancers with new therapeutic agents for a variety of targets, including ALK, CD79b, HER2, PD-L1, and others.

In addition, we have led the spread of cancer genome medicine through cancer genome profiling tests, and have contributed to supporting the decision-making process for treatment based on the genetic profile of each patient.

Alecensa discovered in-house, has been a blockbuster since 2020. This has achieved a worldwide sales growth of more than JPY230 billion last year.

The graph on the right shows the percentage of sales in the domestic market of products launched in the oncology area over the past 10 years. These products continued to grow and accounted for more than 30% of our sales in 2022, firmly driving our growth. We boast the industry's top market share in the oncology area.

Our three value delivery divisions, Sales, Medical Affairs, and Drug Safety, work together to support team medicine and regional collaboration, generate clinical and non-clinical data that meets medical needs, and rapidly share and utilize safety information, all of which are highly valued by our clients.



However, there are still many unmet needs in the oncology area that need to be addressed. CHUGAI will continue to seek solutions to unmet medical needs that can be approached with our technology. In doing so, we will pursue solutions to issues not based on disease areas or market size, but rather on technology-driven drug discovery that starts with technology.

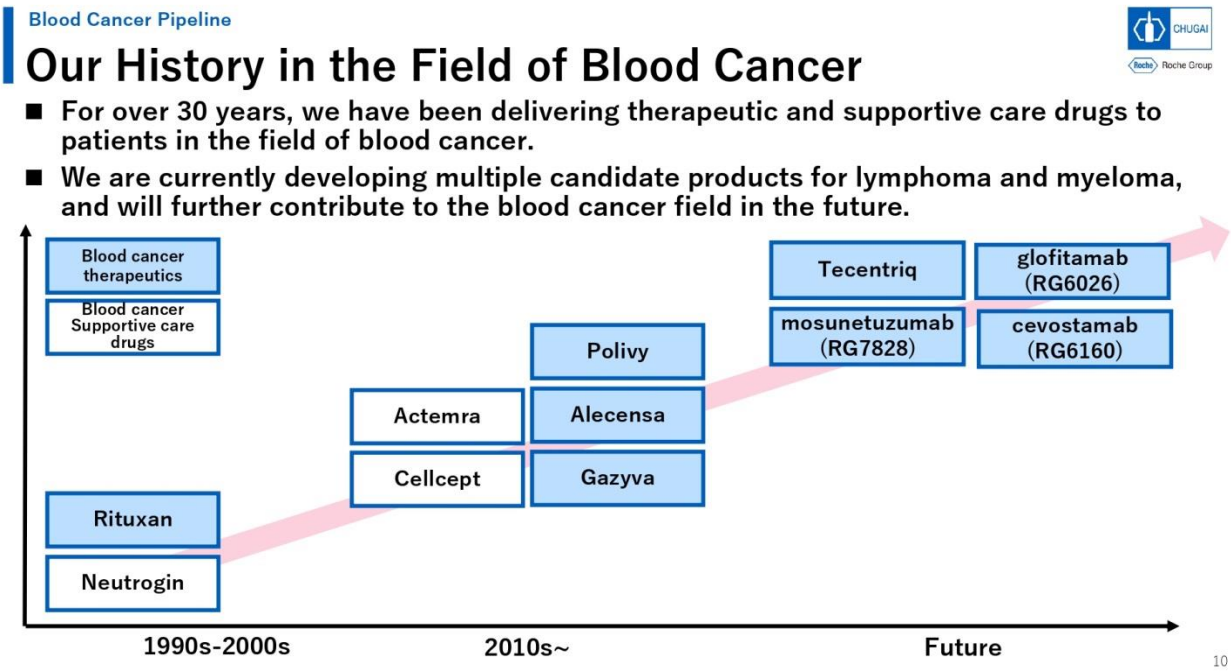
In addition to tri-specific antibodies for strong induction of T cells and immunity, switch antibodies that are effective only in tumors and middle molecules that target tough intracellular targets, we are also developing further technologies.

F. Hoffmann-La Roche Ltd., our strategic partner, has also positioned the oncology area as a therapeutic area of focus and continues to challenge new modalities such as bispecific antibodies, CAR-T, and cancer immunotherapy vaccines.

Going forward, CHUGAI will continue to work with Roche to maximize value on a global basis, while also pursuing development tailored to local needs in Japan, Asia, and globally, as well as development that leverages the Roche Group's portfolio.

As you can see on the slide, our portfolio in the oncology area, which is currently responsible for our future growth, is very well developed in both research and early/late-stage development. The late-stage development we are introducing today includes a great variety of projects with nine items and 23 indications. CHUGAI will continue to do its utmost to develop and deliver many innovative new drugs to patients.

That concludes my explanation.



Hashizume: My name is Hashizume, and I am Franchise Lead for Hematological Malignancies. I would like to talk about our portfolio in the field of blood cancer and give an overview of three of our antibodies.

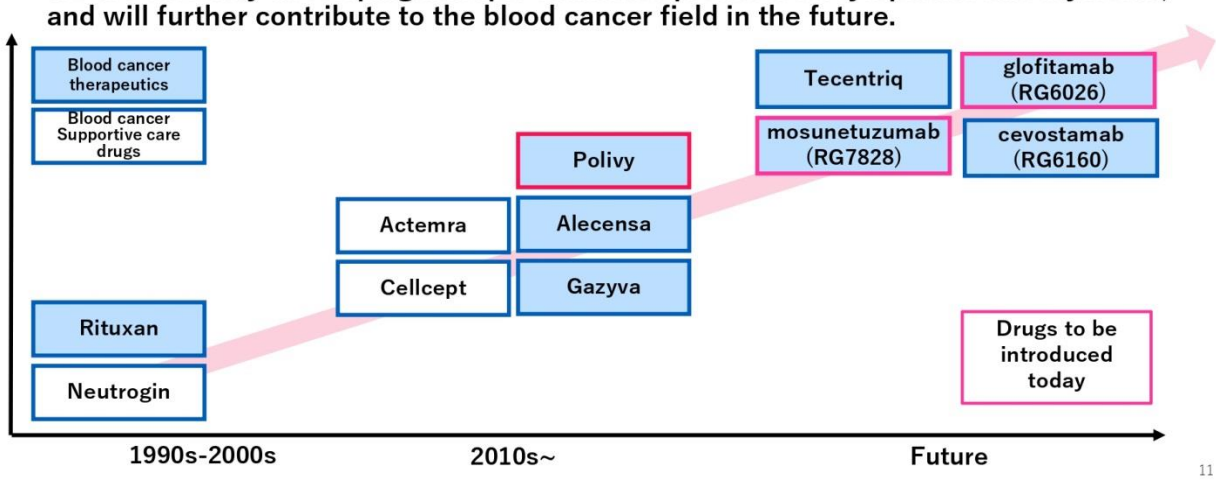
The history of our company and the field of blood cancer spans more than 30 years. In the early 1990s, hematopoietic stem cell transplantation was developed as a supportive therapy for blood cancer treatment, and Neutrogin, a G-CSF preparation, was launched for neutropenia associated with cancer chemotherapy. Starting with this, we have delivered supportive care drugs such as Actemra and Cellcept to patients with hematologic cancers, along with anti-CD20 antibodies, Rituxan, and Gazyva, which are the base drugs for B-cell tumor treatment.

In March of this year, we filed an application for approval of mosunetuzumab for the treatment of relapsed or refractory follicular lymphoma. In October of this year, we also filed an application for approval of Tecentriq for relapsed or refractory NK/T-cell lymphoma nasal type. In addition, the Company has several late-stage development products, including glofitamab, which is being developed for B-cell lymphoma, and cevostamab, which is being developed for multiple myeloma. We hope to continue to bring new treatments to patients with blood cancers.

Blood Cancer Pipeline

Our History in the Field of Blood Cancer

- For over 30 years, we have been delivering therapeutic and supportive care drugs to patients in the field of blood cancer.
- We are currently developing multiple candidate products for lymphoma and myeloma, and will further contribute to the blood cancer field in the future.



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Today, I would like to introduce Polivy, mosunetuzumab, and glofitamab, which are expected to be novel therapeutic agents for B-cell lymphoma.

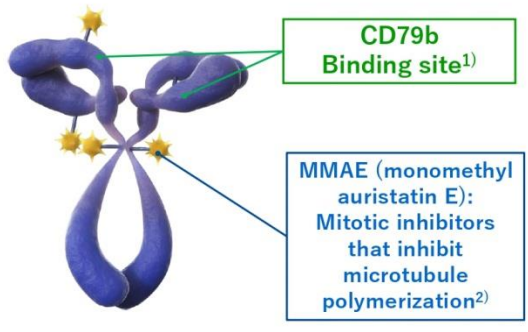
Blood Cancer Pipeline

The Overview of Polivy

- Polivy is an antibody-drug conjugate (ADC) targeting CD79b expressed on B cells
- Launched in May 2021 for relapsed or refractory diffuse large B-cell lymphoma, followed by additional indication in August 2022 for untreated diffuse large B-cell lymphoma

Brand name	Polivy® for Intravenous Infusion 30 mg Polivy® for Intravenous Infusion 140 mg
Generic name	Polatuzumab vedotin (genetical recombination)
Launch	Initial: May 19, 2021 Additional indication: August 24, 2022
Indications	Diffuse large B-cell lymphoma

Structure of Polivy (image)



1) Polson AG, et al. Expert Opin Investig Drugs. 2011; 20(1): 75-85. (authors include Genentech employees), 2) Doronina SO, et al. Nat Biotechnol. 2003; 21(7): 778-784. (authors include Genentech employees)
ADC: anti-drug conjugate

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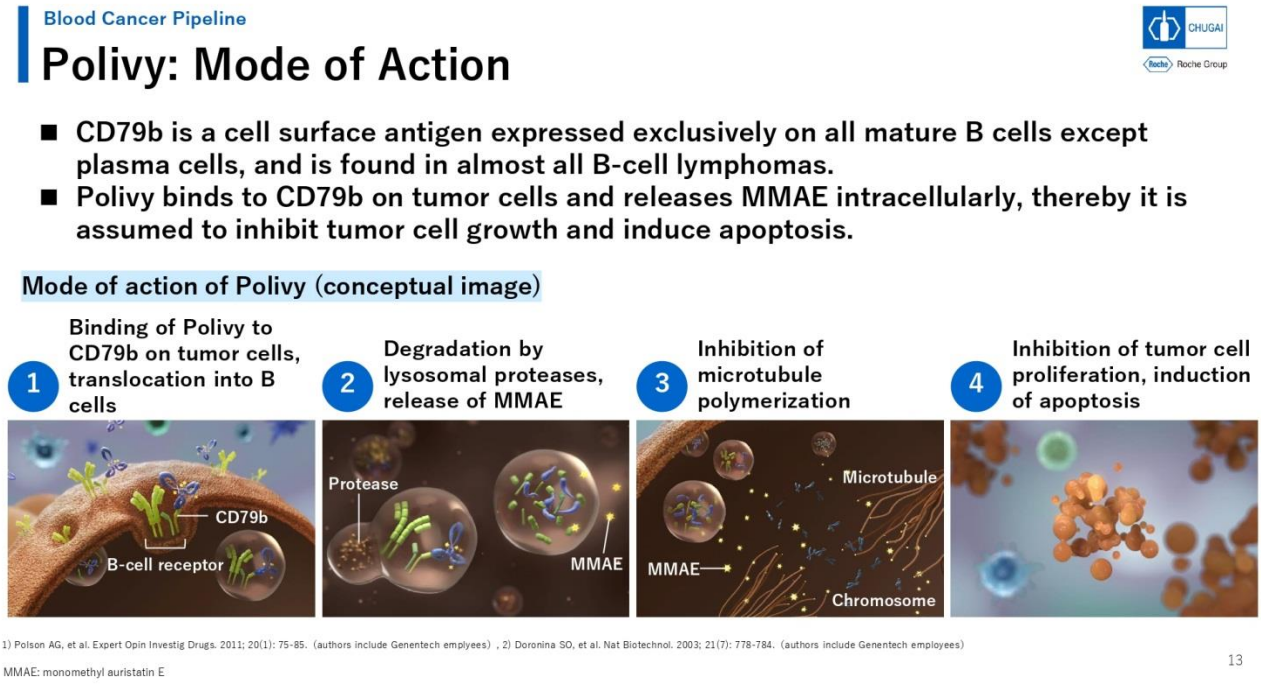
First, let me explain about Polivy.

Polivy is an antibody-drug conjugate, ADC, in which a mitogenic inhibitor, monomethyl auristatin E, is bound to an antibody that targets the CD79b molecule widely expressed on the surface of B cells.

It was first launched in 2021 for first-line treatment of patients with relapsed or refractory diffuse large B-cell lymphoma. Subsequently, an additional indication was added in 2022 for the first-line treatment of patients with untreated, first-line diffuse large B-cell lymphoma. It is now used as a treatment for diffuse large B-cell lymphoma regardless of line.



This slide explains the detailed mode of action of Polivy.

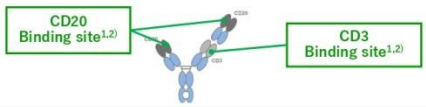
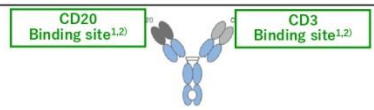
CD79b, the antigen recognized by Polivy, is expressed exclusively on all mature B cells except plasma cells and is considered highly B cell selective.

Since CD79b is expressed in almost all B-cell lymphomas, treatment can be initiated without the need for pre-treatment testing to confirm its expression. Polivy binds to CD79b on B cells and migrates intracellularly, releasing monomethyl auristatin E when the linker is cleaved by intracellular proteases. It is believed that monomethyl auristatin E inhibits the polymerization of microtubules, an important step in cell division, resulting in the inhibition of tumor cell growth and induction of apoptosis.

Blood Cancer Pipeline

Overview of T-Cell Engaging Bispecific Antibody in Development

- **Glofitamab and mosunetuzumab are T-cell engaging bispecific antibodies targeting CD20/CD3, designed to target CD20 on B cells and CD3 on T cells**
- **Both drugs are being developed in parallel due to their different characteristics, leading to distinct indications under development and formulations in development**

Generic name	glofitamab	mosunetuzumab
Development code	RG6026	RG7828
Indications under development in Japan	• Untreated diffuse large B-cell lymphoma (Polivy + R-CHP combination)	• Relapsed or refractory follicular lymphoma (monotherapy) • Relapsed or refractory follicular lymphoma (combined with lenalidomide) • Untreated follicular lymphoma (combined with lenalidomide) • Relapsed or refractory aggressive non-Hodgkin's lymphoma (combined with Polivy)
Dosage form under development in Japan	• Intravenous injection	• Intravenous injection • Subcutaneous injection
Structure of mosunetuzumab (conceptual image)		

1) Bacac M, et al. Oncoimmunol 2016;5:e1203498 (authors include Roche employees), 2) Bacac M, et al. Clin Cancer Res 2018;24:4785–97 (authors include Roche employees), 3) Ferl GZ, et al. Clin Transl Sci 2018;11:296–304 (authors include Genentech employees), 4) Sun LL, et al. Sci Transl Med 2015;7:287ra70 (authors include Genentech employees), *Marketing authorization application submitted in Japan in March 2024, R-CHP: rituximab, cyclophosphamide, doxorubicin, prednisone

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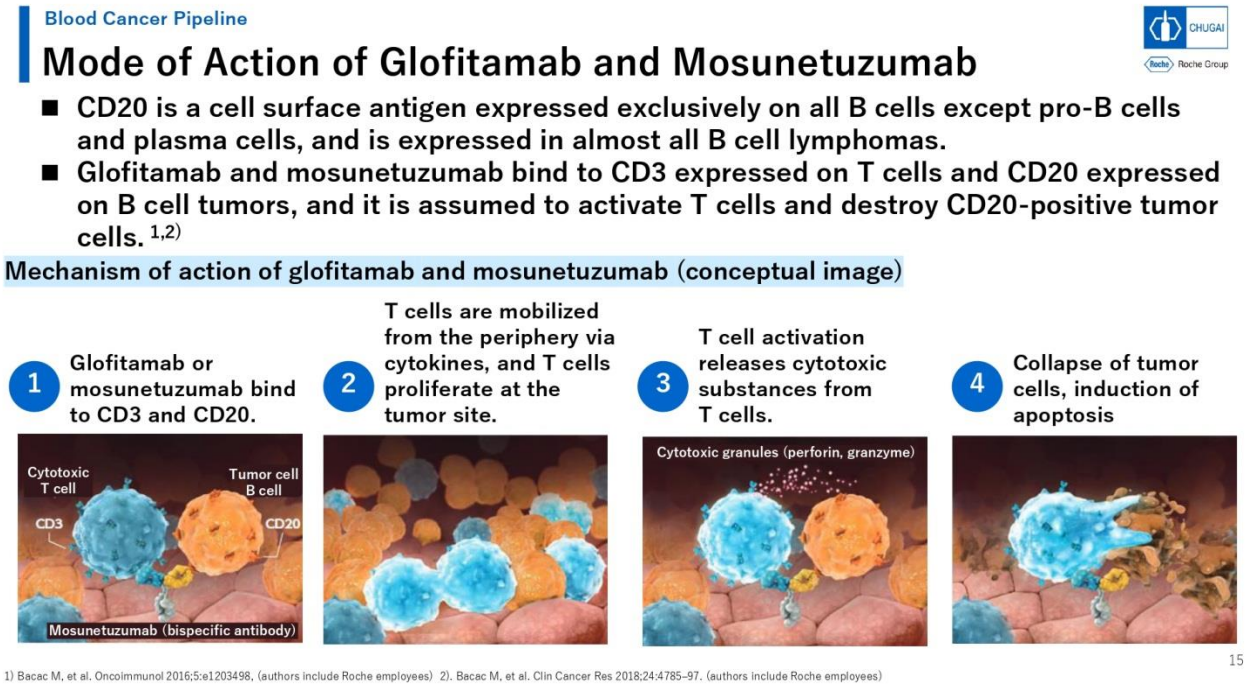
Next, I would like to explain about 2 T-cell-engaging bispecific antibodies that we are developing for B-cell lymphoma.

Both glofitamab and mosunetuzumab are T-cell-engaging bispecific antibodies targeting CD20/CD3, designed to target CD20 on B cells and CD3 on T cells. Each has different indications for development and different dosage forms under development, along with differences in the structure of the antibodies.

On the left side, we show you about glofitamab. A study of Polivy in combination with rituximab, cyclophosphamide, doxorubicin, prednisolone, and glofitamab for untreated diffuse large B-cell lymphoma is ongoing.

On the other hand, for mosunetuzumab on the right side, in addition to the filed application for mosunetuzumab as a monotherapy for relapsed or refractory follicular lymphoma, we are developing the drug in combination with lenalidomide for relapsed or refractory, and untreated, follicular lymphoma. In addition, development in combination with mosunetuzumab and Polivy for relapsed or refractory aggressive non-Hodgkin's lymphoma is underway.

For glofitamab, we are developing an intravenous formulation, while for mosunetuzumab, we are developing a subcutaneous injection formulation along with the intravenous formulation. Since the characteristics of each drug, the indications for which it is being developed, and the dosage forms under development differ, both drugs are being developed in parallel according to the unmet needs for each indication.



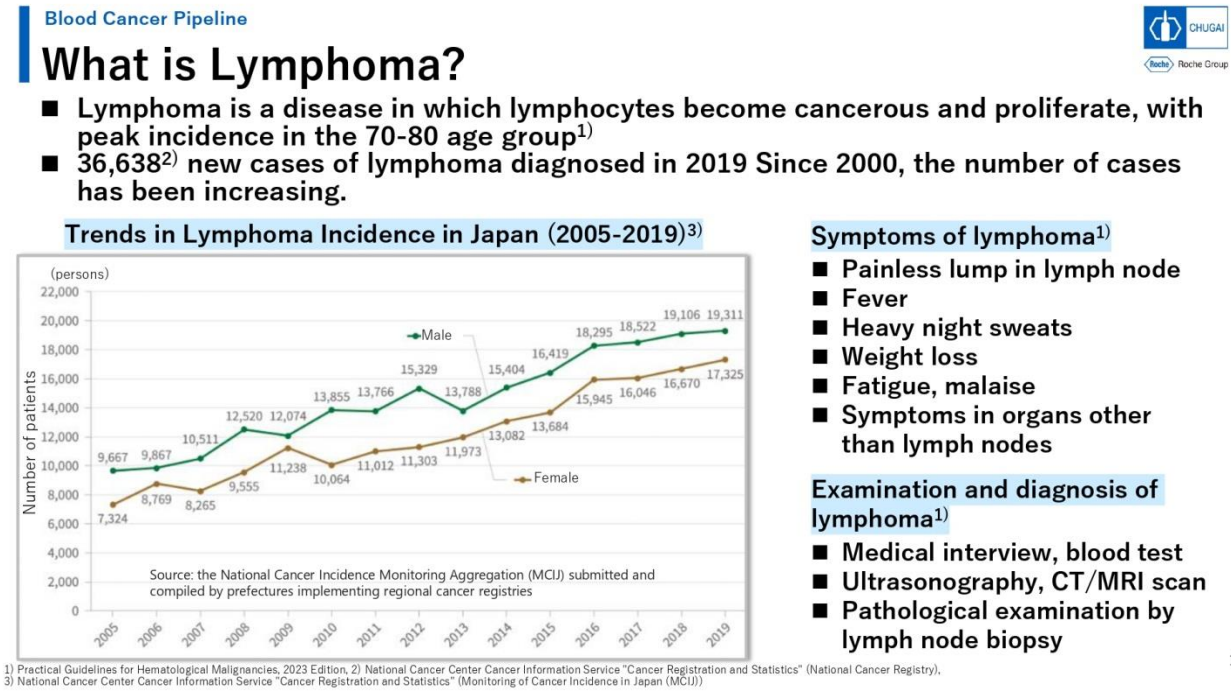
This slide explains the detailed mode of action of glofitamab and mosunetuzumab.

CD20 is a cell surface antigen expressed on all B cells except pro-B cells and plasma cells, and is found in almost all B-cell lymphomas. CD3 is also a cell surface antigen expressed on all T cells.

When glofitamab or mosunetuzumab binds to CD3 on the surface of T cells and CD20 on the surface of B cells, T cells are activated by CD3-mediated T cell signaling. Through cytokine release from T cells, T cells are recruited from the periphery to the tumor site, and further T cell stimulation results in T cell proliferation at the tumor site.

It is believed that T-cell activation induces the release of cytotoxic substances such as perforin and granzyme B from T cells, which in turn induce apoptosis by disintegrating nearby tumor cells.

