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CHUGAI PHARMACEUTICAL CO., LTD.

A member of the Roche group

CHUGAI PHARMACEUTICAL CO., LTD.

Information Meeting on Lunsumio

March 24, 2025

Event Summary

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[Participants]	

[Number of Speakers]	3	
	Dr. Kenichi Aoki	NHL Lifecycle Leader
	Dr. Dai Maruyama	Department of Hematology Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research
	Kae Miyata	Head of Corporate Communications Department
[Analyst Names]*	Seiji Wakao	JPMorgan Securities
	Kazuaki Hashiguchi	Daiwa Securities
	Fumiyoshi Sakai	UBS Securities
	Shinichiro Muraoka	Morgan Stanley MUFG Securities
	Miki Sogi	Sanford C. Bernstein

*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

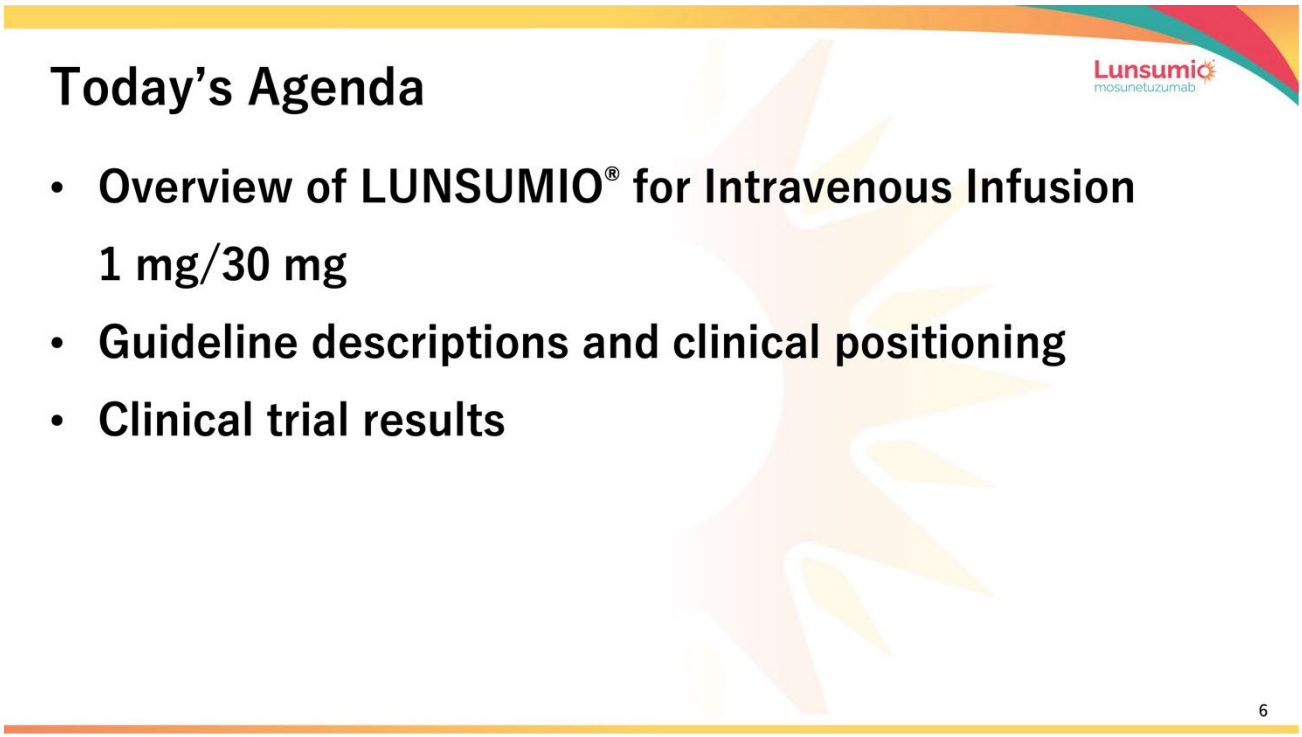
Miyata: Thank you very much for attending today's briefing on antineoplastic agent/humanized anti-CD20/CD3 bispecific antibody, Lunsumio despite your busy schedule. I'm Miyata from the Corporate Communications Department, and I will be your facilitator today. Thank you for your cooperation.

Today's event is held on an on-site basis and also distributed on a Zoom webinar basis at the same time. The agenda for today's meeting is shown on the venue screen, on the web screen and on the third page of the presentation materials. I will explain the contents accordingly.