Thus, Polivy, glofitamab, and mosunetuzumab are antibodies that target antigens specific to B-cell tumors, and each has a unique mode of action.

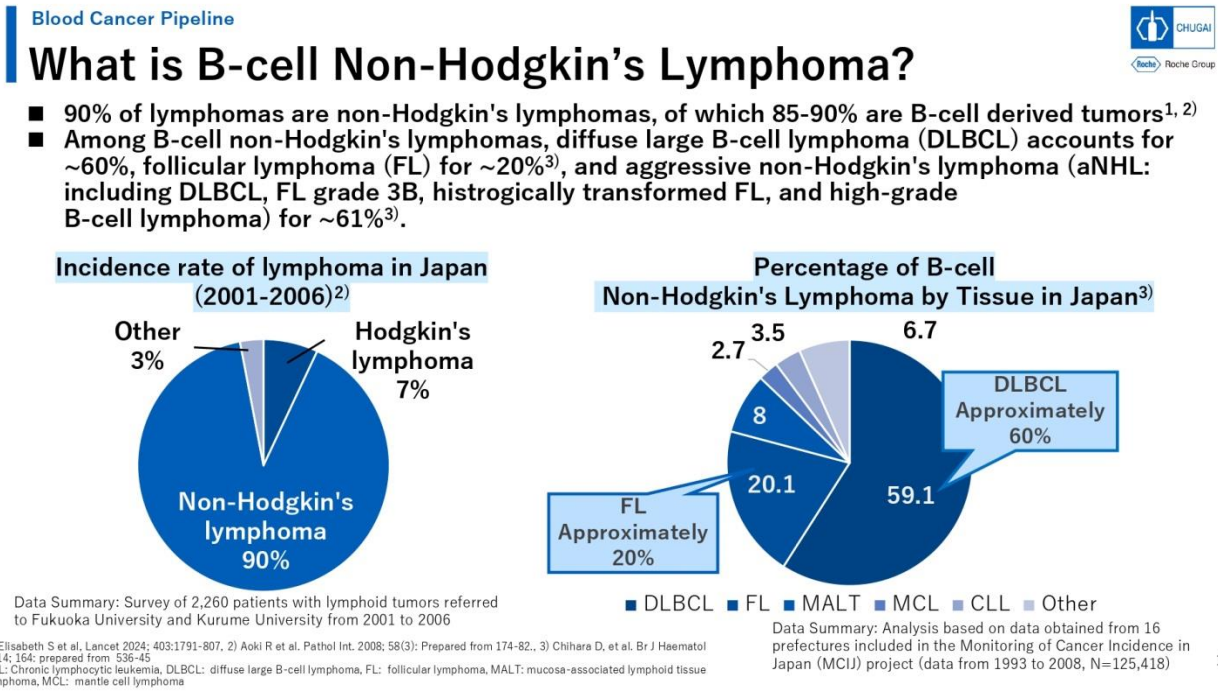


I would now like to explain about B-cell lymphoma, for which we are developing Polivy, glofitamab, and mosunetuzumab.

Lymphoma is a disease in which lymphocytes become cancerous and proliferate, with peak incidence between the ages of 70 and 80. According to a survey by the National Cancer Institute, 36,368 patients were newly diagnosed with lymphoma in 2019. The number of patients is said to have been increasing since 2000.

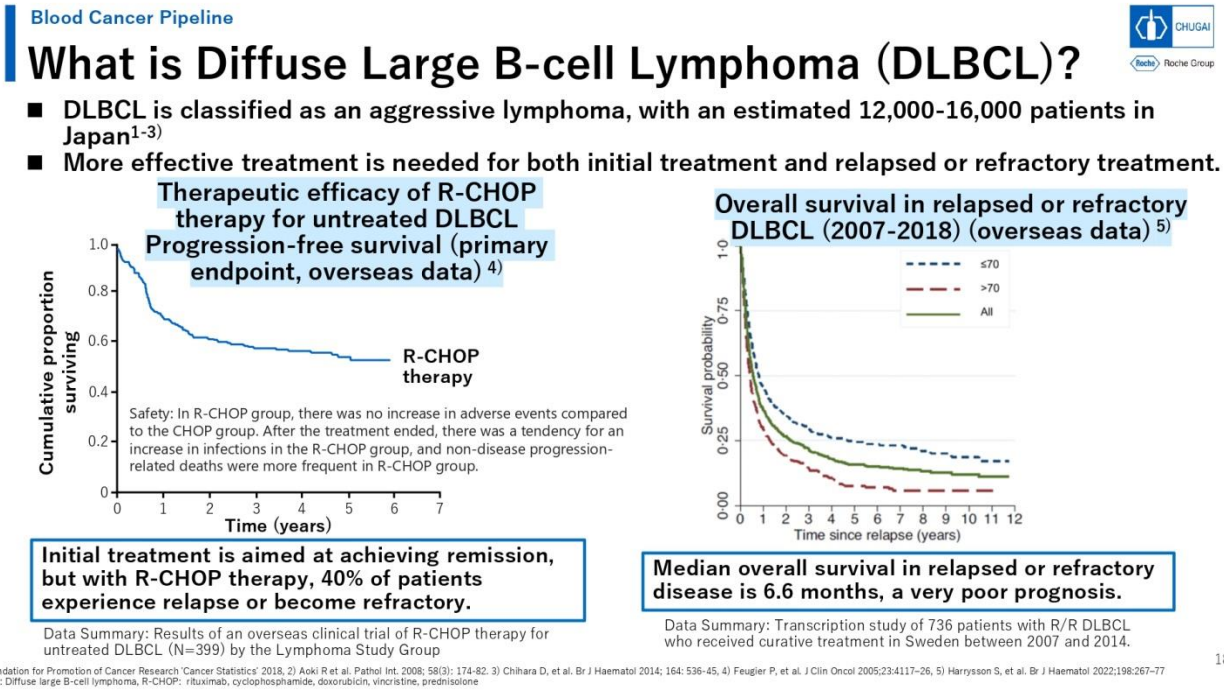
As shown on the right, symptoms of lymphoma include painless lumps in the lymph nodes, sweating, night sweats, and weight loss, which are known as B symptoms. However, since lymphoma is not a single disease, it is the various manifestations of these symptoms that lead to the detection of the disease.

Lymphoma is not a single disease; there are many types and forms, and the course and treatment differ depending on the type of disease. For this reason, imaging studies and pathological examination of lymph node biopsies are also performed to make a diagnosis.



90% of lymphomas are classified as non-Hodgkin's lymphomas, of which 85% to 90% are known to be of B cell origin. In other words, about 80% of lymphomas are B-cell tumors, which affect about 29,000 people per year.

Among B-cell non-Hodgkin's lymphomas, diffuse large B-cell lymphoma, DLBCL, accounts for about 60% of all cases, as shown on the right. Follicular lymphoma, FL, is about 20% of all cases. Among DLBCL and FL, aggressive non-Hodgkin's lymphoma, including fast-progressing FL grade 3B and transformed FL, is known to be 61% of all cases.

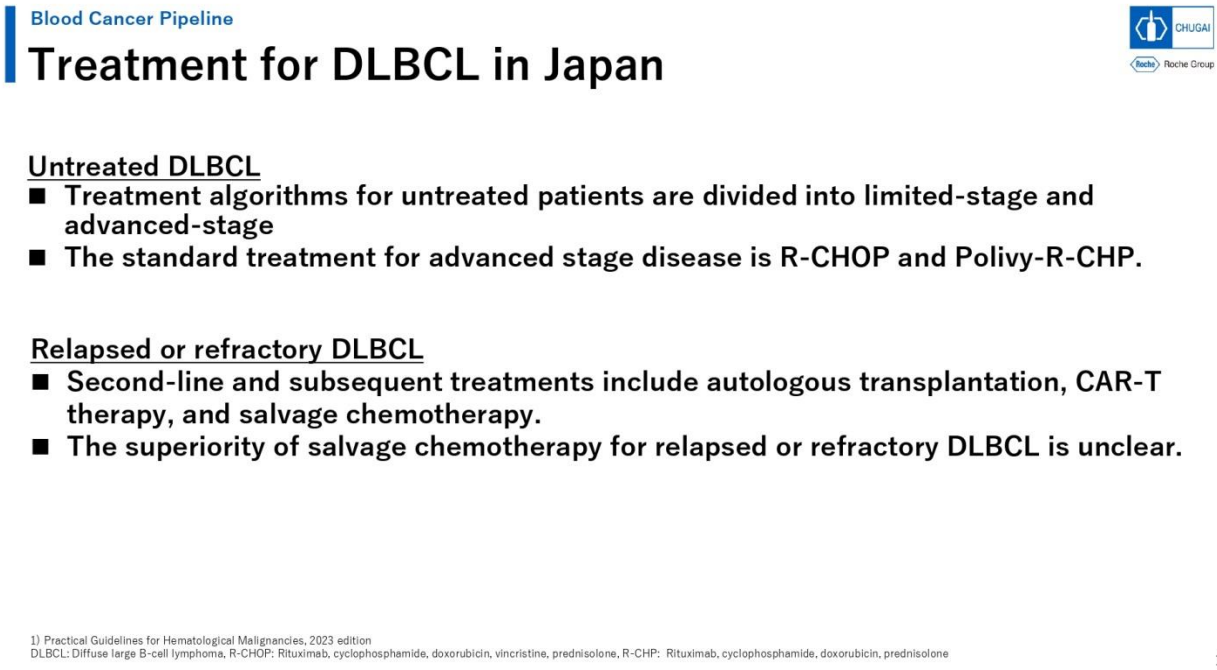


Among B-cell non-Hodgkin's lymphomas, diffuse large B-cell lymphoma, DLBCL, is classified as an aggressive form of lymphoma, with an estimated 12,000 to 16,000 patients.

Initial treatment for untreated DLBCL is aimed at remission. However, even with one of the standard treatments, rituximab, cyclophosphamide, doxorubicin, prednisolone, R-CHOP, 40% of patients experience relapse after the first treatment or become resistant to the first treatment, as shown on the left.

As shown on the right, according to a Swedish study, if the disease relapses after initial treatment or is resistant to initial treatment, the overall survival time is 6.6 months, which is an extremely poor prognosis.

Therefore, there is a need for first-line therapy that allows more patients to achieve remission than standard therapy, and for new treatment after the second line that can be expected to have a longer progression-free survival period even when patients experience relapse or become refractory to first-line therapy.

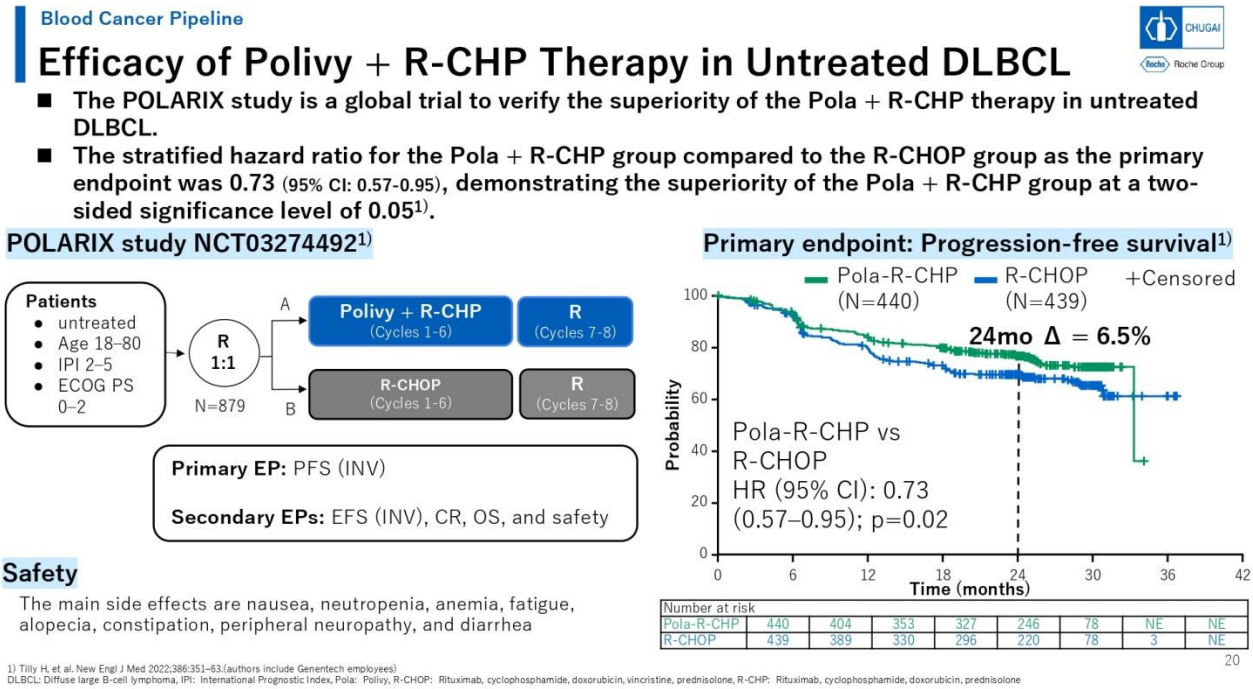


Here, I would like to introduce the treatment of DLBCL as described in the current guidelines in Japan.

Depending on the tests performed at the time of diagnosis of untreated DLBCL, this can be classified into two treatment categories: lymphoma in a limited stage, in which there is one or contiguous sites of lymph node involvement, and advanced stage, in which there are involvement of multiple lymph node sites.

R-CHOP and Polivy-R-CHP therapies are listed in parallel as standard therapies for advanced stages. On the other hand, for relapsed or refractory DLBCL, autologous transplantation, salvage chemotherapy combining Rituxan and chemotherapy, and CAR-T therapy are described.

Salvage chemotherapy is a combination of chemotherapy, and although there are multiple regimens available, there is no data verifying their superiority, and the guidelines state that superiority is not clear. In addition, CAR-T therapy is available at only about 60 facilities nationwide, or slightly more than 10% of hospitals treating hematologic cancers, and is known to have limitations in terms of access to medical care.



Here I would like to introduce the POLARIX study. The POLARIX study was the basis for the listing of Polivy-R-CHP as the standard therapy for untreated DLBCL in the Japanese guidelines.

The POLARIX study is a global study testing the superiority of Pola + R-CHP therapy over R-CHOP therapy in untreated DLBCL. Japan also participated in this study, and 85 patients from Japan entered the study.

The median observation period was 28.2 months, and the stratified hazard value for the Polivy-R-CHP group versus R-CHOP therapy, the primary endpoint at this point, was 0.73, validating the superiority of the Polivy-R-CHP group.

The percentage of patients with progression-free survival at two years was 70.2% in the R-CHOP group and 76.7% in the Polivy-R-CHP group, 6.5% more in the Polivy-R-CHP group. Regarding safety, side effects of Polivy-R-CHP included nausea and neutropenia.

Blood Cancer Pipeline

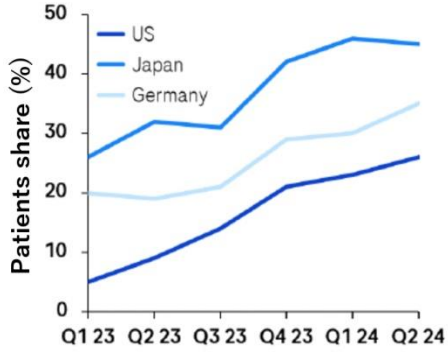
Penetration of Polivy + R-CHP Therapy in Untreated DLBCL

- Polivy + R-CHP therapy is one of the standard therapies in Japanese guidelines for untreated DLBCL* and is gaining popularity.

Positioning of Polivy + R-CHP therapy in untreated DLBCL

- Expanded domestic indications in August 2022
- Delivered to more than 33,000 untreated DLBCL patients worldwide
- The patient share of untreated DLBCL in major countries including Japan is increasing. Especially in Japan, just over 45%.
- Five-year follow-up data from the POLARIX study presented at ASH24

Patient share in 1L DLBCL and IPI 0-5[1)]



1) Roche Pharma Day 2024
DLBCL: Diffuse large B-cell lymphoma, IPI: International Prognostic Index, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, R-CHP: Rituximab, cyclophosphamide, doxorubicin, prednisolone
* Advanced stage, aged 18 to over 80, with an IPI score of 2 or higher

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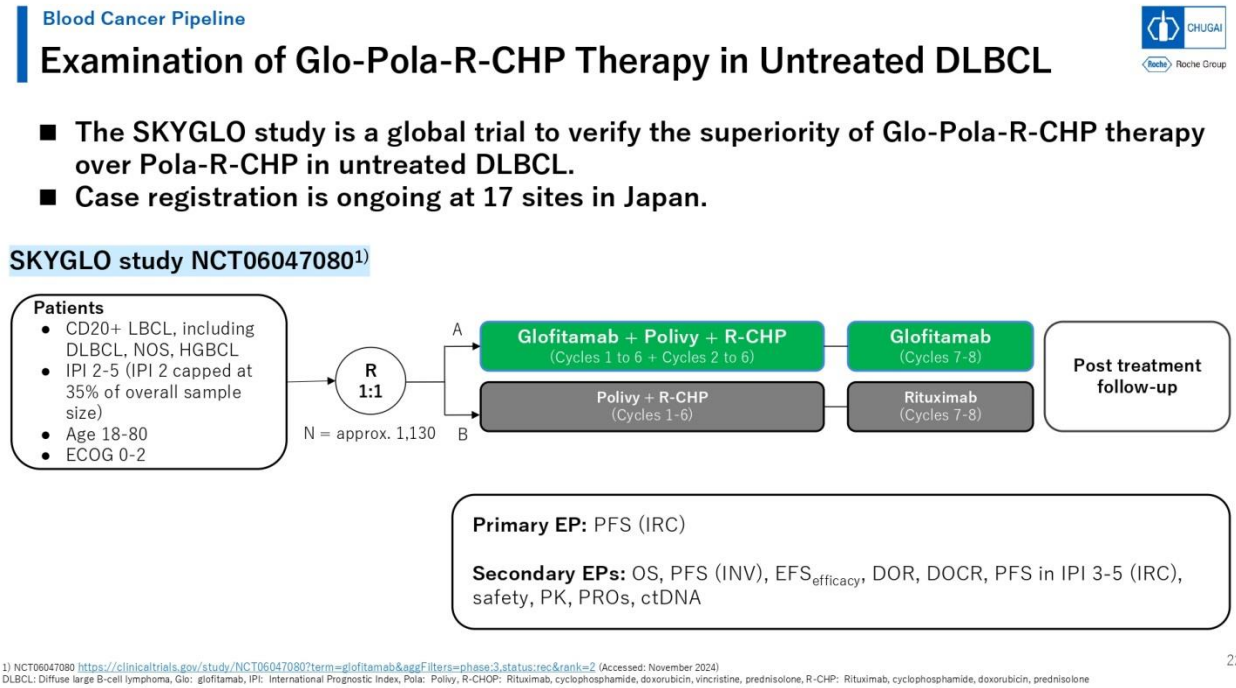
Based on the POLARIX study, the indication of Polivy was expanded in Japan for untreated DLBCL patients in August 2022. Since then, more than 33,000 patients with untreated DLBCL globally have received Polivy.

Penetration of Polivy in major countries, including Japan, has been steady, as shown in the figure on the right. Especially in Japan, as shown here, Polivy has been delivered to more than 45% of DLBCL patients as of the end of H1.

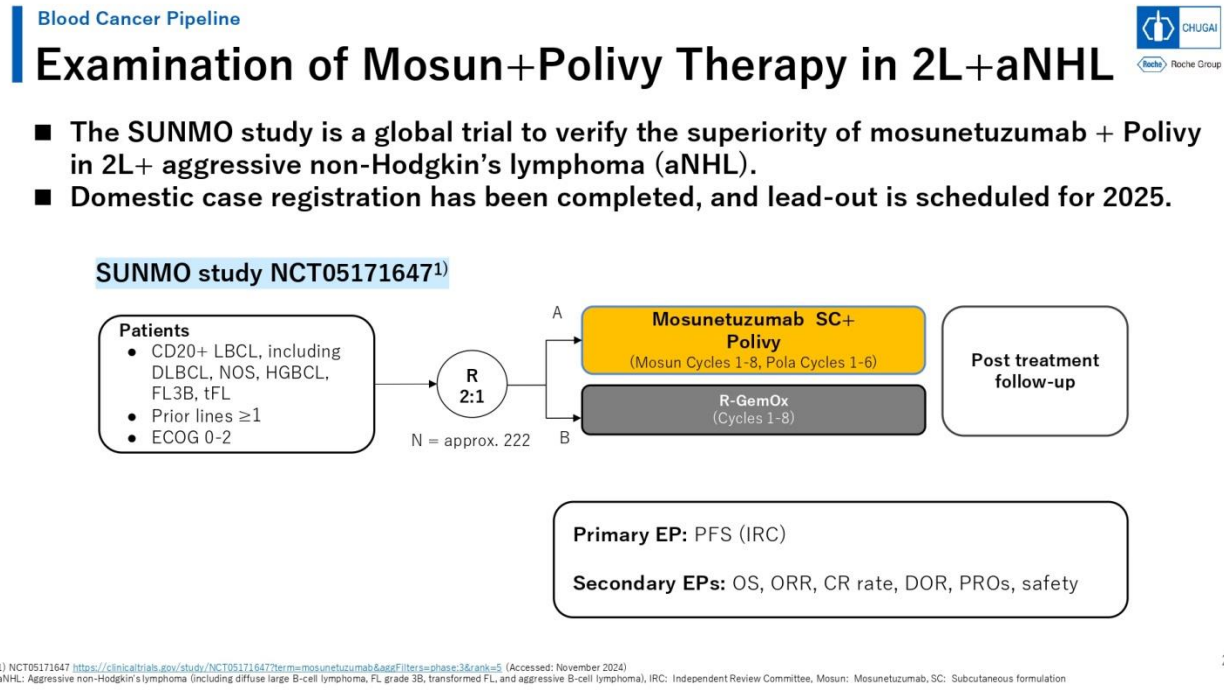
Data from an even longer five-year follow-up than the POLARIX study data presented earlier were presented at the American Society of Hematology meeting this month. As in the primary analysis, Polivy-R-CHP was found to be effective in terms of progression-free survival. In addition, a positive trend in survival has been observed for Polivy-R-CHP.



Polivy-R-CHP is gaining ground as the standard treatment for untreated DLBCL. However, we have a vision to develop more effective therapies and are investigating glofitamab-Polivy-R-CHP, which combines Polivy-R-CHP therapy with glofitamab.

The SKYGLO study shown here is a global trial testing the superiority of glofitamab-Polivy-R-CHP therapy over Polivy-R-CHP therapy in untreated DLBCL. Starting this year, case registration is underway at 17 facilities in Japan.