Today we have a special lecturer, Dr.Dai Maruyama, MD, PhD, Chief of Department of Hematology Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research. We have already sent you Dr. Maruyama's biography along with today's presentation materials, so due to time constraints, we will skip the introduction of his biography at this time. Please note that there will be time for screen capture before each presentation.

Questions will be taken after all presentations have been completed. The Q&A session is expected to last 30 minutes, so we hope you will be proactive and ask questions. Please note that your audio will be muted during the presentation.

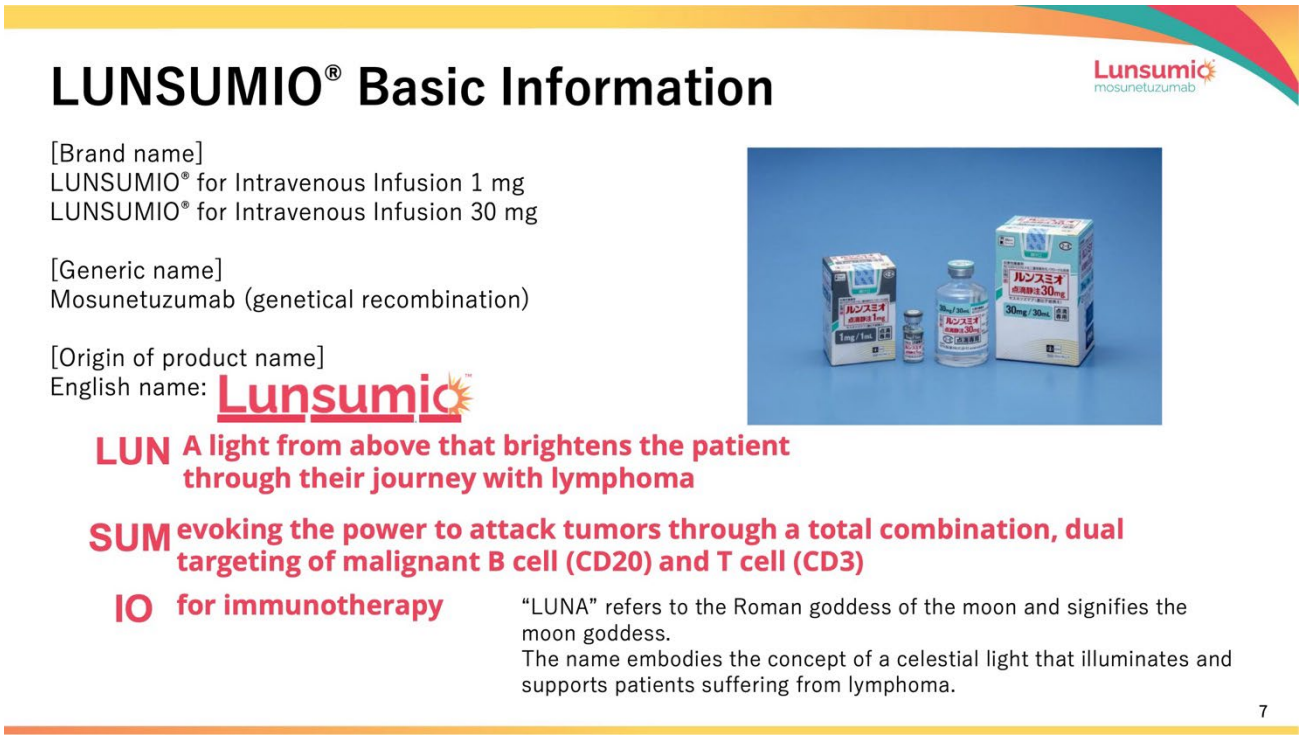
Now, Dr. Aoki, NHL Lifecycle Leader of Chugai will give an overview of Lunsumio. There will be a short pause at the beginning, so if you would like to take a screen capture, please use this opportunity. Thank you.



Aoki: Thank you very much for taking your time to join us today. My name is Aoki, and I am responsible for the entire lymphoma field. I would like to introduce the product outline of Lunsumio, which was launched on March 19 for relapsed or refractory follicular lymphoma. Before I begin, I would like to show you a key visual video that we have created for Lunsumio. I have just played the key visual video. How did you find it? In fact, we at Chugai have created this video with some essence of our thoughts and expectations for Lunsumio.