Even with Polivy-R-CHP therapy, recurrence occurs within two years in less than 25% of patients. In order to further increase the number of patients who can achieve remission, we are conducting the SKYGLO study to verify the efficacy of combination with glofitamab, a T-cell-directed bispecific antibody.



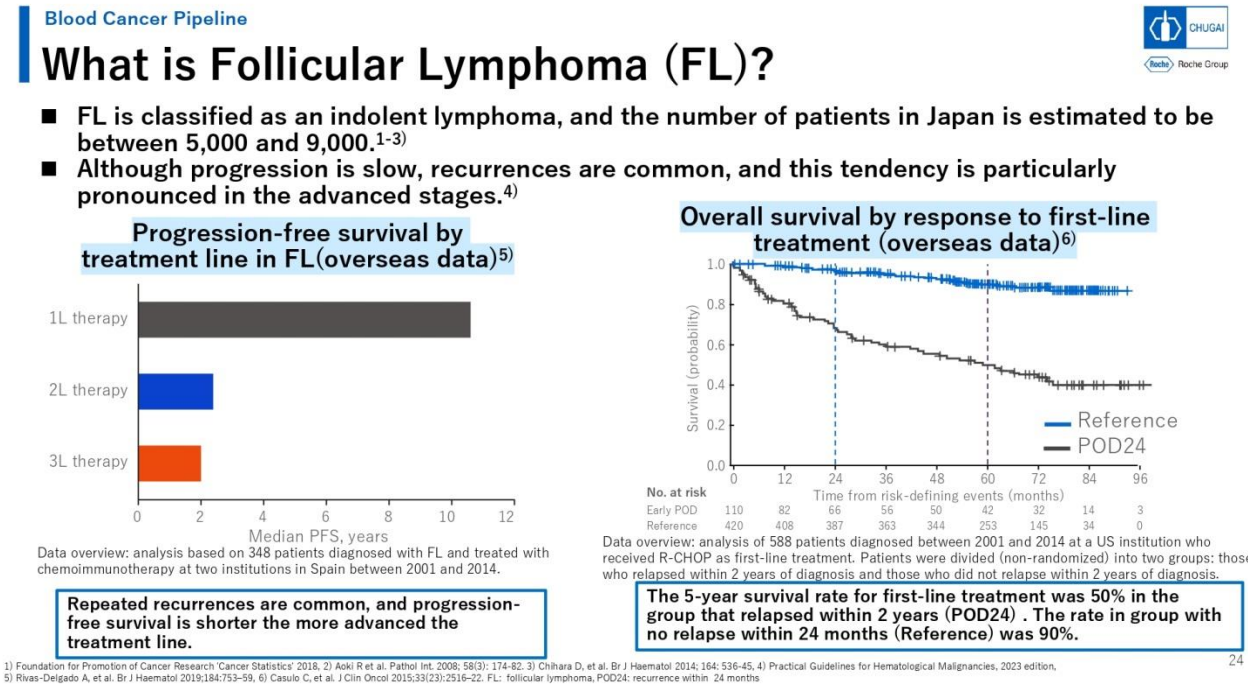
Next, I will discuss the development of novel therapies for aggressive non-Hodgkin's lymphoma in the second line and beyond.

As mentioned earlier in the introduction to disease characteristics and guidelines, relapsed or refractory DLBCL has a very poor prognosis and limited access to effective treatment.

This SUNMO study is a global study to test the superiority of the combination of mosunetuzumab and Polivy over one of the salvage chemotherapy regimens, Rituxan, gemcitabine, and oxaliplatin, in aggressive non-Hodgkin's lymphoma in the second line and beyond. Japan is also participating in this study and has met the required number of patients in Japan, so enrollment is now complete.

The SUNMO study tested the superiority of mosunetuzumab plus Polivy in terms of efficacy, with progression-free survival as the primary endpoint. Regarding safety, this is a new combination therapy of T-cell-engaging bispecific antibodies and ADCs, which causes less nausea and prolonged blood cell loss as has been observed with conventional chemotherapy. In terms of access, this is an off-the-shelf drug that can be removed from the drug shelf and handled immediately and is expected to be used in hospitals nationwide.

We plan to lead out this SUNMO exam next year.

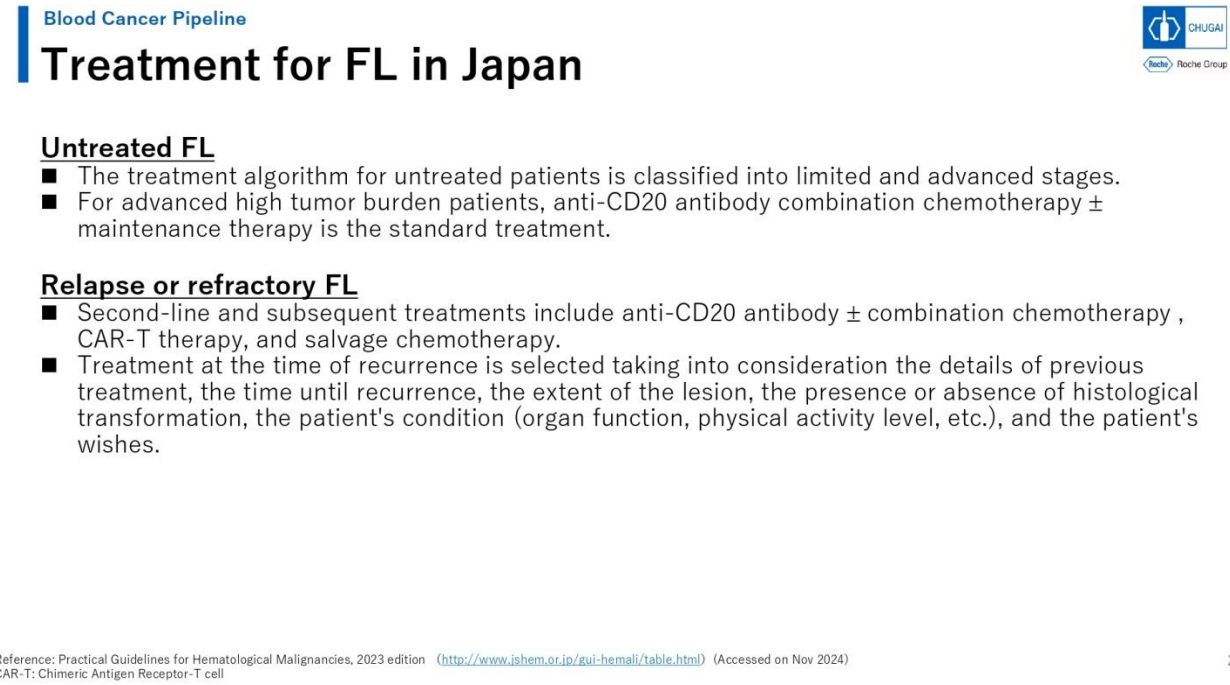


Next, I would like to introduce the pathogenesis of follicular lymphoma and our development pipeline.

Unlike DLBCL, FL is classified as an indolent lymphoma. The number of patients in Japan is estimated to be between 5,000 and 9,000. As the classification of indolent indicates, it is a lymphoma with slow progression. On the other hand, the disease usually recurs rather than remaining in remission, and this tendency is more pronounced in the advanced stages when the disease is spreading to multiple lymph nodes.

As the Spanish data on the left show, progression-free survival is just over 10 years for first-line treatment, whereas it is about two years for second- and third-line treatment, indicating that the prognosis is worsened by recurrence.

Also, as shown on the right, in about 20% of all patients treated the first time, this recurs within 24 months, and the five-year survival rate for the group that relapsed within two years is 50%, shorter than for the group that did not.

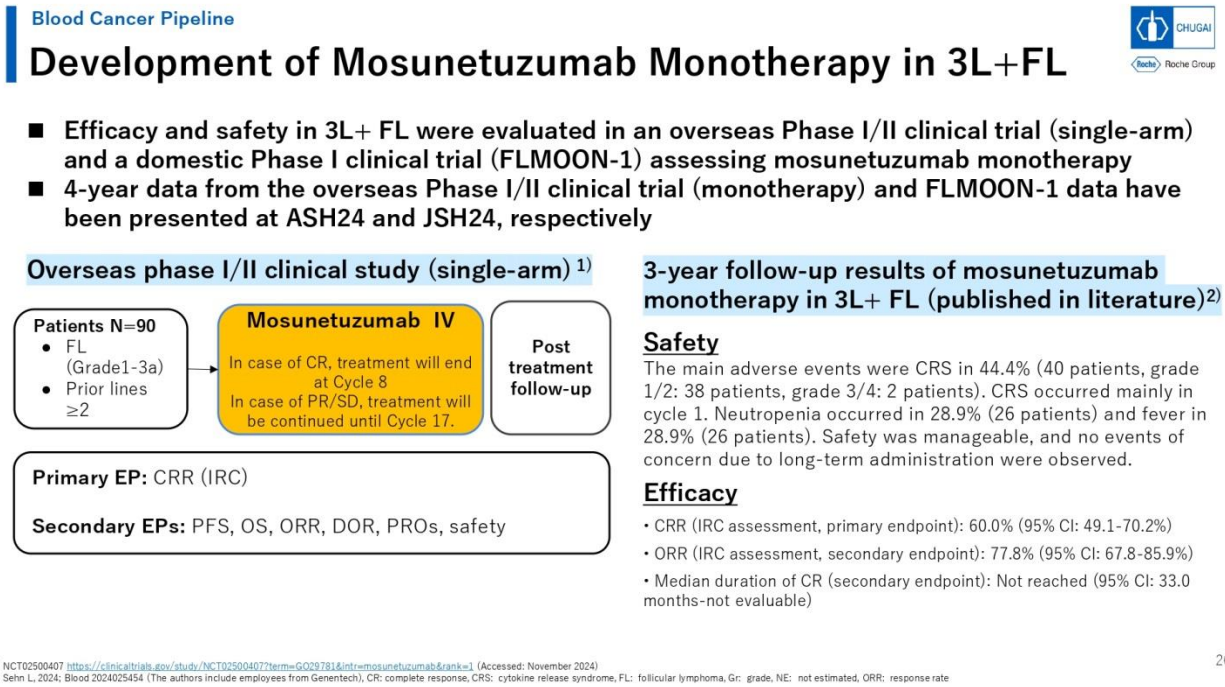


The following are the current guidelines for follicular lymphoma in Japan.

As with DLBCL, the algorithm for treatment of untreated is divided into limited and advanced stages. For patients with advanced disease and high tumor volume, the standard of care is the combination of chemotherapy with the anti-CD20 antibodies Rituxan and Gazyva, as well as maintenance therapy with anti-CD20 antibodies.

On the other hand, for relapsed or refractory FL, there is the option of combining the anti-CD20 antibody Rituxan, Gazyva, and chemotherapy again, CAR-T therapy, or hematopoietic stem cell transplantation. The superiority of the treatment options for relapsed or refractory follicular lymphoma is also not clear. The guidelines state that treatment for follicular lymphoma is selected based on previous treatment, time to relapse, extent of disease, histological transformation, and importantly, the patient's condition, especially organ function and physical activity level, as well as wishes.

Follicular lymphoma is characterized by the fact that many patients develop the disease at an older age, and treatment can take as long as five or 10 years. Therefore, there is a need to develop new drugs that are not only effective but also safe and considerate to the lives of patients and their families.



For FL, we are developing mosunetuzumab. For FL after the third line, we are evaluating mosunetuzumab monotherapy in the overseas PI/II study and in the FLMOON-1 study for PI in Japan.

The dosing period for mosunetuzumab is fixed at eight or 17 cycles, with a complete response requiring eight cycles, or approximately six months. If the patient has a partial response or stable disease at the eight-cycle point, the treatment is completed after 17 cycles or approximately one year.

The results of the overseas test are shown on the right. First, in terms of safety, the main adverse event was cytokine release syndrome, characteristic of CD3 bispecific antibodies, which occurred in 44% of patients, mostly in manageable grades one and two, and more frequently in cycle one.

In terms of efficacy, complete response was 60%, response rate was 78%, and the median duration of complete response was not reached.

The data shown here are follow-up data at three years that have already been published in *Blood*. Even longer four-year follow-up data were presented at the American Society of Hematology meeting this month. At the four-year follow-up, the efficacy of the drug has been sustained even after the completion of administration.

The data from the FLMOON-1 trial in Japan also showed efficacy and safety similar to the overseas data and was published in the *International Journal of Clinical Oncology*, IJCO, this month.

Based on the results of these two studies, we filed an application in March of this year for approval of single-agent mosunetuzumab for the treatment of relapsed or refractory follicular lymphoma.

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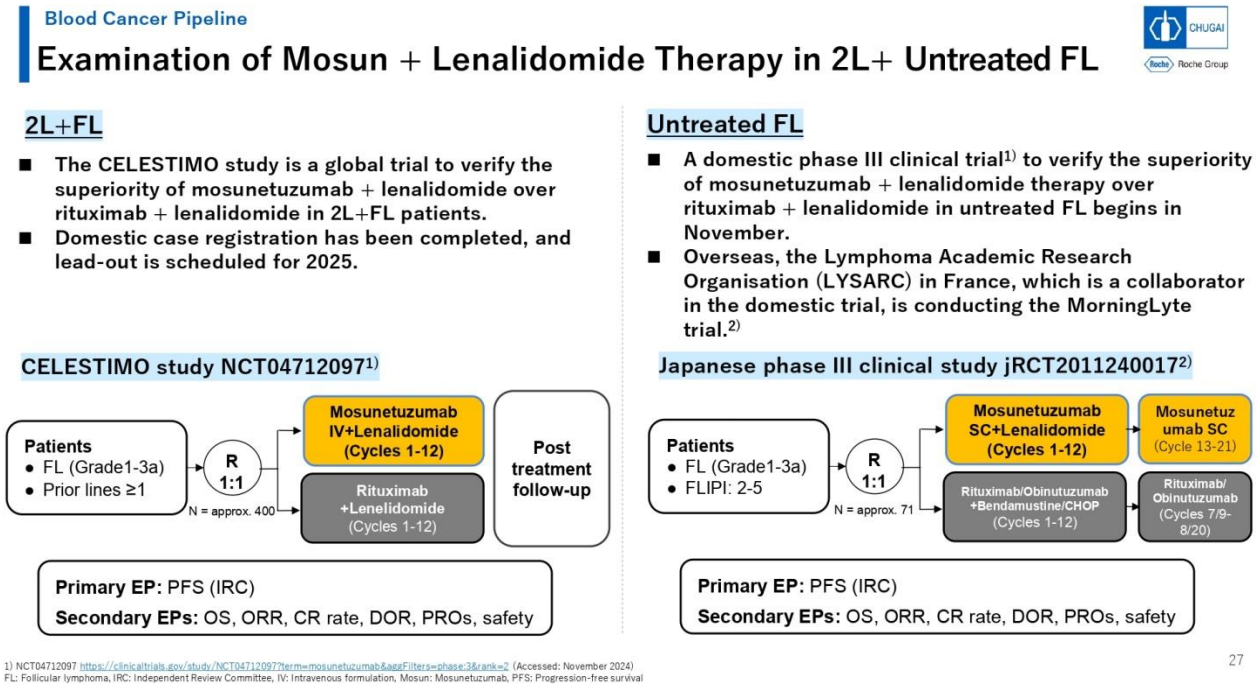


For second-line and untreated follicular lymphoma, the combination of mosunetuzumab and lenalidomide is being investigated and tested, respectively.

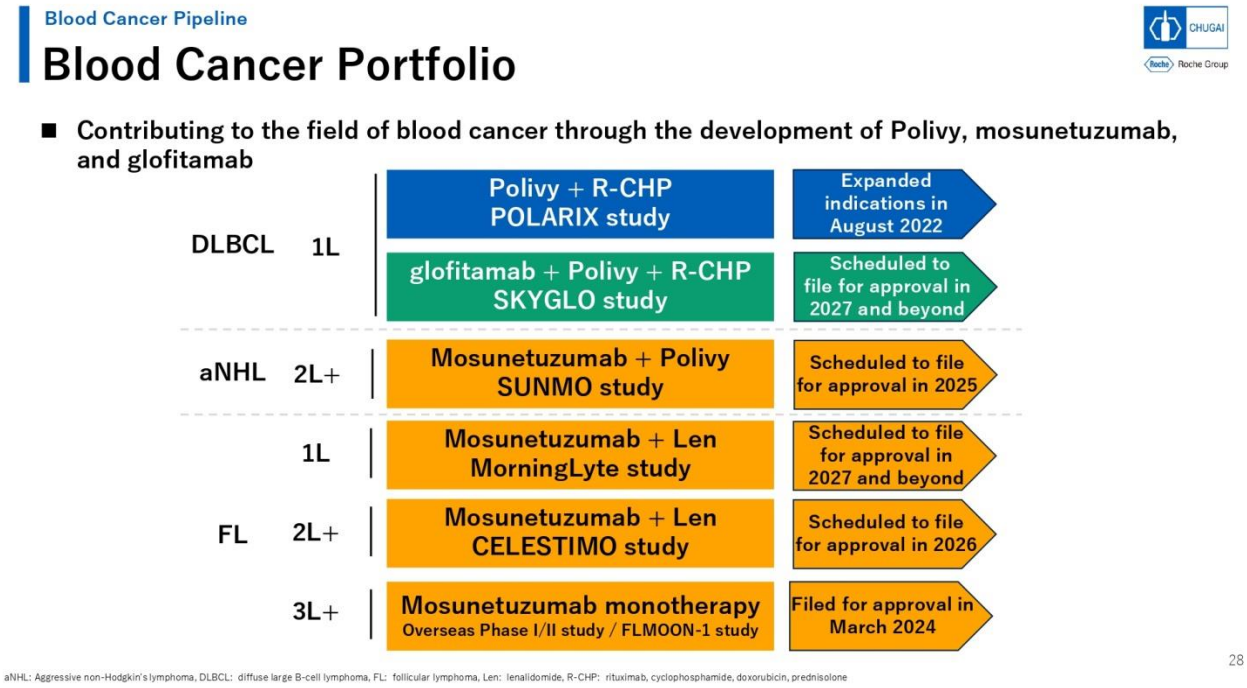
The trial for second-line follicular lymphoma on the left is called the CELESTIMO study. The CELESTIMO study is testing whether the combination of mosunetuzumab and lenalidomide is superior to the combination of Rituxan and lenalidomide, one of the treatment options for second-line FL, in terms of progression-free survival after 12 cycles of treatment.

This CELESTIMO study is a global trial. Domestic case enrollment has already been completed and lead-out is scheduled for next year.

The trial for untreated follicular lymphoma on the right is the MorningLyte trial in Japan. We are testing the superiority of 12 cycles of mosunetuzumab plus lenalidomide plus maintenance therapy over the standard therapy of Rituxan or Gazyva, an anti-CD20 antibody, plus chemotherapy plus maintenance therapy, in terms of progression-free survival.

The domestic case registry started in November and is currently registering cases. Overseas, the French physician group LYSARC, which is collaborating on this study, is conducting the MorningLyte study in Europe using the same protocol.

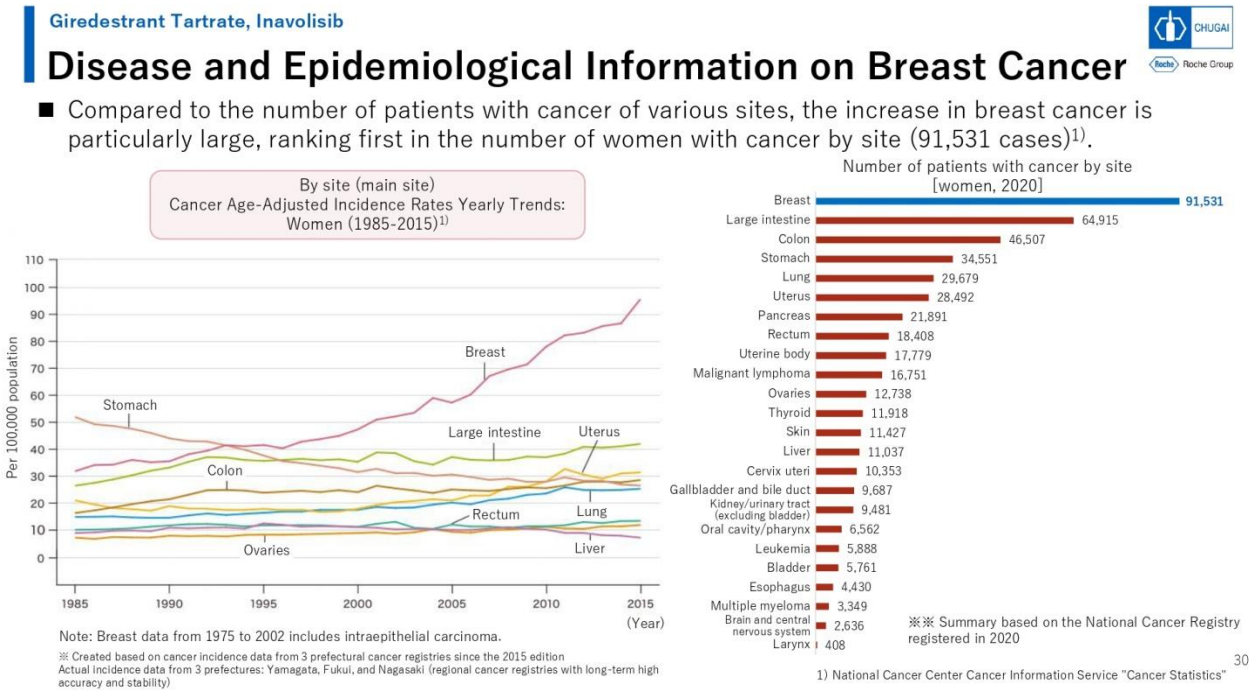
Follicular lymphoma is characterized by older patients and treatment lasts as long as five or 10 years. Through these trials, we hope to develop a treatment with a long progression-free survival period, that is, a treatment that is effective for a long period of time before the next treatment, and a promising treatment with a fixed administration period that reduces the burden of hospital visits, is administered by subcutaneous injection, and requires a short hospital stay.



This slide summarizes the studies I have presented to you today.

In lymphoma, we are conducting studies that will contribute to many of these regulatory filings. Data lead-outs and approval applications are scheduled annually in the future. We will continue to contribute to the field of hematologic oncology with the vision of developing even more effective treatments with Polivy, mosunetuzumab, and glofitamab.

Miyata: Next, Mr. Habara will explain about giredestrant and inavolisib.