To sum up the essence of this, we have created this video with the hope that this newly developed Lunsumio will be like a ray of light from heaven for patients suffering from lymphoma, and in particular, for those suffering from relapsed or refractory follicular lymphoma, which becomes a new indication this time.

Lunsumio has several advantages and points that can contribute to patients that meet their expectations. The content of this presentation is a summary of our product, and it also includes the content that Dr. Maruyama will explain later, so I have sprinkled in the essence of this information, and I hope that you will be able to feel the essence of it as you go through this presentation.

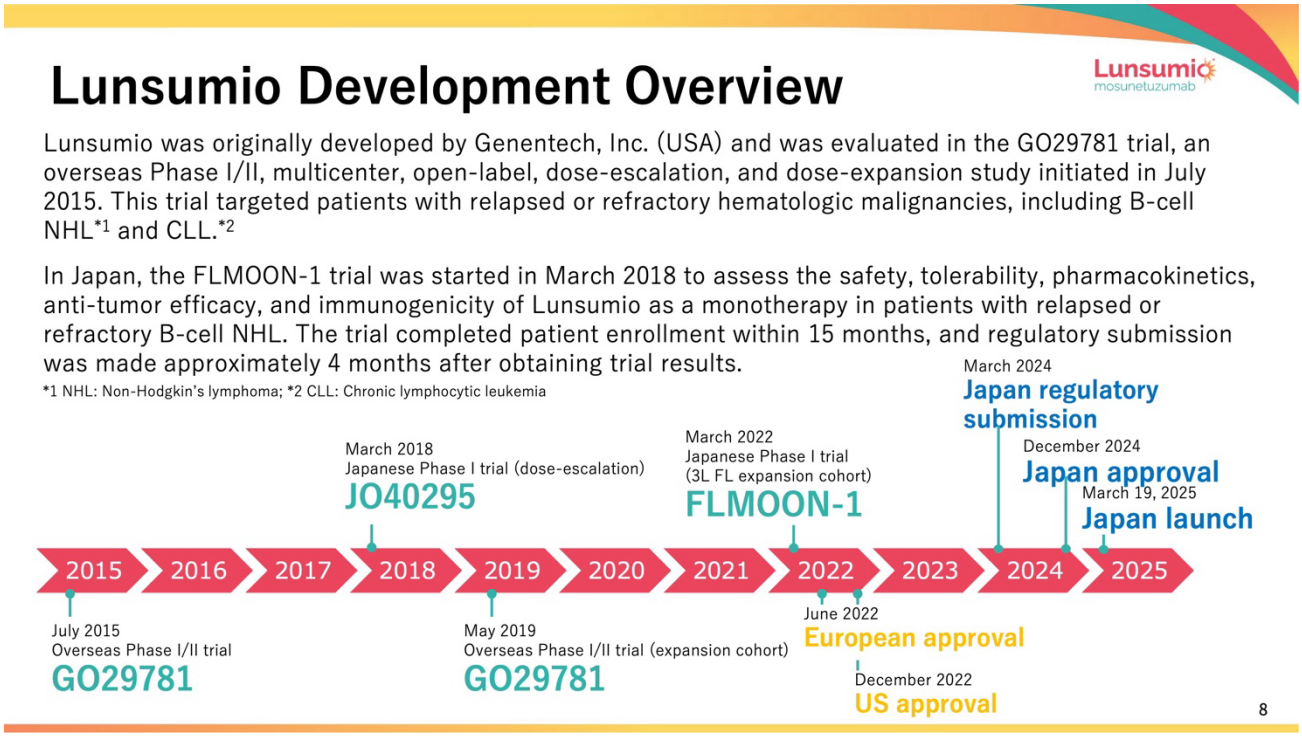


I will provide basic information and a product overview. First, Lunsumio, with the generic name mosunetuzumab, is now available in two dosage forms. Which is in the forms of 1 mm and 30 mm.

Let me briefly introduce the origin of the name of this Lunsumio, which is made up of three parts, LUN, SUM, and IO. As I mentioned earlier, the name LUN was taken from the Roman goddess of the moon, LUNA, so that we can always be a light that is close to patients suffering from follicular lymphoma.

And as for SUM, Chugai and the Roche Group have been studying lymphoma for 30 years and have provided innovative medical treatments using antibodies such as Rituxan, Gazyva, and Polivy. This time, LUNSMIO is a combination of CD20 and CD3, which means that it is possible to perform immunotherapy by adding CD3 to the target we have been targeting so far, CD20.