Habara: My name is Habara, and I am the product manager for giredestrant and inavolisib. Today, I am primarily introducing our development pipeline of two drugs for hormone receptor-positive breast cancer.

First, I will discuss breast cancer disease and epidemiological information. Compared to the number of patients with various types of cancer, the increase is particularly large in breast cancer. On the left side, we show the change in cancer incidence rates from 1985 to 2015. As you can see, the incidence of breast cancer is outstandingly high.

On the other hand, as shown on the right, breast cancer ranks first in the number of cancer cases by site among women, with more than 91,000 cases. The data in blue on the right is for 2020.

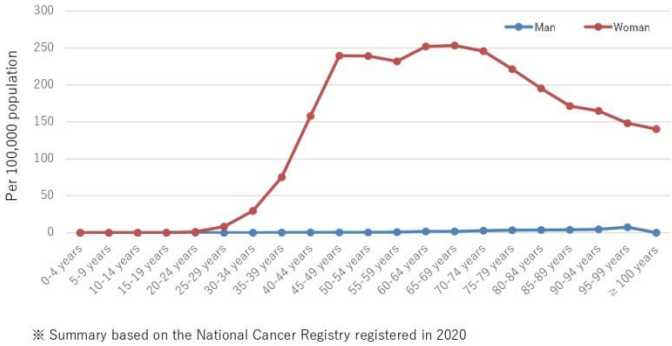
Giredestrant Tartrate, Inavolisib

Disease and Epidemiological Information on Breast Cancer

- Breast cancer occurs frequently in women in their 40s and 50s[1)]
- Breast cancer is the most common cancer among Japanese women, but it ranks fourth in cancer deaths[1)]. Although the number of women who develop breast cancer is high, there are many women who overcome it.

Incidence rate by age group[1)]

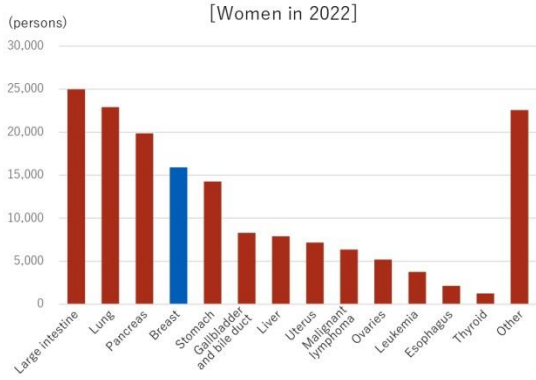
[Breast in 2020]



※ Summary based on the National Cancer Registry registered in 2020

Number of cancer deaths by site[1)]

[Women in 2022]



※※ Tabulated based on Vital Statistics (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare)

1) National Cancer Center Cancer Information Service "Cancer Statistics"

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Please see another slide with epidemiological information. Breast cancer occurs most frequently in women in their 40s and 50s. These are the so-called working-age people, those who are working, and balancing work with childcare and nursing care is very important.

As shown on the right, breast cancer is the most common cancer among Japanese women, while ranking fourth in terms of cancer deaths. Although the number of cases is high, it has been shown that many women have survived breast cancer.

Giredestrant Tartrate, Inavolisib

Main Therapeutic Agents Under the Guidelines for Breast Cancer Treatment

- Breast cancer is classified into four main subtypes, and therapeutic agents are selected for each subtype.

	Hormone receptor (HR) positive	Hormone receptor (HR) negative
HER2 positive	**HR positive/HER2 positive** • Subtype ratio[1)]: 7.3% • Main therapeutic agents[2)]: Hormone therapy drugs + anti-HER2 drugs + chemotherapy	**HR negative/HER2 positive** • 8.2% • Anti-HER2 + Chemotherapy
HER2 negative	**HR positive/HER2 negative** • 69% • Hormonal therapy (+ chemotherapy ± molecular targeted drugs)	**Triple-negative** • 15.5% • Chemotherapy ± immune checkpoint inhibitor

1) Iwase H, et al. Breast Cancer 2010; 17: 118-124.
2) Partially modified from "Cancer Treatment Resident Manual 6th Edition," edited by Internal Medicine Residents of the National Cancer Center, Igaku-Shoin, 2013
3) Cancer Information Service Breast Cancer Treatment 4. Drug Therapy

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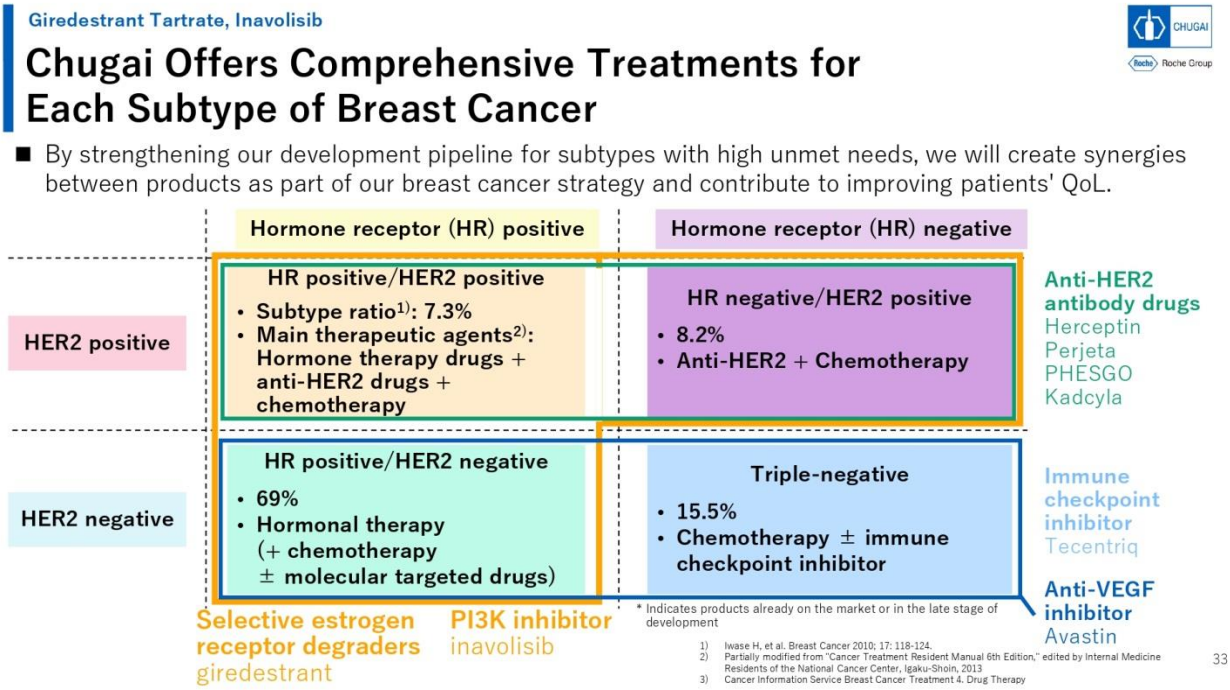
This slide shows the main therapeutic agents in the breast cancer treatment guidelines.

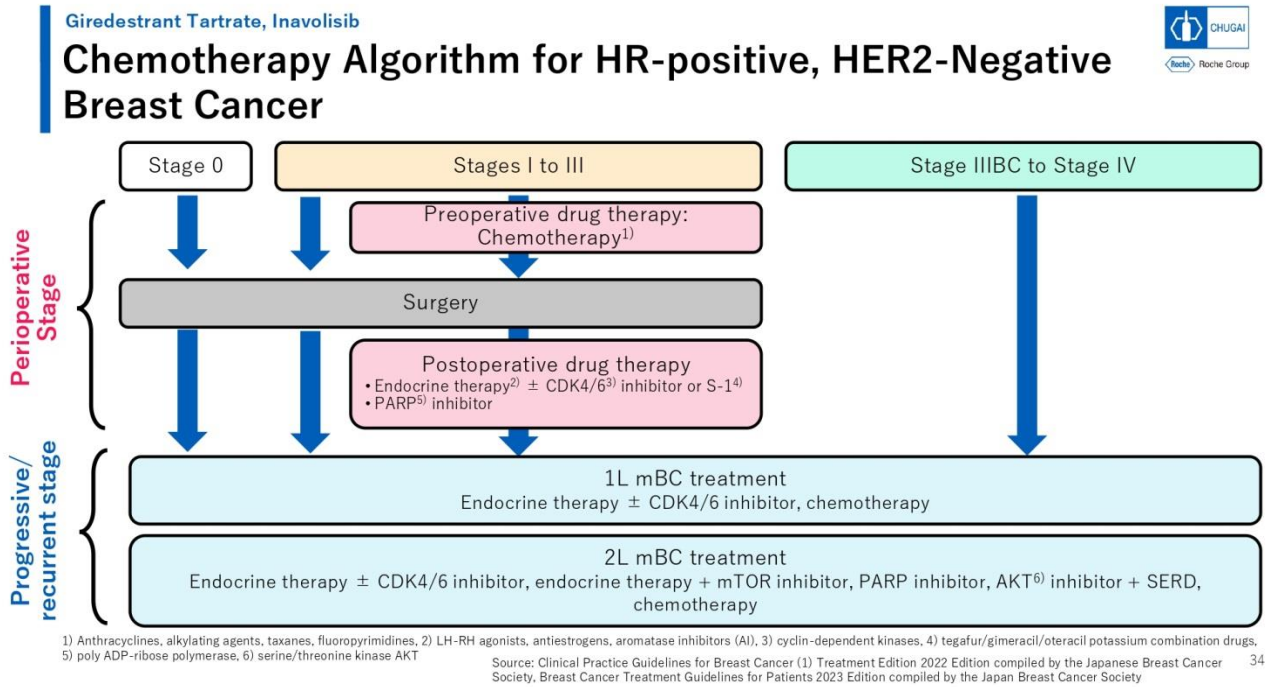
Breast cancer is generally divided into four main subtypes. The four axes include the horizontal axis for hormone receptor-positive or negative and the vertical axis for HER2 positive or negative.

Percentages are listed for each subtype. Hormone receptor-positive, when combined with HER2 positive and negative, exceeds 70%. It can be seen that among breast cancers, hormone-positive patients are very common.



CHUGAI will continue to provide comprehensive therapeutic agents for each subtype. The anti-HER2 drugs offered in the area circled in green are Herceptin, Perjeta, Kadcyla, and Phesgo. Below that, primarily for triple-negative breast cancer, we offer Tecentriq and the anti-VEGF inhibitor Avastin.

The two drugs I am introducing here are giredestrant, a selective estrogen receptor degrader, and inavolisib, a PI3K inhibitor, both shown in orange.



You will see the current drug treatment algorithm for hormone receptor-positive, HER2-negative breast cancer. Surgery is possible in stages one through three, and this treatment is administered either preoperatively or postoperatively.

On the right side, in the case of advanced disease, perioperative drug therapy will be omitted and the patient will proceed to first-line metastatic and advanced recurrence therapy in the progressive/recurrent stage.

First, in the perioperative period, chemotherapy is now mainly used in the preoperative period, as indicated by the pink color. In so-called endocrine therapy after surgery, hormones are administered long-term, from 5 to 10 years, depending on what is used.

In the blue progressive/recurrent stage, first-line endocrine therapy in combination with a CDK4/6 inhibitor is used as one of the standard treatments, and chemotherapy is the other.

In the second line and beyond, the development of molecular-targeted drugs has advanced greatly in recent years. In addition to the endocrine therapy plus/minus CDK4/6 inhibitors and chemotherapy I just mentioned, there are more options for mTOR inhibitors, PARP inhibitors, and AKT inhibitors.

Giredestrant Tartrate, Inavolisib

Overview of Pharmacotherapy Approaches for HR-Positive Breast Cancer

- Giredestrant is a selective estrogen receptor degrader (SERD), and inavolisib is a PI3K inhibitor under development.

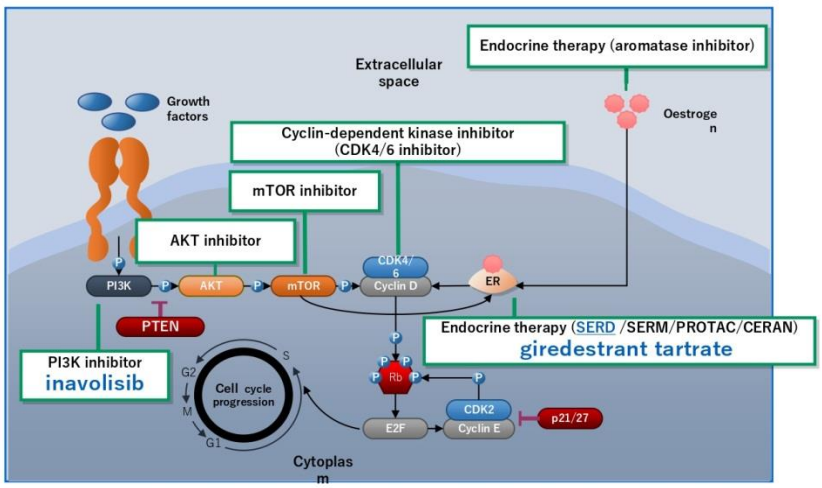


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Figure taken from reference: Brufsky AM & Dickler MN. Oncologist 2018; 23:528 – 539.

This is an overview of approaches to pharmacotherapy of HR-positive breast cancer. A three-way approach is now known.

See left side. We refer to PI3K, AKT, and mTOR as PAM pathways. The PI3K inhibitor inavolisib, which captures the top level of signaling action, is the first drug we will discuss today.

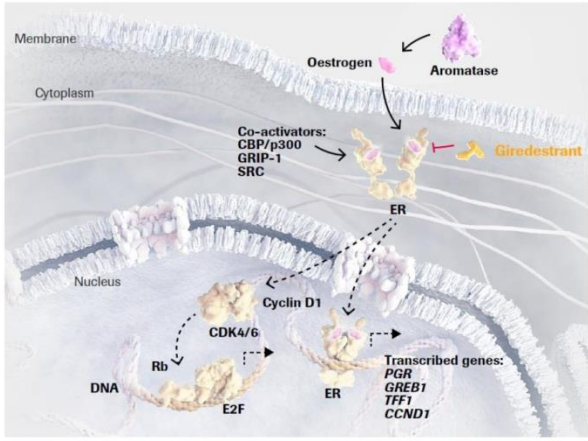
On the other hand, endocrine therapy on the right side, the so-called hormonal agents, started with aromatase inhibitors and has been developed, including SERDs, SERMs, and several other agents that act directly on the estrogen receptor. I will today introduce this giredestrant.

Furthermore, in the middle, we have a cyclin-dependent kinase inhibitor, CDK4/6 inhibitor, which I described earlier as one of the first-line standard treatments.

Giredestrant Tartrate

Giredestrant (SERD)'s Mechanism of Action

- Giredestrant is a selective estrogen receptor degrader (SERD)
- It binds to estrogen receptors (ER) on the surface of breast cancer cells and inhibits the binding of estrogen. It also promotes the breakdown of estrogen receptors and reduces the number of estrogen receptors in cells[1]. These mechanisms of action are thought to suppress cancer growth.



conceptual illustration

1) Metcalfe C. Presented at: Virtual Annual Meeting II of AACR. June 2020.

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First, let me introduce giredestrant.

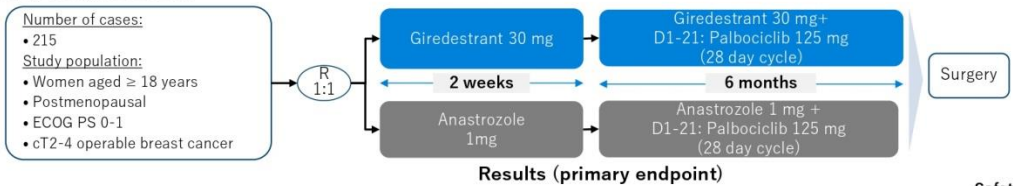
This figure illustrates the mode of action. This is a selective estrogen receptor degrader, commonly referred to as a SERD. It binds to estrogen receptors on the cell surface of breast cancer cells and inhibits estrogen binding. In addition, it promotes the breakdown of estrogen receptors and decreases intracellular estrogen receptors. Through these mechanisms of action, the drug is believed to inhibit cancer growth.

Giredestrant Tartrate

CoopERA Study (Overseas Phase II Clinical Study)

- **Giredestrant showed a significantly greater relative geometric mean decrease in Ki67 from baseline to week 2 compared to anastrozole.**

Study design overview



Primary endpoint

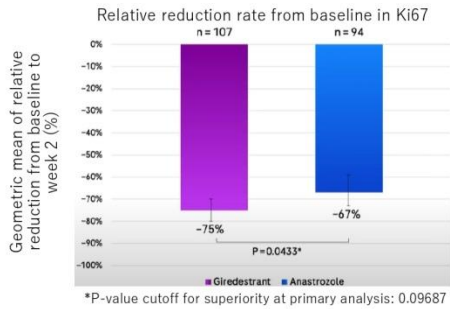
- Ki-67 reduction rate at 2 weeks
- Evaluation by a central laboratory using validated Ki-67 clinical trial assays

Secondary endpoints

- Ki-67 CCCA at 2 weeks and EOT, ORR at EOT, safety, PK and PRO
- RNAseq ER pathway activity and changes in ER and PR IHC H scores

Ki67: A nuclear protein present in proliferating cancer cells that is an indicator of the degree of cell proliferation, CCCA: complete cell cycle arrest, EOT: end of treatment, PK: pharmacokinetics, PRO: patient-reported outcome, RNAseq: RNA sequencing, ER: estrogen receptor, PR: progesterone receptor, IHC: immunohistochemical staining

Results (primary endpoint)



*P-value cutoff for superiority at primary analysis: 0.09687

Safety

Giredestrant demonstrated good tolerability both as monotherapy and in combination with palbociclib. The main side effects were neutropenia, decreased neutrophil count, asthenia, hot flush, and nausea.

- **Giredestrant: -75%**
- **Anastrozole: -67%**
- **P-value: 0.0433***

Hurvitz SA, et al. Lancet Oncol 2023; 24:1029–1041

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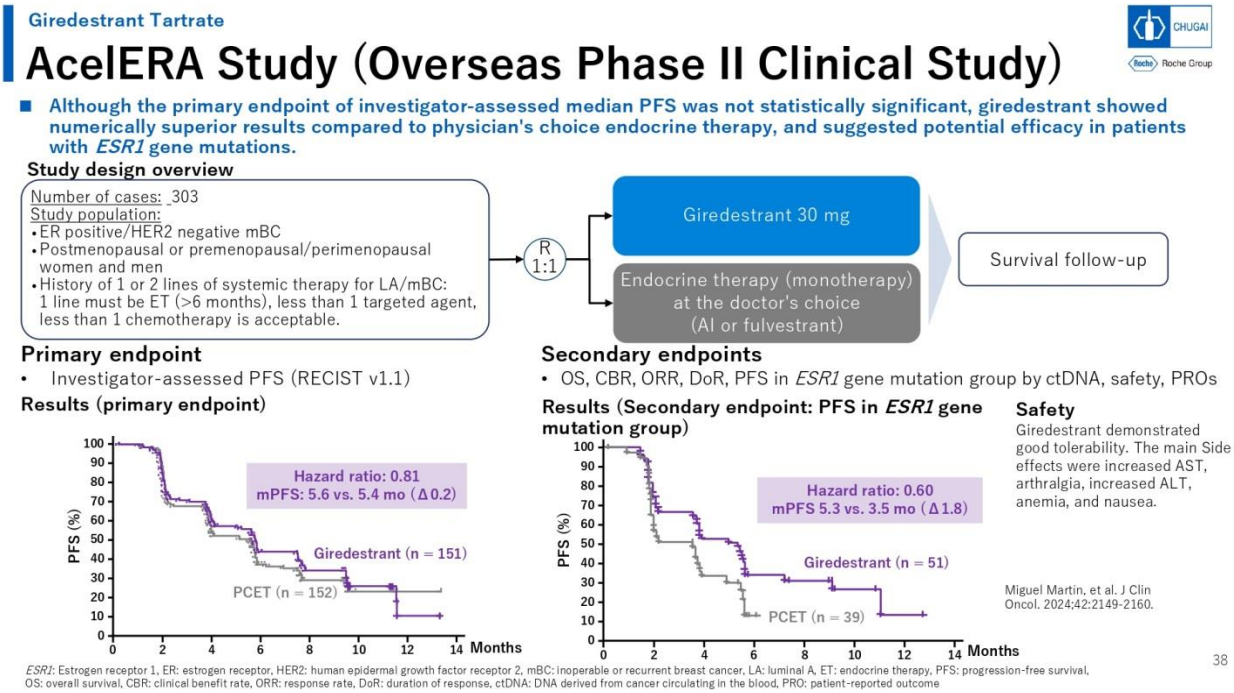
I would like to introduce two overseas Phase II trials.

The first is what we call the coopERA study.

Highlights include a significantly greater relative geometric mean decrease in Ki67 from baseline to week two and beyond with giredestrant compared to anastrozole for endocrine therapy. Ki67 is a nuclear protein present in proliferating cancer cells and is said to be an indicator of the degree of cell proliferation. We believe that the larger this decrease is, the more anti-tumor effect can be expected.

The numbers were significantly larger for preoperative patients and patients with operable breast cancer.



The other is the acelERA study.

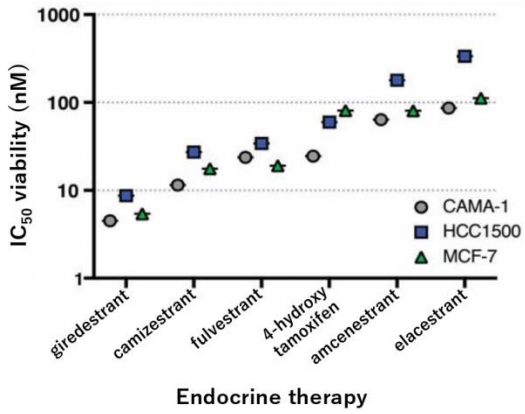
This is for patients with advanced relapse or meta who have had at least one or two treatments. Looking at the primary endpoint, the results on the left side, the hazard ratio was 0.81, which is not statistically significant.

However, on the other hand, the numbers exceeded those of endocrine therapy and may be particularly effective in patients with *ESR1* mutation, a genetic mutation that shows mutations after anastrozole administration.