And above all, this Lunsumio is named Lunsumio taken from an immunotherapy, IO, that destroys tumors using the patient's own immune system.



Lunsumio was discovered by Genentech, a subsidiary of Roche, and overseas Phase I and Phase II clinical trials started 10 years ago in 2015. In Japan, as you can see here, a domestic Phase I trial started in March 2018.

We initially envisioned a Phase II study as a cohort study to confirm safety and efficacy in the Japanese population, but after negotiations with the authorities, we have started FLMOON-1 as an expansion cohort of Phase I.

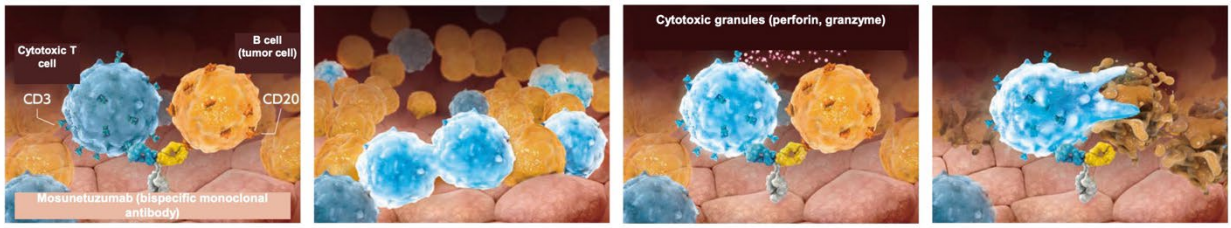
As you know, we were in the midst of the COVID-19 situation in 2022, and it was difficult to proceed with clinical trials, but we achieved the target number of patients in 15 months and filed for approval in four months after the data lead out, which was a whole team effort.

Mechanism of Action of Lunsumio (Mosunetuzumab)

Lunsumio mosunetuzumab

- Mosunetuzumab is a bispecific monoclonal antibody targeting CD20 and CD3.
- CD20 is a cell surface antigen expressed on nearly all B-cell lymphomas, except for pro-B cells and plasma cells.
- Mosunetuzumab is thought to bind to CD3 expressed on T cells and CD20 expressed on B-cell tumors, thereby activating T cells and damaging CD20-positive tumor cells.

Illustrative diagram



1. Mosunetuzumab simultaneously binds to T cells and B cells (tumor cells).
2. Cytokine release mobilizes T cells from the periphery.
3. T cells proliferate at the tumor site.
4. T cell activation triggers downstream signaling and the release of cytotoxic granules such as perforin and granzyme.
5. Tumor cell lysis and apoptosis are induced.

Illustrative diagram

1) Chen DS, et al. Immunity. 2013; 39(1): 1-10. [Conflict of interest: The authors include Genentech employees.]
2) Dieckmann NM, et al. J Cell Sci. 2016; 129(15): 2881-2886.
3) Sun LL, et al. Sci Transl Med. 2015; 7(287): 287ra70. [Conflict of interest: This study was conducted with support from Genentech. The authors include Genentech employees.]
4) Thiery J, et al. Nat Immunol. 2011; 12(8): 770-777.

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I would like to briefly introduce the mechanism of action of Lunsumio. Lunsumio is an antibody drug that has two targets, CD20 and CD3. Once inside the body, Lunsumio binds to B-cell tumors that express CD20, and then binds to cytotoxic T cells, while the T cells induce other T cells. In addition, these injurious T cells destroy B cells while releasing perforin, granzyme, and other substances. We are pleased to announce the launch of this innovative drug.

Indications, Dosage, and Administration

Lunsumio
mosunetuzumab

[Indications]

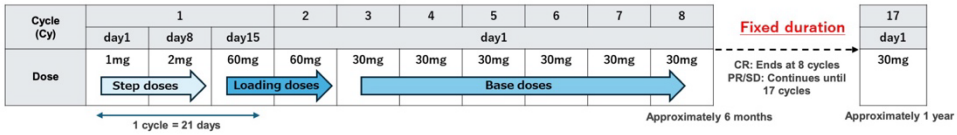
Relapsed or refractory follicular lymphoma

Precautions related to indications

This treatment is intended for **patients who have relapsed or failed to respond to at least 2 standard therapies**, including an anti-CD20 monoclonal antibody.
The drug should be administered to patients diagnosed with Grade 1–3A follicular lymphoma by a pathologist with sufficient experience.

[Dosage and administration]

For adults, mosunetuzumab (genetical recombination) is administered intravenously in 21-day cycles. In the first cycle, 1 mg is administered on Day 1, followed by 2 mg on Day 8 and 60 mg on Day 15. In the second cycle, 60 mg is administered on Day 1. From the third cycle onward, 30 mg is administered on Day 1 of each cycle, continuing up to the eighth cycle.
At the end of the eighth cycle, treatment is discontinued for patients who achieve complete response (CR). However, patients with stable disease (SD) or partial response (PR) continue treatment for up to 17 cycles.



***Fixed duration is a treatment approach developed by Chugai Pharmaceutical, embodying its unwavering commitment to supporting healthcare professionals and patients in the fight against lymphoma over many years.**

CR: complete response, PR: partial response, SD: stable disease Lunsumio for Intravenous Infusion 1 mg/30 mg Electronic Package Insert, Created in December 2024 (Version 1)

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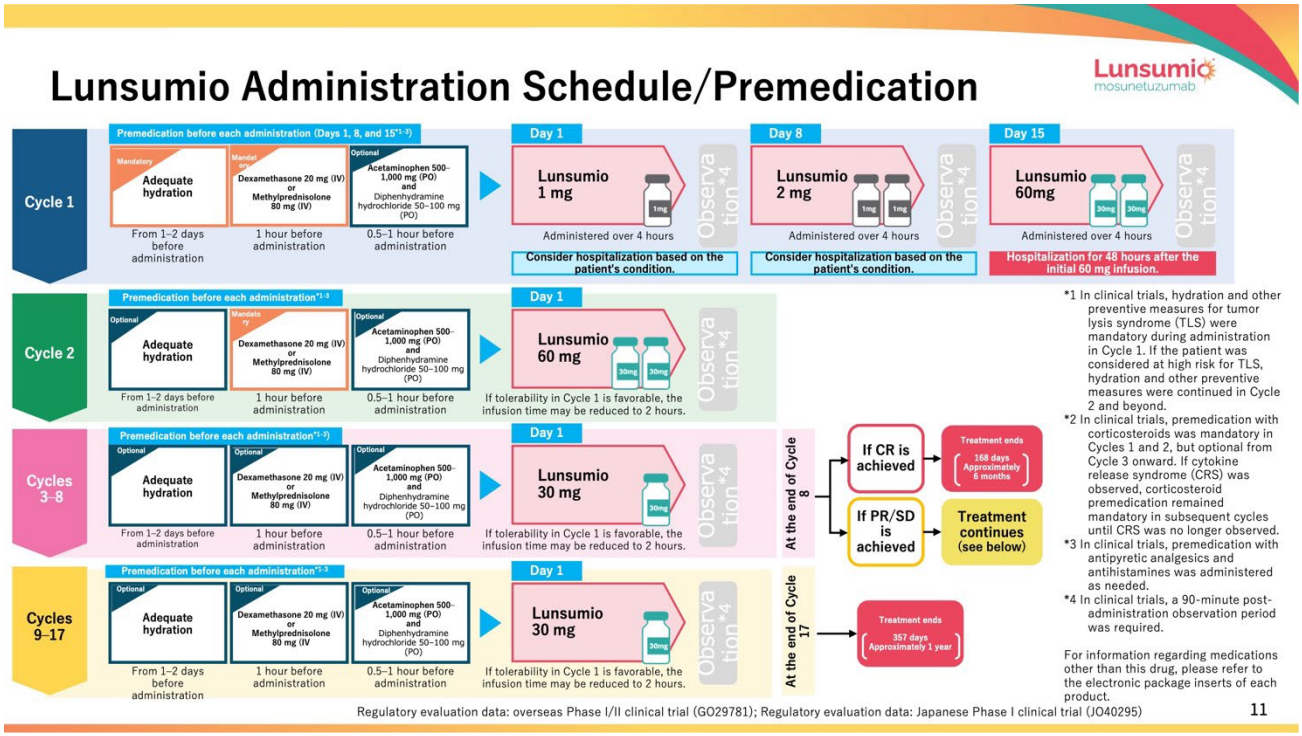
Next, we will introduce the efficacy and effects, as well as the dosage and administration. The efficacy and effects for which the drug has been approved is follicular lymphoma that has failed two or more standard therapies or has relapsed after such therapies. In other words, patients with third line or later follicular lymphoma are eligible.