Giredestrant Tartrate

Giredestrant is a Highly Potent Oral SERD Aiming to be Best-In-Class

Viability assay: Potency of ER antagonists in three types of ER-positive cell lines[1)]



Endocrine therapy	Potency (IC_{50}) of ER antagonists in three types of ER-positive cell lines[1)]
giredestrant	**4.5–8.7 nM**
camizestrant	11.5–27.2 nM
fulvestrant	19.1–34.1 nM
4-hydroxy tamoxifen	24.5–80.7 nM
amcenestrant	63.7–179 nM
elacestrant	86.3–334.8 nM

ER: Estrogen receptor, IC_{50}, half maximal inhibitory concentration, SERD: Selective estrogen receptor degrader
1) Liang J, et al. J Med Chem 2021; 64:11841–11856 (Incl. suppl.)

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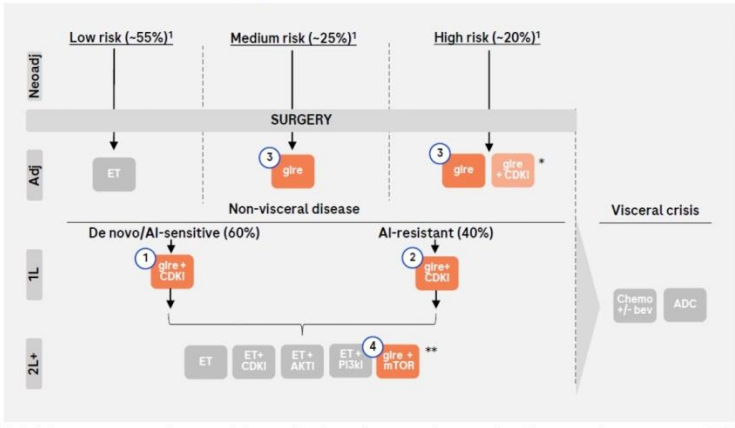
Another feature of giredestrant is that, non−clinical data show this drug is an oral SERD with high potency. We are aiming for it to be the best in class.

The figure on the left and the table on the right correlate and show the potency of estrogen receptor antagonists in the three ER, estrogen receptor-positive cell lines. The lower this number is, the more selective the effect, and the higher the potency are expected to be. Non-clinical results indicate that compared to other SERD agents, giredestrant may have the highest potency.

Giredestrant Tartrate

Overview of Clinical Trials, Treatment Lines, etc. for Giredestrant

Giredestrant aims to replace standard of care ET across eBC & mBC



gire giredestrant

1	gire + palbociclib (persevERA)	1L ER+/HER2-mBC (Endocrine therapy sensitivity)
2	gire + CDK4/6 inhibitor (pionERA)	1L ER+/HER2-mBC (Endocrine therapy resistant)
3	giredestrant (lidERA)	Postoperative ER+/HER2-eBC
4	gire + everolimus (evERA)	2L ER+/HER2-mBC
	gire + PHESGO (heredERA)	1L ER+/HER2+mBC

(1)(4) Test results will be available in 2025.
(1)(3)(4) Studies in which Japan is participating.

1 Risk definitions vary according to guidelines and tools used: stage at diagnosis based on internal estimates using SEER data *giredestrant + CDK4/6i in adjuvant HR+ BC being evaluated as single arm substudy as part of Ph 3 lidERA
**giredestrant + everolimus in 2L+ HR+ BC is being investigated as Medical Affairs study; AI=aromatase inhibitor, ET=endocrine therapy , eBC=early breast cancer, mBC=metastatic breast cancer, neoadj=neoadjuvant , adj=adjuvant , SERD=selective estrogen receptor degrader

Quoted from the presentation slides of Roche Pharma Day 2024

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I am presenting you with an overall picture of our current clinical trials and treatment lines.

See left side. First, regarding the perioperative period, the figures shown in parentheses for high risk, medium risk, and low risk, respectively, are roughly the share of the global total number of patients. This figure is also shown for the subsequent progressive/recurrent stage.

First, one is the combination of giredestrant and palbociclib in patients with first-line estrogen receptor-positive, HER2-negative, advanced recurrent breast cancer who are sensitive to endocrine therapy, the persevERA trial.

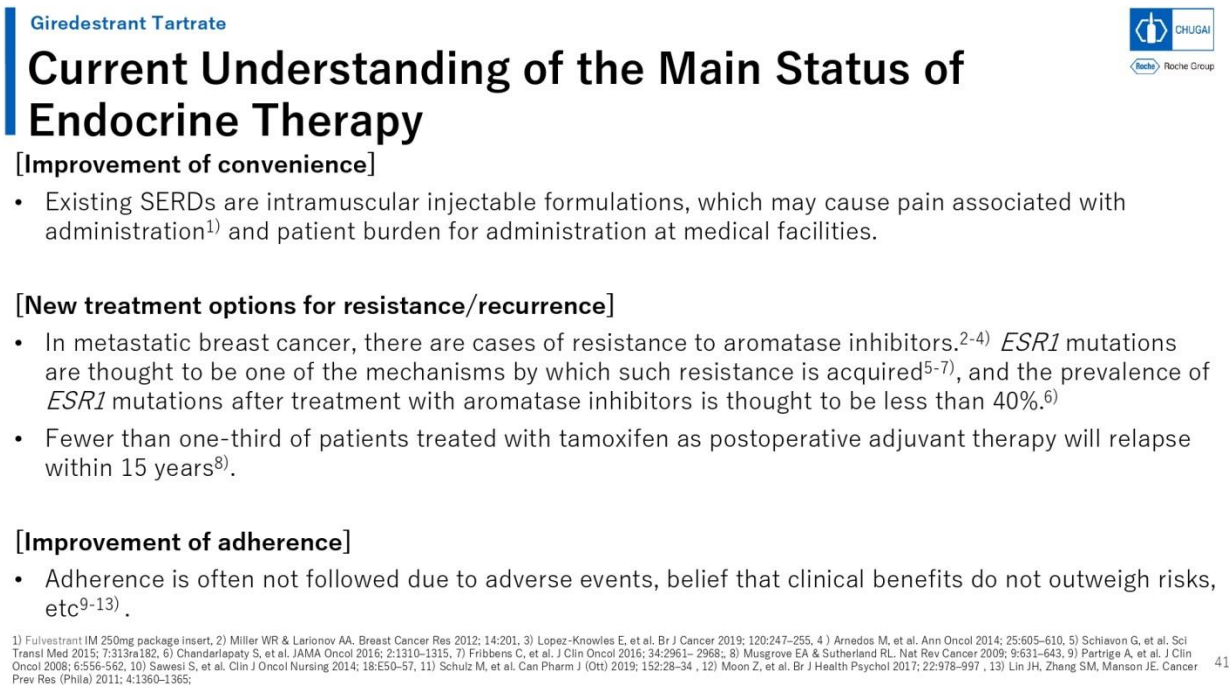
On the other hand, two is the combination of giredestrant and a CDK4/6 inhibitor for AI-resistant, endocrine therapy-resistant patients. Development of combinations with drugs other than palbociclib is now underway.

Three is a single-agent clinical trial. This is a single agent being tested against an adjuvant after surgery.

Four is what we call the evERA study. It is intended for second-line and beyond hormone-positive, HER2-negative metastatic breast cancer patients and is being developed for use in combination with everolimus.

Listed outside the box is a fixed-dose combination of giredestrant and Phesgo, pertuzumab, and trastuzumab for patients with HER2-positive breast cancer. Trials are underway for use in combination with a combination subcutaneous formulation.

Currently, the results of the studies for one and four are expected to be available by the end of 2025. In addition, Japan is also participating in this global Phase III study for one, three, and four.



I would like to discuss three main current perceptions of endocrine therapy.

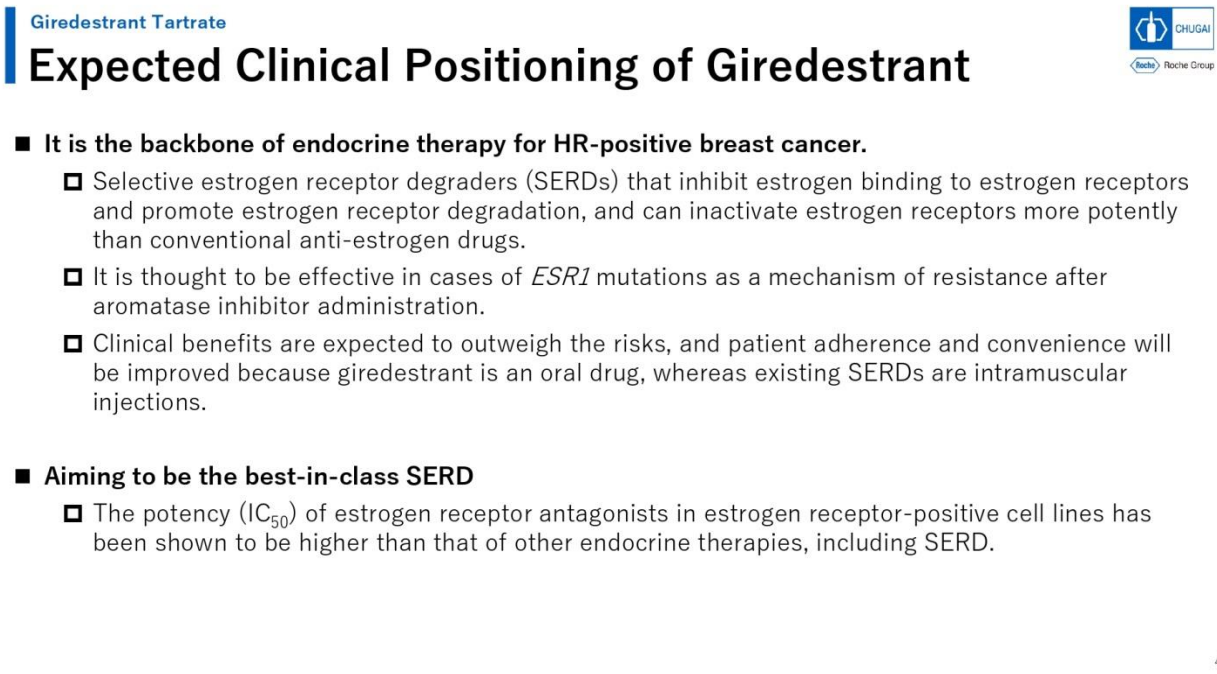
First, let's talk about improving convenience. Current SERDs are injected intramuscularly into the buttocks, and the pain associated with administration and the burden of the patient's commute to the medical facility is considered.

The second is about resistance mechanisms and new treatment options for relapse. There are cases of resistance to aromatase inhibitors, especially in metastatic breast cancer. ESR1 mutation is considered as one

of the possible mechanisms of its resistance acquisition, and the retention rate of ESR1 mutation after aromatase inhibitor administration is thought to be up to 40%.

In addition, recurrence occurs within 15 years in approximately one-third of patients treated with tamoxifen as adjuvant or postoperative therapy. There are a certain number of patients who are administered the drug for a long time after surgery, but unfortunately, it progresses as it is and treatment is initiated again.

Improved adherence also translates into improved convenience. We are aware that there are many cases where treatment is not continued due to adverse events and the belief that the clinical benefits do not outweigh the risks.



Against this background, our expectation for the clinical positioning of giredestrant is that it will become the backbone of endocrine therapy for HR-positive breast cancer. It is a selective estrogen receptor degrader that inhibits estrogen binding to estrogen receptors, promotes estrogen receptor degradation, and can inactivate estrogen receptors more potently than conventional anti-estrogen drugs.

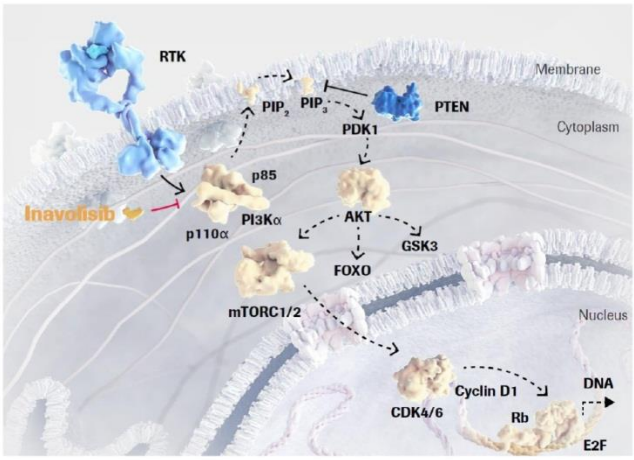
It is expected to show efficacy against resistance mechanisms after aromatase inhibitor administration. As the clinical benefits outweigh the risks, we expect to see further improvements in adherence and convenience.

We also aim for it to be best-in-class for both oral and injectable SERDs, as I have just shown in our non-clinical data.

Inavolisib

Inavolisib (PI3K Inhibitor): Mode of Action

- Inavolisib is a highly potent, selective inhibitor of p110α, the catalytic subunit of PI3Kα. In addition, inavolisib promotes the degradation of mutated p110α (mutant degrader)



- Inavolisib is a new targeted molecular agent that specifically inhibits PI3Kα[1], a key molecule involved in oncogenesis and tumor progression.
- PI3Kα is composed of 2 subunits, p110α and p85, and p110α, called the catalytic subunit, is responsible for the main function of PI3Kα. On the other hand, p85 is called a regulatory subunit and plays a role in controlling the activity of p110α.
- A key feature of inavolisib is that it acts on both of these two subunits, thereby dual inhibiting PI3Kα function. The effect on p110α inhibits PI3Kα and promotes the degradation of mutated p110α (mutant degrader). These effects result in potent and sustained blockade of the PI3Kα pathway.
- In addition, inavolisib selectively inhibits PI3Kα, expected to result in less impact on other PI3K molecules and a reduced risk of side effects.

1) Multiple PI3K isoforms (α, β, γ, δ) exist, with the PI3Kα isoform playing a pivotal role in cellular proliferation and survival, exerting its oncogenic effects from the earliest stages of tumorigenesis. In contrast, the other PI3K isoforms are implicated in distinct physiological processes such as immune function and metabolic regulation, distinct from their roles in oncogenesis. Consequently, it is hypothesized that selective inhibition of the PI3Kα isoform could suppress tumor cell proliferation while minimizing disruption of normal physiological functions mediated by the other PI3K isoforms.

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Next, let me explain about inavolisib.

inavolisib was licensed from Roche in July of this year.

There are multiple isoforms of PI3K, one of which, PI3Kα, is said to be deeply involved in oncogenesis and tumor progression in particular. It has the dual action of selectively inhibiting p110α kinase activity, the catalytic unit of PI3Kα, and promoting the degradation of p110α mutant proteins.

Because inavolisib selectively inhibits PI3Kα, it is thought to have less effect on other PI3Kα isoforms, which are involved in physiological functions different from oncogenesis, and is expected to reduce the risk of side effects.

Inavolisib

Status of *PIK3CA* Gene Mutations in Breast Cancer

- Mechanisms that lead to resistance to CDK4/6 inhibitors include upregulation of growth factor signaling pathways such as the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway[1-2)]
- It has been reported that approximately 40% of HR-positive breast cancer patients have tumors with *PIK3CA* gene mutations that lead to upregulation of the PI3K pathway[3-4)]
- Activation of the PI3K pathway has been shown to predict poor prognosis after adjuvant endocrine therapy[5)]

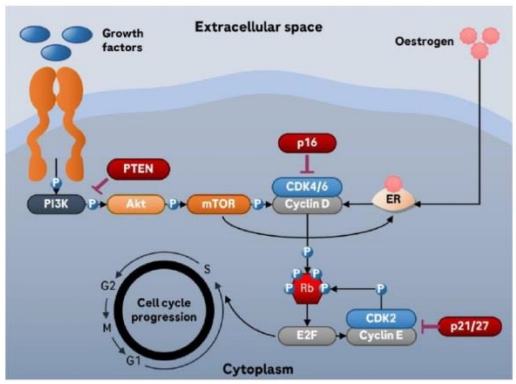


Figure taken from reference: Brufsky AM & Dickler MN. Oncologist 2018; 23:528 – 539.

Breast cancer subtype[6-8)]	*PIK3CA* mutation rate
HR+	Approximately 35-40%
HER2 +	Approximately 23-31%
Triple-negative	<16%

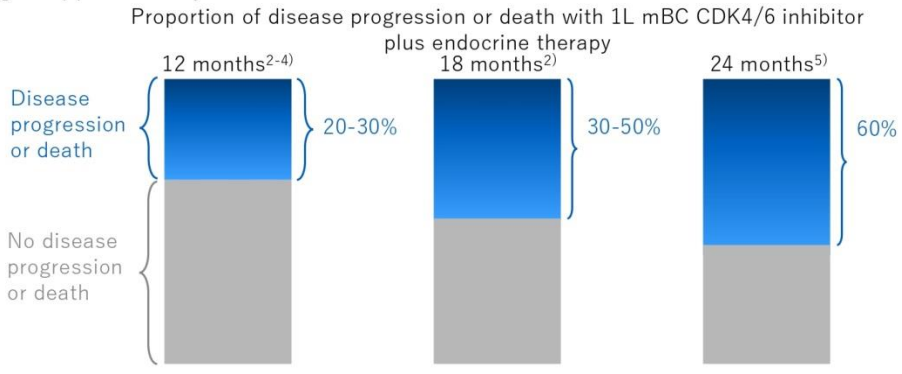
1) O'Leary B, et al. Cancer Discov. 2018;8(11):1390-403. 2) Portman N, et al. Endocr Relat Cancer. 2019;26(1):R15-R30. 3) Saal LH, Holm K, Maurer M, et al. Cancer Res 2005;65:2554 – 9., 4) Stemke-Hale K, Gonzalez-Angulo AM, Lluch A, et al. Cancer Res 2008;68:6084–91., 5) Miller TW, Hennessy BT, González-Angulo AM, et al. J Clin Invest 2010;120:2406–13., 6) Anderson EJ, et al. Int J Breast Cancer 2020; 2020:3759179. 7) LoRusso PM, et al. J Clin Oncol 2016; 34:3803 – 3815. 8) Martinez-Sáez O, et al. Breast Cancer Res 2020; 22:45.

In addition, it has been reported that approximately 40% of patients with HR-positive breast cancer have PIK3CA mutation-positive tumors that result in upregulation of the PI3K pathway. The activity of the PIK3 pathway is said to predict poor prognosis after adjuvant endocrine therapy.

Inavolisib

Rate of Disease Progression etc. with CDK4/6 Inhibitors + Endocrine Therapy

- CDK4/6 inhibitors plus endocrine therapy is one of the standard 1L treatments for HR-positive, HER2-negative mBC[1)]
- It has been shown that approximately 20%-30% of patients treated with CDK4/6 inhibitors plus endocrine therapy in 1L mBC experience disease progression or death after 12 months,[2-4)] with this increasing to approximately 30%-50% after 18 months.[2)]



1) Breast Cancer Treatment Guidelines 2022 Edition. 2) De Laurentiis M, et al. SABCS 2019 (Poster P3-11-25). 3) Suzuki DA, et al. JCO Glob Oncol 2024; 10:e2300484. 4) Nozawa K, et al. Breast Cancer 2023; 30:657–665. 5) Brufsky A, et al. Clin Breast Cancer 2019; 19:317 – 325.

Currently, one of the main standards of care used in the first line of this HR-positive breast cancer is a combination therapy with CDK4/6 inhibitor inhibitors and endocrine therapy.

However, data show that approximately 20% to 30% of first-line patients who receive this combination therapy experience disease progression or death after 12 months, reaching 60% after 24 months.

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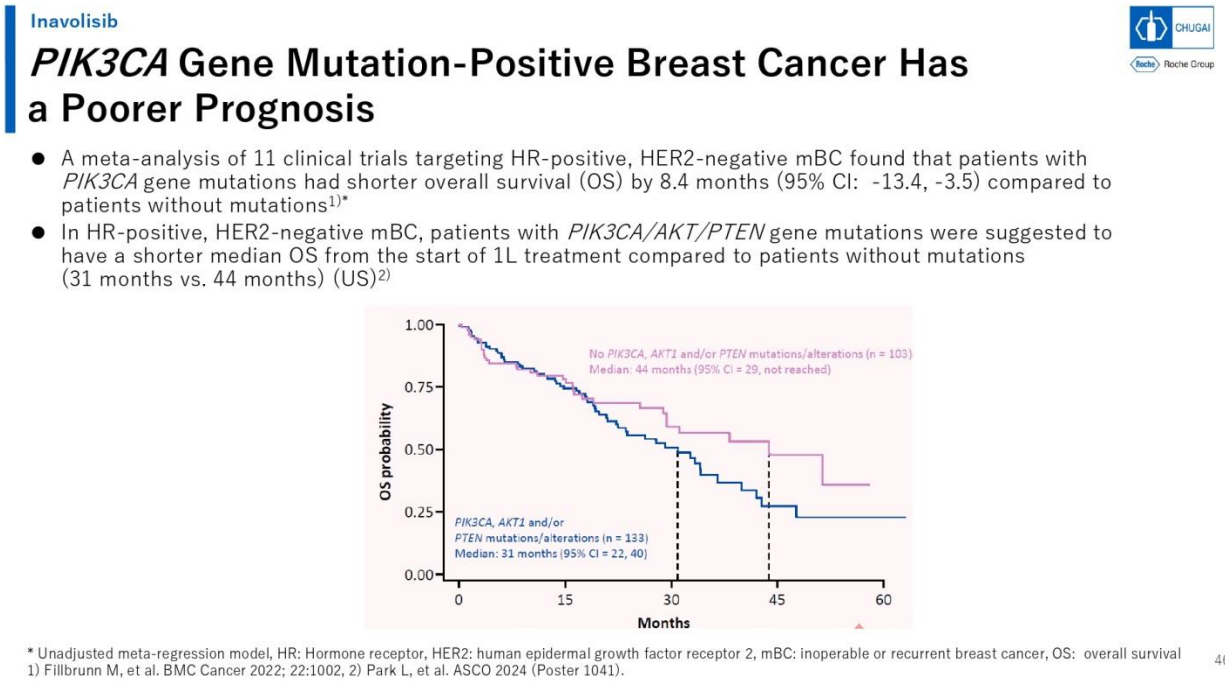
In addition, patients with PIK3CA mutation-positive breast cancer have a worse prognosis. A meta-analysis of 11 clinical trials shows that patients with PIK3CA mutation, a positive gene mutation, have an overall survival time that is more than eight months shorter than that of patients without the mutation.



In addition, U.S. data suggest that patients with PIK3CA/AKT/PTEN mutations have a shorter median overall survival from initiation of first-line therapy than those without.

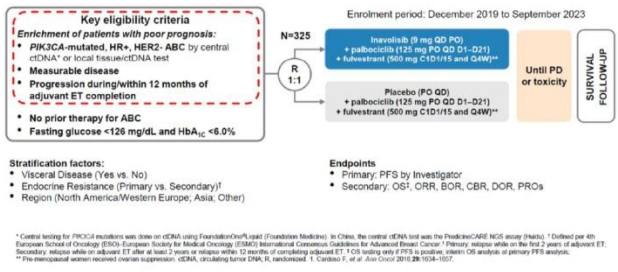
From this perspective, we believe there is a high unmet need in this segment.

Inavolisib

Global Phase 3 Study (INAVO120) of Inavolisib

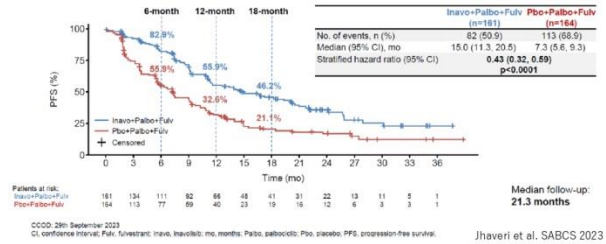
- Expected to become a new standard molecular-targeted drug by combining CDK4/6 inhibitors and anti-estrogen drugs in hormone receptor-positive, HER2-negative advanced breast cancer with a *PIK3CA* mutation

【Study design】



【Results】

Primary endpoint: PFS (investigator-assessed)



Jhaveri et al. SABCS 2023

- Patients with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative locally advanced/metastatic breast cancer
  - ✓ relapsed during/within 12 months of adjuvant endocrine therapy completion in 1st line
- Palbociclib + fulvestrant (one of the standard of care) with inavolisib/placebo on the above segment

Turner N., et al. N Engl J Med 2024;391:1584-1596

- The study met its primary endpoint, with a statistically significant and clinically meaningful improvement in PFS (15.0 months vs 7.3 months; hazard ratio, 0.43 [95% CI = 0.32, 0.59]; p<0.0001)
- Overall survival was immature, but with clear positive trend (HR=0.64, [95% CI=0.43, 0.97]; p=0.0338)
- The safety and tolerability profile of inavolisib + palbociclib + fulvestrant was confirmed to be manageable. The major adverse events were neutropenia, stomatitis or mucositis, hyperglycemia, diarrhea, and rash.

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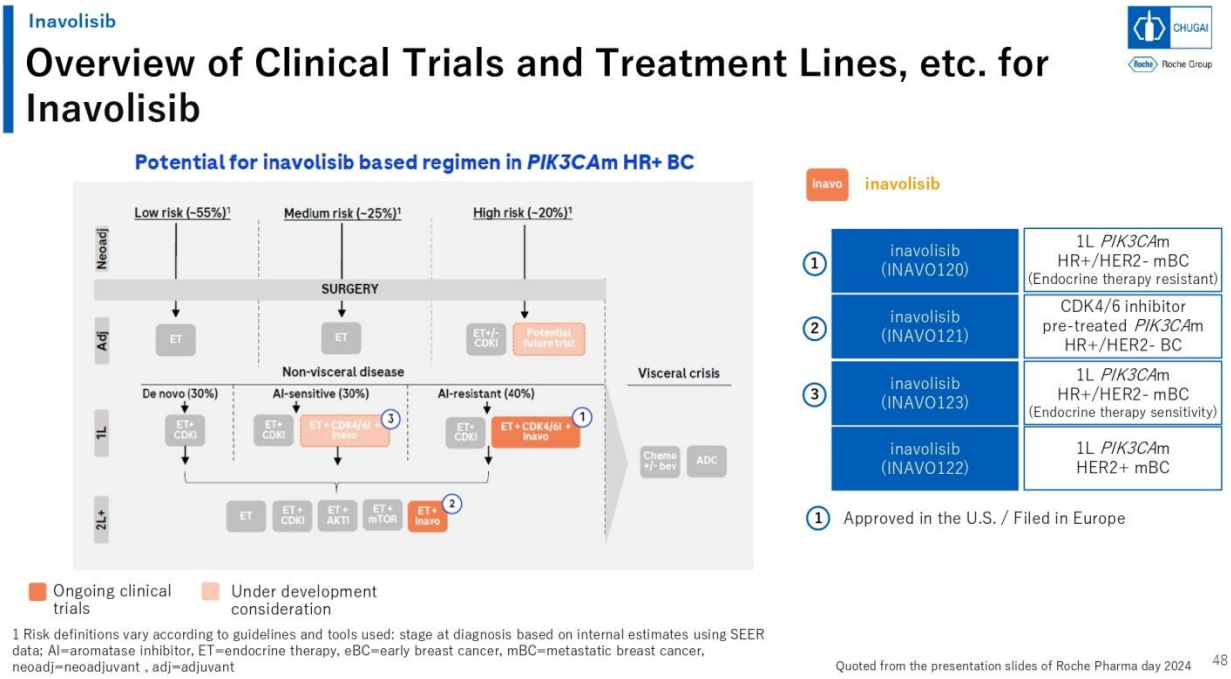
Here I would like to introduce the INAVO120 global Phase III study.

Based on this study, the FDA approved the product in October of this year, and it is already on the market in the United States.

Regarding the study design on the left, this is for HR-positive, HER2-negative recurrent breast cancer with PIK3CA mutation, a segment with a worse prognosis. As I mentioned earlier, CDK4/6 inhibitors and endocrine therapy are said to be one of the standards of care, and this is a trial design in which inavolisib is added to the combination of palbociclib and fulvestrant.

The primary endpoint, PFS, is shown on the right. Statistically significant and clinically meaningful improvement was observed. The hazard ratio is 0.43.

Overall survival is still immature, but there are clear, positive trends. Furthermore, with regard to safety, the tolerability profile has been confirmed to be manageable. Major side effects include neutropenia, stomatitis, mucositis, hyperglycemia, diarrhea, and rash.



In addition to the INAVO120, we are currently developing the inavolisib program on a global basis.

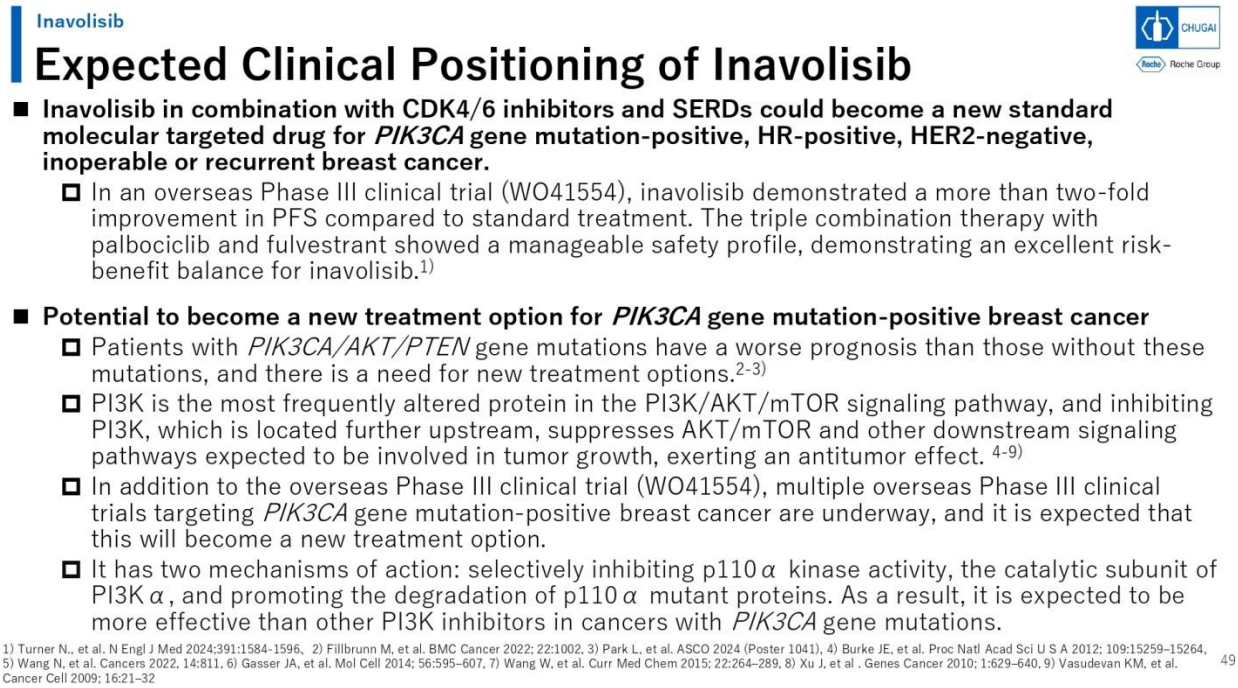
As shown in the previous figure, we first classify the risk into preoperative and postoperative, and then further divide first-line and other patients into those who are sensitive or resistant to endocrine therapy.

I will explain again along the order from the top. INAVO120, which I indicated earlier that results are already available, is for patients with first-line PIK3CA mutation, and furthermore HR-positive and HER2 negative patients who are endocrine therapy resistant.

Below that, INAVO121 study, one step lower, is the development of endocrine therapy in combination with fulvestrant for second-line and beyond patients with a history of treatment with CDK4/6 inhibitors.

The difference of ③ from ① is that it is intended for endocrine therapy-sensitive patients. Of the first line, which represents a significant share of the patient population, trials are underway in both resistant and sensitive patients.

Furthermore, as I mentioned earlier, for HER2 positive, shown outside the frame, a trial in combination with PHESGO is underway.



I would like to explain the expected clinical positioning of inavolisib, or our expectations.

We believe inavolisib could be a new standard of care in PIK3CA mutation-positive, HR-positive, HER2-negative, inoperable, or recurrent breast cancer in combination with a CDK4/6 inhibitor and a SERD.

The basis for this is, as I mentioned earlier, the INAVO 120 study. The rationale is that the trial demonstrated a more than two-fold improvement in PFS compared to standard of care and a balance of risk-benefit of safety and efficacy.

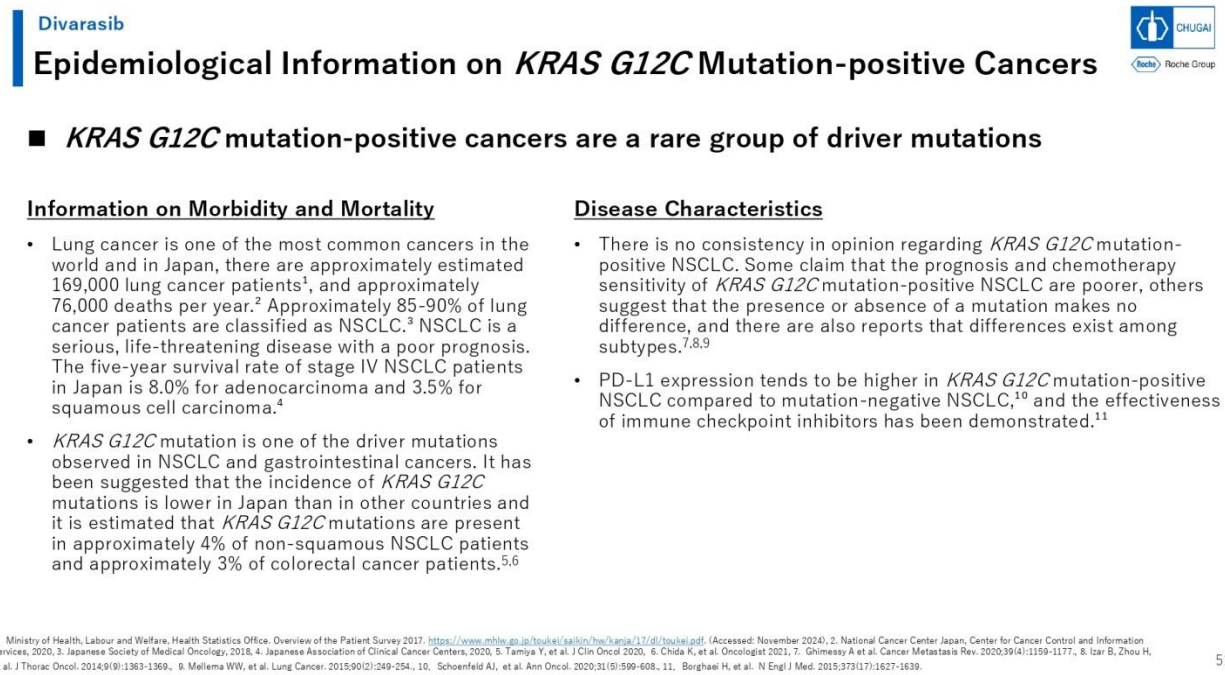
Second, inavolisib could be a new treatment option for PIK3CA mutation-positive breast cancer. Inavolisib could be a new treatment for this segment, which is known to have a particularly poor prognosis. These include AKT inhibitors and mTOR inhibitors. However, inavolisib is expected to have a higher antitumor effect by inhibiting PI3K, which is the most frequent and more upstream signaling, thereby suppressing AKT, mTOR, and multiple other downstream signaling involved in tumor growth.

In addition, I have just shown you several ongoing global trials for breast cancer. We look forward to delivering therapeutics to patients with PIK3CA mutations in this comprehensive manner, which will provide more new treatment options.

Finally, because it has two mechanisms of action, selectively inhibiting p110α kinase activity and promoting its degradation, we intend to further develop it for other cancer types.

That's all for the explanation.

Miyata: Next, the Lifecycle Leader will explain about divarasib.



Divarasib Lifecycle Leader: I would like to briefly introduce divarasib, RG6330, which is currently in clinical development as a KRAS G12C inhibitor.

First, here is some epidemiological information on KRAS G12C mutation-positive cancers targeted by divarasib.

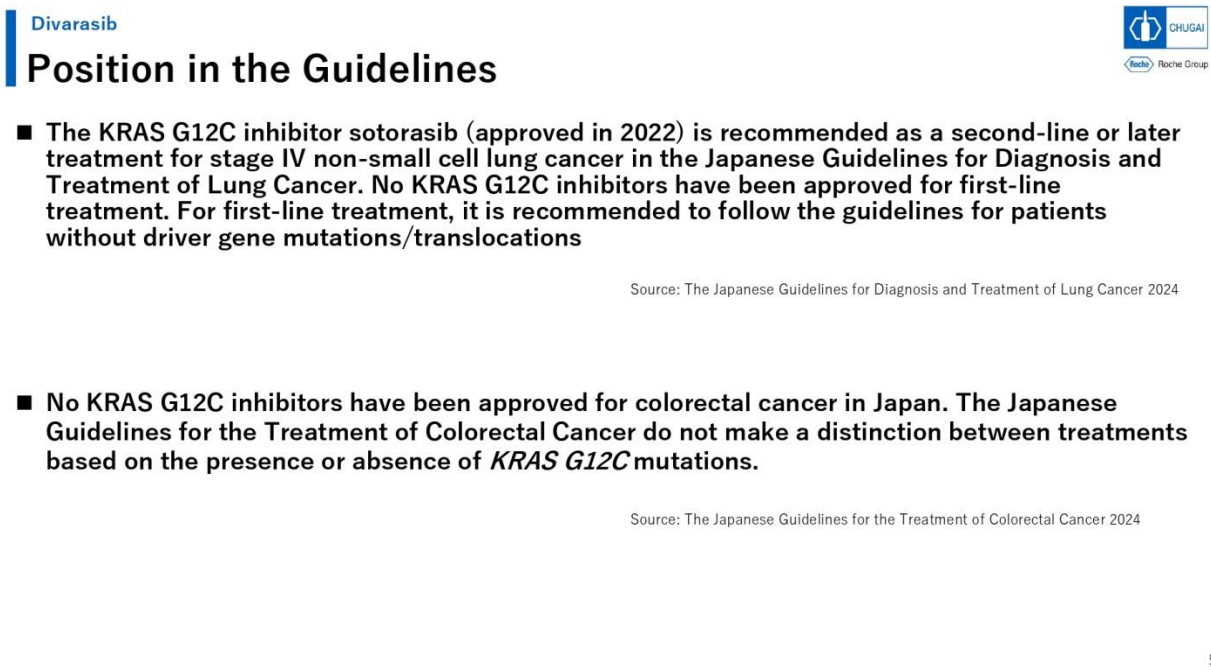
Lung cancer is currently the focus of attention in the development of new treatments for KRAS G12C-positive cancers. As you may know, lung cancer is one of the most common cancers in the world, with a total of approximately 169,000 patients in Japan. About 85% to 90% of them are classified as non-small cell lung cancer, or NSCLC, as shown here.

NSCLC is a serious and life-threatening disease, and we recognize that the development of new treatments for this disease is highly desired in Japan as well.

Among others, one of these driver mutations, the KRAS G12C mutation, has been found in NSCLC with KRAS G12C mutation or in gastrointestinal cancer. It is suggested that the frequency of expression is reduced especially in NSCLC compared to overseas, and it is estimated that about 4% of non-squamous lung cancers and about 3% of rectal and colon cancers have KRAS G12C mutations.

The prognosis and chemotherapy sensitivity of KRAS G12C mutation-positive NSCLC, which is shown on the right side as a characteristic of the disease, varies from report to report, with some stating that the prognosis is poor and others stating that there is no difference depending on the mutation. It is also recognized that reports vary by subtype.

Second, it has been reported that PD-L1 expression tends to be higher in KRAS G12C mutation-positive NSCLC compared with KRAS G12C mutation-negative, suggesting the efficacy of immune checkpoint inhibitors.



Here is a brief overview of where it stands on the current national guidelines.

First, as noted above, domestic guidelines for lung cancer treatment recommend sotorasib, a KRAS G12C inhibitor approved in 2022, for second-line treatment or later for stage IV NSCLC.

Unfortunately, there are no approved inhibitors for first-line treatment. So, currently, the treatment is supposed to be equivalent to the initial treatment of a driver gene mutation/translocation negative.

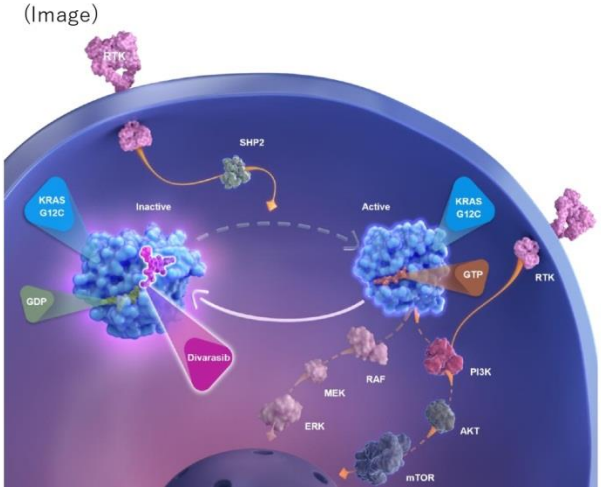
In colorectal cancer, there are no KRAS G12C inhibitors approved in Japan. In domestic guidelines for colorectal cancer, there is currently no distinction in treatment based on the presence or absence of KRAS G12C mutation.

Divarasib

Overview and Mechanism of Action of KRAS G12C Inhibitor Divarasib

Indications under development	Unresectable, advanced and/or recurrent non-small cell lung cancer with *KRAS G12C* mutation

(Image)



- GTP-bound KRAS activates downstream signaling pathways involved in cell proliferation, migration and survival, including the MAPK and PI3K pathways. The KRAS G12C mutant protein is constitutively active and enhances oncogenic signaling, leading to uncontrolled cancer cell proliferation and tumor formation.
- divarasib is an orally bioavailable, KRAS G12C- selective small molecule compound. In non-clinical models, it irreversibly binds to the KRAS G12C protein, fixing it in an inactive state, thereby selectively inhibiting its function in non-clinical models.
- In non-clinical models, it suggests to have stronger cell proliferation inhibitory activity and higher selectivity for *KRAS G12C* mutant cells than sotorasib and adagrasib.

Purkey, H., AACR, 2022, ND11
GTP: guanosine triphosphate, KRAS: Kirsten rat sarcoma viral oncogene homolog, MAPK: mitogen-activated protein kinase, PI3K: phosphatidyl inositol 3-kinase, G12C: glycine 12 to cysteine

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I will now give a brief overview of divarasib, a KRAS G12C inhibitor currently in clinical development, and its mechanism of action.

The indication currently under development is unresectable advanced and/or recurrent non-small cell lung cancer with KRAS G12C mutation.

A simple image including the mechanism of action is shown on the left. GTP-bound KRAS activates downstream signaling involved in cell proliferation or survival, including the MAPK and PI3K pathways. The KRAS G12C mutant protein is constitutively activated and is thought to produce uncontrolled cancer growth and tumorigenesis by enhancing oncogenic signals.

Divarasib is a KRAS G12C-selective small molecule compound that can be administered orally. In preclinical models, it is believed to exert its antitumor effect by irreversibly binding to the GTP form of KRAS G12C protein, the so-called inactive form, and selectively inhibiting its function by immobilizing it in an inactive state.

In preclinical models, it has been suggested to have stronger cell growth inhibition activity and higher selectivity for KRAS G12C mutations than sotorasib and adagrasib.

Divarasib

Overseas Phase I Clinical Study Results (GO42144)

■ **The study suggested that divarasib is well tolerated and has favorable efficacy.**

[Study overview]

An overseas Phase Ia/Ib clinical trial to evaluate the safety, pharmacokinetics, and efficacy of divarasib monotherapy and in combination with other anti-tumor drugs in patients with advanced/metastatic solid tumors that harbor a *KRAS G12C* mutation. The primary endpoint is safety, and the secondary endpoint is pharmacokinetics and efficacy. The study consisted of a dose escalation part (50 mg to 400 mg) and an expansion cohort part. A total of 137 patients were enrolled (60 with non-small cell lung cancer, 55 with colorectal cancer, and 22 with other solid tumors).

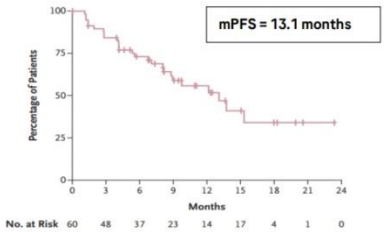
[Study results]

Efficacy

Overall response rates

Indication Regimen	Confirmed ORR
2L+ NSCLC Monotherapy	53% (all doses) 56% (400mg dose)
2L+ CRC Monotherapy	29% (all doses) 36% (400mg dose)
2L+ CRC Divarasib + cetuximab	62%

PFS (all doses) in 2L+ NSCLC monotherapy



Safety

No dose-limiting toxicity was observed. Adverse events occurred in 127 patients (93%), and the major adverse events were nausea (74%), diarrhea (61%), vomiting (58%), and fatigue (22%), loss of appetite (13%).

Sacher A. et al., NEJM Aug 2023 54

Here is a summary of the results of the ongoing overseas Phase I clinical study.

The results of this Phase I study suggest that divarasib is well tolerated and has good efficacy.

Here is a brief overview. This is an overseas Phase Ia and Ib study to evaluate the safety, pharmacokinetics, and efficacy of divarasib when administered alone or in combination with other anticancer agents in patients with KRAS G12C mutation-positive advanced/metastatic solid tumors. The primary endpoints include safety evaluation. Secondary endpoints are pharmacokinetics and efficacy.

The study will consist of a dose-escalation part, from 50 mg to 400 mg, and an expansion cohort part. In all, 137 subjects were enrolled: 60 with NSCLC, 55 with colon and rectal cancer, and 22 with other solid tumors.

See left side below. I will briefly explain its effectiveness from the left. Top left, for second-line NSCLC monotherapy, the ORR, antitumor efficacy rates, were 53%, and 56% for 400 mg. In patients with second-line or later colorectal cancer in the second row, the monotherapy demonstrated an antitumor effect of 29% to 36%.

The middle figure shows the progression-free survival, or PFS, of single agents for second-line NSCLC. The mPFS was 13.1 months.

A brief summary of safety is provided on the far right. No dose-limiting toxicity has been observed, and side effects were observed in 93% of patients, with the most common side effects being nausea in 74%, diarrhea in 61%, vomiting in 58%, fatigue in 22%, and loss of appetite in 13%. Gastrointestinal toxicity is considered the main side effect of this drug.

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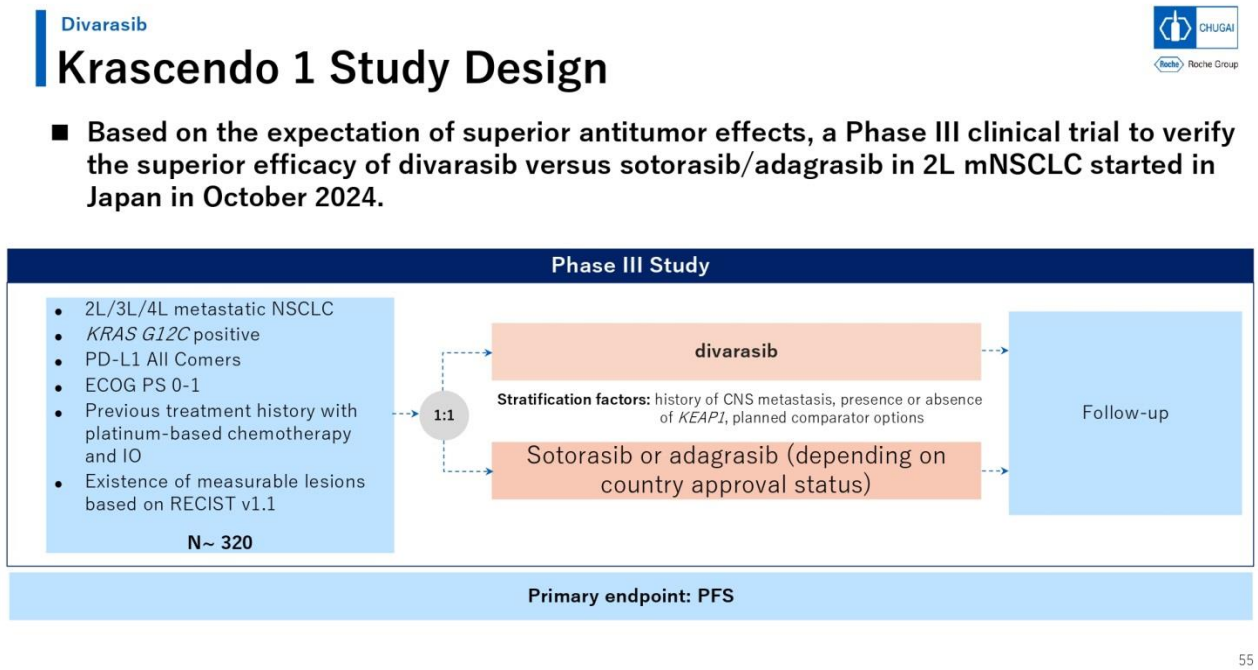

Finally, I would like to briefly describe our ongoing global Phase III clinical trial.

Based on the results obtained from the overseas trials mentioned earlier, and against the backdrop of expectations for divarasib's superior anti-tumor effects, a Phase III clinical trial was initiated in Japan in October of this year. This will test the superiority of the efficacy of divarasib over sotorasib or adagrasib in patients with second-line or later metastatic non-small cell lung cancer.

A study design is shown below. The study includes 320 patients with second-line or later metastatic non-small cell lung cancer with KRAS G12C-positive mutations, as described on the left side. A trial is currently underway in which patients are randomly assigned in a 1:1 ratio to the divarasib arm or to sotorasib or adagrasib, and patients are treated according to the trial protocol until disease progression. The primary endpoint is progression-free survival.

Divarasib

Clinical Studies Under Development

Name of study	Target	Projected submission
Krascendo 1 Study	Unresectable, advanced and/or recurrent non-small cell lung cancer with *KRAS G12C* mutation	2027 or later
–	Solid tumors	–

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This is a list of studies currently under development. We are currently conducting a Phase III study in patients with KRAS G12C-positive unresectable advanced/recurrent non-small cell lung cancer and a study in patients with solid tumors, which I just mentioned.

That is all for my explanation.

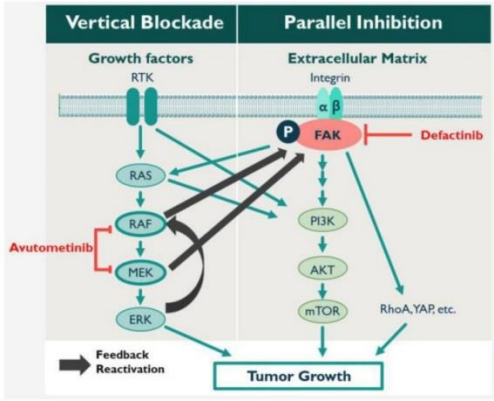
Miyata: Next, Dr. Iwasawa will explain about avutometinib.

Avutometinib

RAS/MAPK Pathway Inhibition by Avutometinib

■ Avutometinib + Defactinib Aims to Inhibit Multiple Resistance Mechanisms in the RAS/MAPK Pathway

- Avutometinib is an oral RAF/MEK clamp that potently inhibits MEK kinase activity while also blocking the compensatory reactivation of MEK by upstream RAF[1-3]
- FAK is activated in response to MAPK pathway inhibition by avutometinib as well as by RAF inhibitors and MEK-only inhibitors[4,5]
- Defactinib is an oral selective FAK inhibitor that inhibits parallel pathway signaling and FAK inhibition has been demonstrated to enhance the antitumor efficacy of avutometinib[6-8]
- Together, avutometinib and defactinib have the potential to offer more complete blockade of the signaling that drives the growth of RAS/MAPK pathway-dependent tumors with the objective of deeper and more durable responses



1. Coma et al., AACR 2022; 2. Ishiiet al., CancerRes, 2013; 3. Lito et al., CancerCell, 2014; 4. Lubranoet al., AACR 2024; 5 Banerjiet al., AACR 2020; 6. Jones et al., Invest New Drugs 2015; 7. McNamara et al., GynecolOncol 2024; 8. Banerjee et al., ASCO 2023 (1,4,5,8 includes employees of Verastem oncology; 2,3 includes employees of Chugai Pharmaceutical)
ERK; extracellular signal-regulated kinase; FAK, focal adhesion kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; mTOR, mammalian target of rapamycin; P, phosphate; PI3K, phosphatidylinositol 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; RhoA, Ras homolog family member A; RTK, receptor tyrosine kinase; YAP, Yes-associated protein.

Grisham R, et al. Int J Gynecol Cancer 2024;0:1–7.

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Iwasawa: My name is Shunichiro Iwasawa, and I am the Lifecycle Leader for avutometinib. Thank you for your cooperation today.

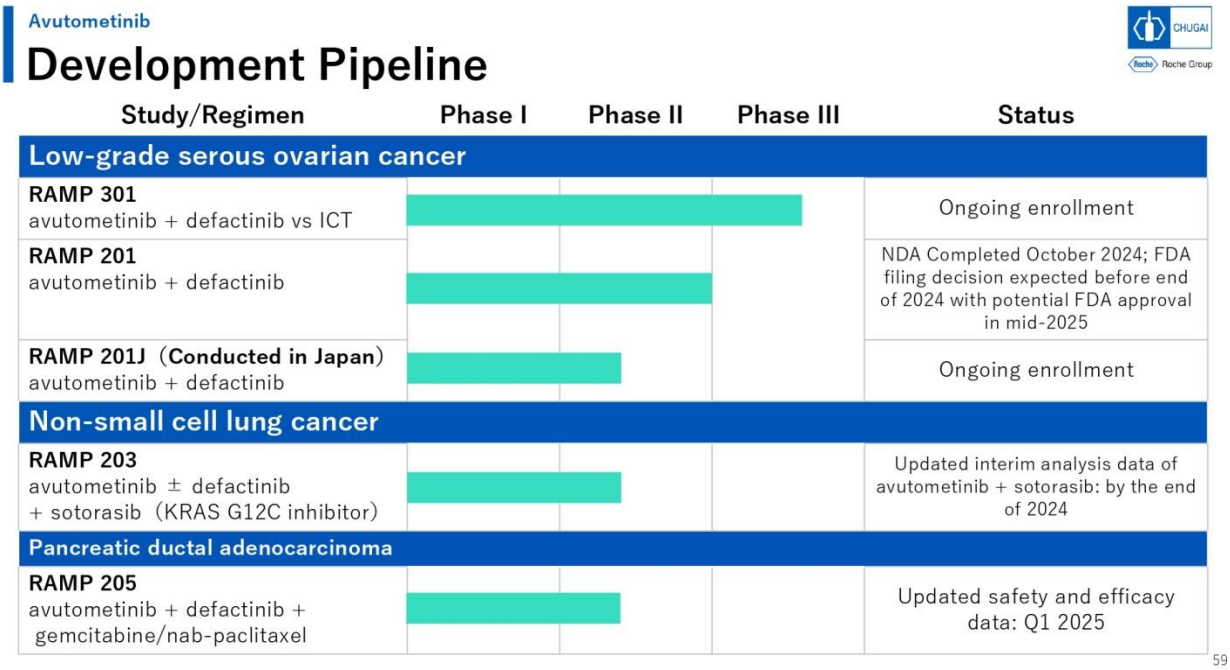
The avutometinib you are looking at was discovered by our company and is currently under development at Verastem Oncology, headquartered in Boston, USA. I would like to explain about this product.

The mode of action of avutometinib is described on the right side of this page, which describes the mechanism by which avutometinib inhibits the major growth pathways in tumors. I will explain each of them. The word RAF/MEK "clamp" is a concept conveyed by Verastem, which in Japanese means to tighten, as in a vise, clamping metal, etc.

Avutometinib inhibits two factors of the MAPK pathway, RAF and MEK, in the middle-left side of the figure. The mechanism is to inhibit tumor growth by strongly clamping the tumor.

Furthermore, when the MAP kinase pathway is inhibited, avutometinib activates the PI3K, AKT, and mTOR pathways in a feedback mechanism. Therefore, this indicates a mechanism whereby the FAK factor on the right side is simultaneously inhibited by defactinib, also owned by Verastem, thereby exerting a powerful anti-tumor effect.

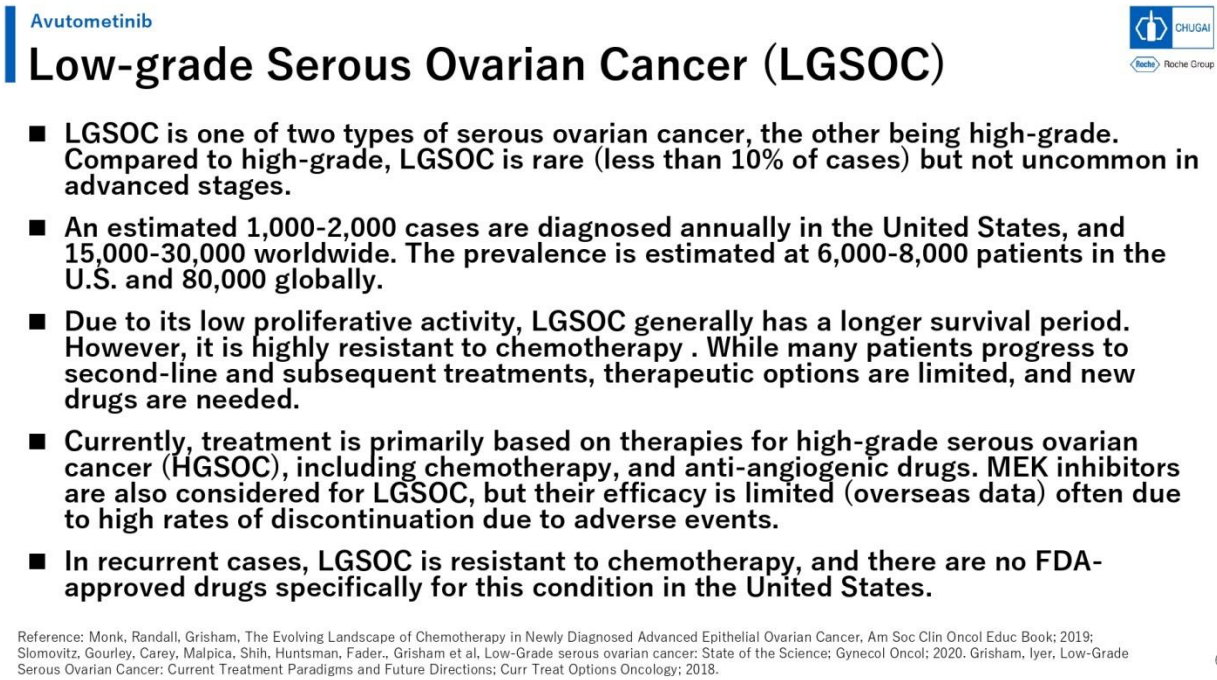
The summary of this pathway is that avutometinib and defactinib exhibit antitumor effects by inhibiting this parallel signaling.



The following is a list of clinical trials currently being conducted at Verastem.

There are three main types of cancer. Today I would like to introduce low-grade serous ovarian cancer, LGSOC. This will be explained in more detail later.

Phase II trials are also being conducted for non-small cell lung cancer, which is the main type of lung cancer accounting for 60% to 70% of all lung cancers. The second is a Phase II trial for pancreatic ductal adenocarcinoma, which accounts for more than 80% of all pancreatic cancers. avutometinib is being developed for these three cancer types.



I would like to explain about LGSOC, low grade serous ovarian cancer, which is currently under review for approval in the United States.

In general, high-grade ovarian cancer is the major type of ovarian cancer, but this low-grade serous ovarian cancer, LGSOC, is rare and has been reported to account for less than 10% of all ovarian cancers. It is not uncommon for these tumors to be advanced by the time they are discovered.

In the United States, 1,000 to 2,000 people are affected each year, and 15,000 to 30,000 people are affected worldwide. The prevalence is estimated at 6,000 to 8,000 in the United States and 80,000 worldwide.

This tumor is characterized by low proliferative activity, or slow cell division, compared to high-grade serous ovarian cancer. Although the survival period is relatively long, the disease is said to be highly resistant to conventional cytotoxic anticancer drugs and chemotherapy, which interfere with cell division.

Therefore, although many cases are transferred to second-line treatment, therapeutic agents are very limited, and new agents are desired. In other words, it is considered a tumor with a high unmet medical need.

Currently, it is mainly applied to the treatment of high-grade serous ovarian cancer as I mentioned earlier. However, its effectiveness is inadequate, and various developments are underway to satisfy this need. Currently, there are no drugs approved in the United States for recurrent cases, LGSOC, or low-grade serous ovarian cancer.

Avutometinib

Overseas Phase II Study (RAMP 201) Result

RAMP 201 study design

RAMP 201 study is a multicenter Phase II study conducted in the U.S., EU, UK, Canada, to evaluate the efficacy and safety of avutometinib alone and in combination with defactinib in patients with recurrent low-grade serous ovarian cancer. The first part of the study (Part A) determined the selection of the go forward regimen, which was the combination of avutometinib and defactinib versus avutometinib alone, based on overall response rates. The expansion phases of the trial (Parts B and C) are evaluating the safety and efficacy of the go forward regimen of avutometinib 3.2 mg twice weekly and defactinib 200 mg twice daily as a recommended dose.

Primary endpoint: confirmed overall response rate assessed by blinded independent central review

[Result of go forward regimen in Part A-C]

Efficacy

Endpoint	All (N=109)*	KRASmt (N=57)*	KRASwt (N=52)*
Primary endpoint			
Confirmed ORR (95%CI)	31% (23, 41)	44% (31, 58)	17% (8, 30)
Secondary endpoints			
Median DoR (95%CI)	31.1 month (14.8, 31.1)	31.1 month (14.8, 31.1)	9.2 month (5.5, NE)
Median PFS (95%CI)	12.9 month (10.9, 20.2)	22 month (11.1, 36.6)	12.8 month (7.4 18.4)

*patients with measurable disease by RECISTv1.1, ORR: overall response rate, DoR: duration of response, PFS: progression-free survival, NE: could not be estimated based on number of patients with loss of response

Safety

Major treatment-related AEs (N=115)	All	≥Grade 3
Nausea	77 (67.0%)	3 (2.6%)
Increased blood CPK	69 (60.0%)	28 (24.3%)
Diarrhea	67 (58.3%)	9 (7.8%)
Edema peripheral	61 (53.0%)	1 (0.9%)
Fatigue	50 (43.5%)	3 (2.6%)
Vomiting	49 (42.6%)	3 (2.6%)
Vision blurred	47 (40.9%)	0

- Discontinuation due to AEs: 12 patients (10%)
- Severe adverse events were typically managed by a treatment pause
- Combination of avutometinib and defactinib was well tolerated

Susana Banerjee etc., IGSC 2024 (LB007 / #1548) (includes employees of Verastem oncology)

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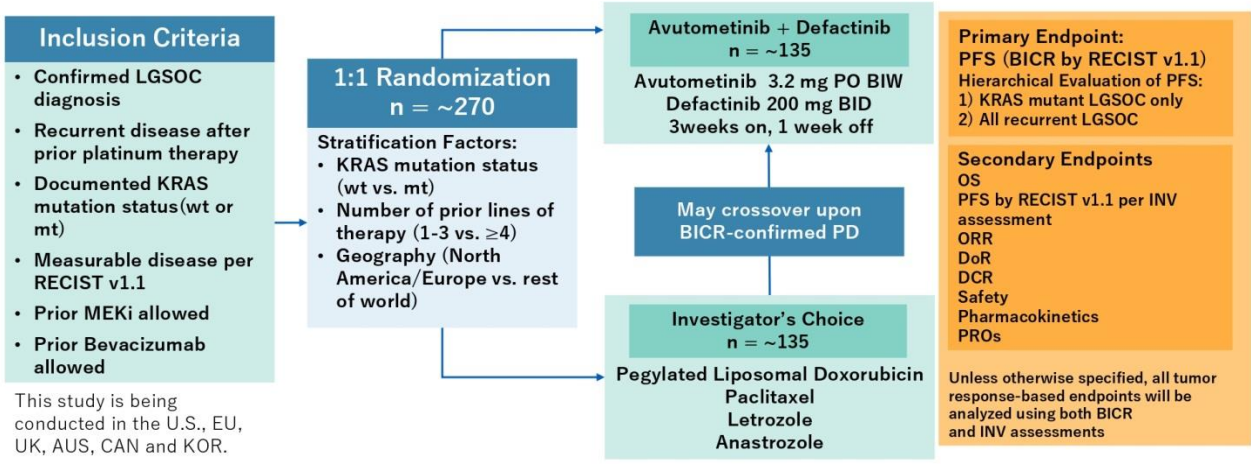
Here are the results of the pivotal Phase II trial for low-grade serous ovarian cancer, the RAMP201 trial being conducted overseas. This is a multicenter Phase II study conducted in the US, Europe, the UK, and Canada.

The table below left shows the efficacy results. Overall, 109 cases were evaluated. In the 57 cases that had KRAS mutations, a major factor in the RAS/MAPK pathway shown on the first slide, the response rate was 44%, and in the negative cases that did not have KRAS mutations, the response rate was 17%.

As for safety, nausea, CPK in blood tests, diarrhea, and edema have been reported. Tolerability was rated as acceptable.

Avutometinib

Overseas Phase III Study (RAMP 301) Design



BICR: blinded independent central review, BID: twice a day; BIW: twice a week, DCR: disease control rate, DoR: duration of response, INV: investigator, KRAS: kirsten rat sarcoma virus, MEKi: MEK inhibitor, mt: mutant, PO: per oral, pts, patients, ORR: objective response rate, OS: overall survival, PD: progressive disease, PFS: progression-free survival, PROs: patient-reported outcomes, RECIST: response evaluation criteria in solid tumors, wt: wild type.

Grisham R, et al. Int J Gynecol Cancer 2024;0:1–7. (includes employees of Verastem Oncology)

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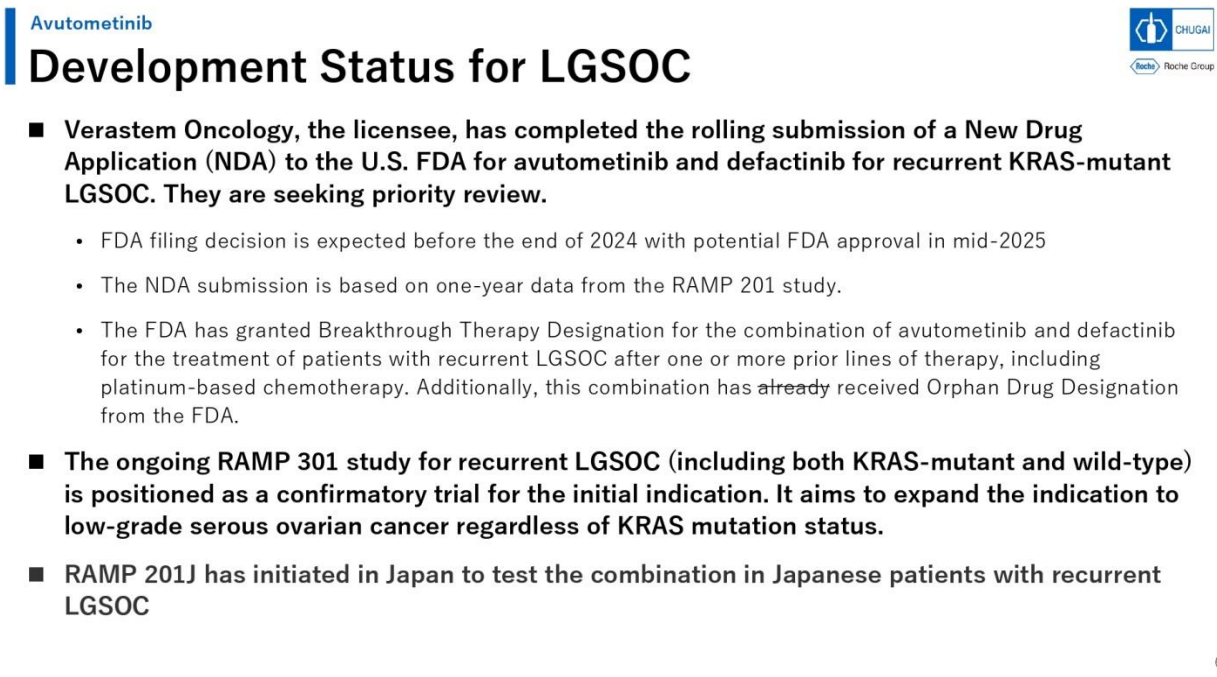
This is a comparative Phase III study currently underway following the results of the Phase II study.

The RAMP301 trial is a randomized, Phase III trial comparing avutometinib in combination with defactinib and an investigator's choice of treatment, assigned 1:1 to patients with confirmed low-grade serous ovarian cancer.

This will be evaluated as the primary endpoint in terms of progression-free survival by central review, which is currently underway.



Here is a summary of developments for low-grade serous ovarian cancer. The rolling submissions to the US FDA for avutometinib and defactinib for the treatment of KRAS mutation-positive recurrent low-grade serous ovarian cancer were completed as of October 31 by Verastem Oncology, the licensee. And we are hoping for a priority review designation.

We expect to know by the end of this year whether this application will be accepted or rejected by the FDA. We have heard that FDA approval is expected to be possible in the middle of next year.

Regarding the RAMP201 study that I just presented, the application for approval is being conducted based on one-year data.

The FDA has already granted Breakthrough Therapy designation for the combination of avutometinib and defactinib for the treatment of recurrent low-grade serous ovarian cancer with one or more prior therapies, including platinum-based chemotherapy. A review is now underway for this.

The RAMP301 study of recurrent low-grade serous ovarian cancer, including both KRAS mutation-positive and KRAS mutation-negative patients, which I indicated earlier that we are currently conducting a Phase III study, is positioned as a confirmatory study for the initial application. We are seeking to expand the indication to LGSOC with and without KRAS mutations.

Furthermore, both the RAMP201 and 301 studies shown so far were conducted only overseas. For introduction in Japan, the RAMP201J study is currently being conducted in Japan to evaluate combination administration for low-grade serous ovarian cancer. Based on these results, Verastem will proceed with development in Japan.

That is all from me.

Miyata: Thank you very much for your attention.

Question & Answer

Miyata [M]: I will now move to the question-and-answer session. We apologize for the inconvenience, but in order to encourage more people to ask questions, we would appreciate your cooperation in limiting the number of questions to two per person. Please note that the audio of your questions will be posted on our website at a later date, along with the presentation.

Hashiguchi [Q]: My name is Hashiguchi from Daiwa Securities. The first question is about your future development policy for inavolisib in Japan. The INAVO 120 study has already been completed and the 121 and 123 studies have already begun. Under these circumstances, what kind of clinical trials do you expect to conduct in Japan in the future, and when do you think you can aim for approval for each indication?

Habara [A]: Thank you for your question, Mr. Hashiguchi. We are currently discussing the development of inavolisib with the regulatory authorities. At this point, there are some products that are eligible to participate in the global Phase III trials that are currently underway and some that are not.

Therefore, I cannot give you any details at this time. However, we will actively participate in global trials in which we can participate, and we will also consider the domestic and international market environment and competitive products, and invest where we should.

Hashiguchi [Q]: Is it possible for you to comment here on which studies you might be able to participate in the middle of?

Habara [A]: I believe that there is still a good chance that we will be able to participate in the 123 study, as this is in the process of starting the site activation. Since some progress has been made on studies 121 and 122, we believe that this needs to be scrutinized.

Hashiguchi [Q]: Thank you very much. My second question is about the concept of how you should make decisions about whether or not to introduce Roche's products.

Although I don't think it is very good to discuss only the results, I wish you had made the decision to introduce inavolisib a little earlier as a result. But on the other hand, there is a natural possibility that a too-early decision could lead to more failures. What are the criteria and what kind of discussions do you currently have at your company to make decisions?

Recently, I believe there have been various regulatory changes in Japan, such as not necessarily requiring Phase I trials in Japanese in order to eliminate drug-lag loss. I would also appreciate your comments on whether or not such changes could have impacts on your strategy in the future.

Habara [A]: Thank you. As I mentioned earlier, we will evaluate whether or not our business is viable by looking at changes in the internal and external environment, and we will propose the introduction of inavolisib if it meets our criteria.

Looking back to that time, we were developing AKT inhibitors at that time. There were also concerns about cannibalization in the market, and market opportunities. We have been evaluating the limited data available, and we have been constantly updating what points we should clear as milestones to move forward and asking for opportunities.

There is also the idea of skipping PI in the future, but again, this is considered on a case-by-case basis, especially for anticancer drugs. We believe that it is necessary to reconcile our ideas with those of the

regulatory authorities, always seeking opportunities for consultation and scrutiny so that we can deliver our products to patients as quickly as possible.

Since the government has indicated such a view, we believe that the industry as a whole is definitely moving in a positive direction.

Hashiguchi [M]: Thank you very much.

Wakao [Q]: My name is Wakao from JPMorgan. Thank you for your explanation.

First, I would like to ask why giredestrant can be best in class. With regard to giredestrant, I believe you explained that the primary endpoint of the acelERA trial did not reach statistical significance. On the other hand, I think AstraZeneca's camizestrant data was solid in the Phase II trial.

In light of this, even with its high potency and potential, camizestrant looks better clinically at this point. If there are any points that you are assuming it will still be best in class, could you please let us know?

Habara [A]: Thank you for your question. Expectations for best-in-class, as you pointed out, are because of the high potency in non-clinical studies.

In addition, as you pointed out earlier, it is quite possible that camizestrant will look better when compared to giredestrant in overseas Phase II trials at this time. Ultimately, we will have to wait and see the results of the global Phase III trial before making a decision, but at this point, based on non-clinical data, we consider this to be best-in-class.

You also mentioned that camizestrant had good results in a Phase II trial. While the acelERA study did not show statistical significance in that sense, it did so at least firmly with ESR1 mutations. So, at this point, we still have hope, because the signal has been shown, although it was not met in all comers ITT in the nonclinical data and the acelERA study.

Wakao [Q]: Thank you very much. How do you interpret the factors behind the fact that it did not statistically meet the primary endpoint in Phase II?

Habara [A]: Regarding the factors, the scope of the patient population is a little different from the camizestrant when you look at the details, so I believe the background of the patients enrolled in the study may also be a factor. Further analysis is still quite difficult, and it is difficult to say without seeing the results of the Global PIII studies.

Wakao [Q]: Okay, thank you very much. I would like to know one more thing briefly. I think the development of the KRAS G12C inhibitor is well underway.

Since your LUNA18 is a RAS inhibitor, I think there is some overlap. Is it safe to consider them as independent? Since there is an overlap, could this affect the development plan for LUNA18 if there is something that precedes it in your company?

Kusano [A]: Thank you for your question, Mr. Wakao.

We are developing LUNA18, a pan-RAS inhibitor drug. As you just pointed out, we will first proceed with the development of each drug separately. However, the one I have shown you is KRAS G12C and the other drug is pan-RAS, and I believe that combination therapy is possible.

For example, if pan-RAS is administered together with KRAS G12C after resistance has developed with KRAS G12C, the effect may be improved. We also believe that there may be a possibility of further improving the

efficacy of the product by using it in combination. We would like to consider various options as we move forward.

Wakao [M]: I understood that having two is not a negative thing. Thank you very much.

Miyata [M]: Thank you very much. Mr. Mamegano of BofA Securities, could you ask your question?

Mamegano [Q]: My name is Mamegano from BofA Securities. Thank you for the opportunity to ask you a question. This may overlap with what Mr. Wakao just asked; based on the data so far on divarasib, I feel that it is quite promising, and I think your company is probably confident enough to do a second-line superiority study. I believe that various other compounds are being considered in the first line.

I am sure that this is being considered, of course, but can you tell me if that consideration includes LUNA18, etc., or is it being considered in conjunction with a second line?

Company Representative [A]: Thank you for your question. Regarding divarasib, as you pointed out, other competing products are currently being developed for first-line treatment of *KRAS G12C* mutation-positive non-small cell lung cancer. As Mr. Kusano mentioned earlier, we are in the process of considering various development options, including the option you have mentioned.

I will refrain from providing details at this time and will reply that we are considering it. I hope that answers your question.

Mamegano [Q]: Yes, thank you. Let me ask you two more questions.

First, two bispecific antibodies, glofitamab and mosunetuzumab, have been developed for blood cancers. By having these two drugs, how did you decide on the use or the development policy?

As for mosunetuzumab, I think there are quite a lot of trials being done for after the second line. What is your opinion on the optimal allocation of treatment lines for these two drugs? We can know from the results how you are doing it, but can you tell us what characteristics are the reasons for this development?

Hashizume [A]: Thank you for your question. First, glofitamab is already approved and marketed as a single agent for third-line DLBCL in the US and Europe. We knew from the beginning of the development that glofitamab was highly effective as a single agent, and we wanted to develop it first for more aggressive DLBCL.

This is an intravenous formulation, but other drugs for first-line treatment are intravenous as well. So, we are making the decision to develop a stronger glofitamab for untreated DLBCL, as we believe that the disadvantages of IV will not be felt as much when comparing subcutaneous and intravenous infusion.

On the other hand, the development of mosunetuzumab for intravenous and subcutaneous injection had started at the same time. So, as I mentioned earlier, we are developing treatment mainly for follicular lymphoma, because the subcutaneous injection formulation would be of great benefit to patients with follicular lymphoma, for whom the treatment would last for five or 10 years.

For relapsed or refractory aggressive non-Hodgkin's lymphoma, we have developed a unique combination with Polivy, which has been shown to be quite effective and has been presented at previous conferences. We believe that mosunetuzumab is valuable not only for its efficacy but also for its convenience.

Mamegano [Q]: Thank you for your very clear explanation. Finally, I have a question regarding inavolisib.

The concomitant medications used are palbociclib and fulvestrant, and I believe the label also binds such concomitant medications.

However, looking at the strength of CDK4/6 inhibitors, I understand that other CDK4/6 inhibitors such as Verzenio and Kisqali are improving OS and will be used in the future.

Is the combination of inavolisib with other CDK4/6 inhibitors likely to be considered? Or will you be working only with palbociclib?

Habara [A]: Thank you for your question. As you pointed out, as for CDK4/6 inhibitors, the market share of abemaciclib is larger than that of our product in Japan. We recognize that this is due to the fact that the OS data of this exceeds that of palbociclib.

Overseas, ribociclib has also gained considerable market presence, although it is not approved in Japan. As you pointed out, considering the medical field, we believe that among CDK4/6 inhibitors, a situation will arise where it will be difficult to use palbociclib alone. In that sense, the current 120 trial is in combination with palbociclib, but we are considering other any CDK inhibitors for other trials with revised protocols and those that are about to start site activation and patient enrollment.

Mamegano [M]: Thank you very much.

Miyata [M]: Thank you very much. Mr. Wada of SMBC Nikko Securities, could you ask your question?

Wada [Q]: I am Wada from SMBC Nikko Securities. Thank you very much. Regarding the picture of RAF/MEK and FAK inhibitors on page 58, I was a bit doubtful when you mentioned that the resistance mechanism occurs with FAK. Isn't it conceivable that the same feedback mechanism could cause resistance in KRAS?

I think KRAS is basically used as a single agent now. I would like to know if there are any signaling pathways that are being considered as candidates for combination drugs.

Iwasawa [A]: As you say, KRAS is also a major factor in the RAS/MAPK pathway, mainly a major factor in the RAS. Therefore, the same resistance mechanism as illustrated here is expected.

This figure may be a little confusing, but when the RAS is inhibited, the downstream is indeed inhibited, but several feedback mechanisms work there. It is assumed that these resistance mechanisms will work in the same way. Therefore, I am sure that you are correct in your perception.

Wada [Q]: I think the receptor kinase is also activated and a feedback mechanism is applied. I wanted to ask if you are considering using it in combination with that, including RAF/MEK inhibitors.

Iwasawa [A]: Thank you. Strictly speaking, its target is different from that of KRAS inhibitors. Regarding the combination with other drugs, the RAMP203 study for non-small cell lung cancer, which is in the middle of the list of clinical trials on page 59, is for non-small cell lung cancer with KRAS mutations. The study is conducted in combination with a KRAS G12C inhibitor Sotorasib, which is already approved in Japan.

However, we do not have information on other drugs at this time. I hope this is an answer to your question.

Wada [M]: Yes, I understand. That is all, thank you very much.

Miyata [M]: Thank you very much. Mr. Yokoyama of Nikkei BP, could you ask your question?

Yokoyama [Q]: I would like to ask you two questions.

The first question I would like to ask is about the oral SERD. The results of EMBER-3 were released at the recent San Antonio Breast Cancer Symposium, and Imlunestrant is met in Phase III, in which Japanese facilities are participating. Please tell us how your company's products will compete with this.

Habara [A]: Thank you for your question.

As you noted, the EMBER-3 results were presented during the recent San Antonio Breast Cancer Symposium. We are aware that discussions with the review authorities will begin in the future, so it will depend on the outcome of those discussions.

It will be interesting to see what the label will be from that perspective. It is difficult to say at this time about our giredestrant strategy.

But on the other hand, we also gained confidence from that result. The hazard ratio was solid, especially in the effect of ESR1 mutation in monotherapy. In this sense, we are aware that the design is similar to our evERA study, and we are confident of the probability of success at this point.

I hope you understand that I am unable to discuss the strategy now.

Yokoyama [Q]: I understand. Secondly, I think inavolisib is contingent on testing for the PIK3CA gene mutation. Also, I believe that if the oral SERD was for ESR1 mutation positive only, a test would be needed. If so, would the companion diagnostic be FoundationOne?

Habara [A]: Thank you for your question.

Regarding inavolisib, the primary CDx in the INAVO120 study testing PIK3CA mutation is FoundationOne Liquid CDx. Another thing about giredestrant and ESR1 mutations, ctDNA and FoundationOne Liquid CDx are also prepared as primary CDx.

With that in mind, as you know, we will be testing for inavolisib specifically from the first line, considering the various limitations of insurance reimbursement for cancer gene panel testing. From this perspective as well, we would like to prepare for the development of CDx so that patients will not be unable to access it.

Yokoyama [M]: I understand. Thank you very much.

Sogi [Q]: Thank you very much. I have a question regarding avutometinib. The Company has licensed out this as well, so am I correct in understanding that your company is not actually involved in the development of this product?

Iwasawa [A]: You are right. Verastem Oncology is conducting the development and we are not involved in the development.

Sogi [Q]: I understand. So, you may not be able to disclose this; is it correct to understand that regulatory milestone, commercial milestone, and royalty will be added to your company's financial results in the future?

Iwasawa [A]: As you mentioned, basically, we have signed the contract of licensing-out, and there is also a royalty agreement, so it is as you mentioned.

We cannot disclose milestones, etc.

Sogi [Q]: Am I correct in understanding that your company does not manufacture this product?

Iwasawa [A]: Yes, you are correct.

Sogi [Q]: I understand. I'm not sure if this question is appropriate since you are all development people. I understand that your monoclonal antibodies and mid-size molecular modalities are technology-based drug discovery engines. What is your company's strategy for drug discovery for small molecules?

Kusano [A]: Thank you for your question, Ms. Sogi.

As you know, we have three major pillars of business: antibodies, mid-size molecules, and small molecules. Each of them focuses on diseases with high unmet needs and the development of transformative drugs.

Research and drug discovery will continue with regard to small molecules.

Sogi [M]: I understand. Thank you very much.

Sakai [Q]: My name is Sakai from UBS Securities. I am sorry to drop the level of questions so suddenly, but perhaps this question should be asked to Mr. Kusano. What was the purpose of choosing this portfolio for today's agenda?

In other words, do you want to appeal to the fact that there is so much unmet? Or, as this includes some of Roche's, do you want to show how much CHUGAI can contribute to Roche's anti-cancer and oncology strategy?

Without that fundamental information, I am not sure how we can take this portfolio back to our company and digest it, and communicate it to investors. I may have this question because my level is low. I would very much appreciate it if you could suggest something.

Kusano [A]: Thank you, Mr. Sakai.

Of course, it is difficult to say which one is the best, and we would like to introduce all of them if I could, but time is limited. So, we have made a few introductions regarding what we think you might be very interested in and what we think we will soon see results from.

If it is too early and still needs more time, there will be another opportunity. Therefore, we have tried to focus on those that are of interest to those who are listening and for which applications for approval we believe are quite close to being made.

Sakai [Q]: I understand. I have one more question about avutometinib. I think you are talking about developing this because it is now working for high-grade serous ovarian cancer but not for low-grade. I would like to ask why it is not very effective for low-grade.

Also, if you get to non-small cell lung cancer, the marketability will be quite high. Does your company handle this solely domestically? Please let me know about right-related relationships.

Iwasawa [A]: First of all, the target is the low-grade ovarian cancer.

One reason is that the low-grade has a higher unmet medical need and a higher frequency of KRAS mutations. Compared to high-grade, though. In addition, since cytotoxic chemotherapy, conventional chemotherapy, may be effective in treating high-grade cancer, the focus of development is on low-grade cancer.

You mentioned high-grade and low-grade in reverse, but you are right that high-grade is not the target of development.

With regard to non-small cell lung cancer, this development is also for KRAS mutations. Therefore, the targets are limited even among non-small cell lung cancers to some extent. However, this is currently under development and the results of its efficacy and safety are not yet available, so we cannot provide details at this time. We are unable to answer about royalties and other contracts at this time.

Sakai [M]: I understand. Thank you very much.

Miyata [M]: Thank you very much.

Yoshimizu [Q]: My name is Yoshimizu from Pharmaceutical Economics. Let me ask Mr. Kusano. As the first person asked, there are various changes in pharmaceutical regulations, such as the omission of Phase I study. Any comments on the resulting changes in development and implementation strategies from an overall perspective?

Kusano [A]: Thank you for your question.

Mr. Habara has already answered this question. I believe that the authorities have made considerable changes to the regulations regarding the handling of Phase I, based on various advanced opinions. On the other hand, we are still hearing opinions that the safety of anticancer drugs and new modalities should be thoroughly confirmed in Japanese patients.

As a matter of fact, CHUGAI has been talking with the authorities quite a bit before this move was made, and we have had the experience of omitting Phase I for Japanese patients when possible and starting with Phase II.

We will continue to consult with the authorities on the character of each drug and what data is currently available, and I am sure that our strategy will remain the same, skipping Phase I for those drugs that can be skipped.

However, recent moves by the authorities suggest that we have risen a little in the ranks of ease of development.

Yoshimizu [M]: I understand very well, thank you. That is all.

Miyata [M]: Thank you very much. Next, Mr. Mizuno of Tokio Marine Asset Management.

Mizuno [Q]: Thank you very much.

I have two questions. You gave a presentation on T-cell engagers, and I think the following question was touched on at that time. If these two T-cell engagers are approved with the expected profile, what are the possible scenarios in which CAR-T is still chosen by medical institutions in Japan that are currently able to provide CAR-T therapy?

In short, can you tell us if there are aspects of T-cell engagers that you think are not competitive with CAR-T?

Hashizume [A]: CAR-T has an access challenge in that it is currently being treated in less than about 10% of the facilities that provide hematological treatments in Japan. In such a CAR-T facility, will this T-cell inducible T-cell bispecific antibody be used, and if so, in what kind of cases?

CAR-T was developed earlier, so there are long-term follow-up data, and I think this may be a weakness of our T-cell bispecific antibody. However, although we have a disadvantage in terms of long-term follow-up data at this point, I believe that the data gap will be filled in the future as the drug is launched and used in the market. So, from that perspective, one of the first things to consider in terms of effectiveness is that in the long run, T-cell engagers will be widely used in CAR-T facilities.

In terms of safety, immunological neuropathies such as cytokine release syndrome and ICANS occur with both CAR-T and T-cell engagers, but the frequency and severity of these disorders are said to be higher with CAR-T than with T-cell engagers. From this perspective, we believe that T-cell engagers have the advantage in terms of safer, off-the-shelf use.

Mizuno [Q]: I understand very well. Thank you very much. One more question, on page 44, I would like to ask about the status of PIK3CA mutation in breast cancer and the combination study with palbociclib or other CDK4/6, etc., which I believe Mr. Wakao asked about earlier.

CDK2 is included at the bottom of the figure. I understand that Roche recently introduced CDK4 and CDK2 inhibitors as the next generation of CDK4/6. Do you believe that this will be the subject of a combination study in the future? I don't know if you can comment on this.

One more thing, not only for this compound, but in general, for the stage of in-licensing by your company from Roche, I understand that there is no fixed milestone, such as the completion of Phase I or Phase II, but the decision is made after considering various comprehensive factors such as marketability and the promise of the clinical trials. Is this correct?

Habara [A]: Thank you for your question. As for CDK2, Roche has recently introduced one. We are also aware that there are several other CDK inhibitors in development.

From that perspective, and this is just my personal opinion, we need to consider what kind of drugs should be used in combination considering the algorithm in the future. As I mentioned earlier, the drugs on the market today are palbociclib, abemaciclib, and overseas, ribociclib. In general, those in charge of development will evaluate a product's profile from such a perspective as far as they can see, and then consider what drugs to use in combination with it, or how to respond to future changes in the algorithm.

Regarding the second point, the timing of the introduction is as I mentioned at the beginning. We do not have a specific stage in mind. We will propose and evaluate the introduction of new products at the appropriate time from a comprehensive, multifaceted perspective, taking into account the internal and external environment, and whether there is a high unmet need in the area, as well as whether the business is viable.

Mizuno [M]: I understand very well. Thank you very much.

Miyata [M]: Thank you very much. As the scheduled time has arrived, we will now conclude the Q&A session.

This concludes the CHUGAI R&D Meeting. If you have additional questions, please contact the Corporation Communications Department. The phone number and email address are listed on the last page of the presentation material.

We have a questionnaire on the table for those in the audience, and on Zoom for those participating via Zoom. We would appreciate your cooperation in this regard for future reference.

Thank you very much for taking time out of your busy schedule to join us today.

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