In terms of dosage and administration, as is the case with T-cell engagers, other bispecifics, and CAR-T therapy, which are mediated by T-cells, there are specific adverse events associated with T-cell engagers, the most common of which is cytokine release syndrome, and in order to reduce these, we have a three-phase step-up dosing administration schedule.

Another of Lunsumio's most important features is the Fixed Duration, which is written in red here. For patients who achieved a complete response or CR during treatment, treatment was completed after eight cycles. Patients whose disease has stabilized or who have achieved a partial response, SD or PR, can complete treatment after 17 cycles, or about one year. This is the greatest feature of Lunsumio.

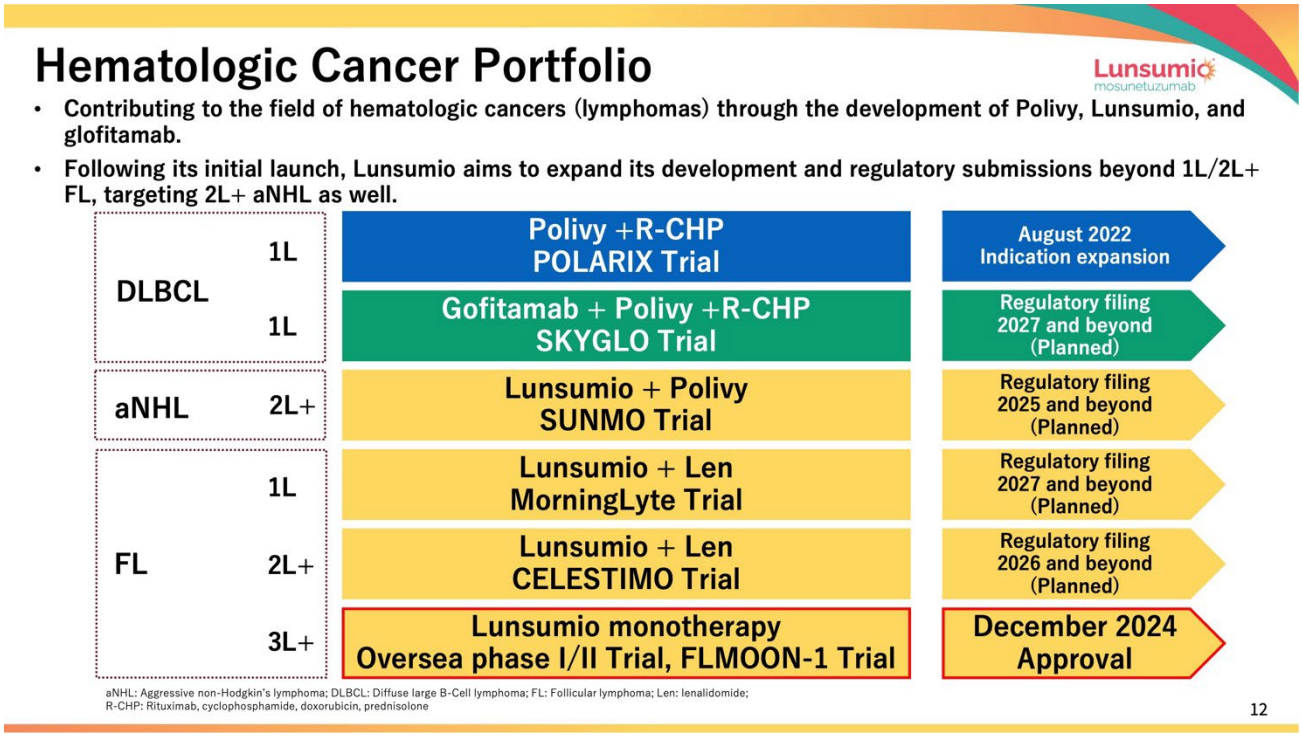
I think there is a question as to why we have been developing this treatment without continuing it until the cancer has worsened so much. However, it is precisely because we at Chugai and the Roche Group have been fighting lymphoma for 30 years together with doctors and cancer patients, including Dr. Maruyama who is just next to me, that we have developed this Fixed Duration as a non-negotiable commitment.



This is a detailed schedule. For Cycle 1, in order to suppress the immunological adverse events mentioned earlier, we ask that patients take corticosteroids, antihistamines, and antipyretics as premedication, and then take 1 mm or 2 mm on days one and eight, which are low doses but can demonstrate tolerability and efficacy, and then take 60 mm on Day 15, which can demonstrate maximum efficacy. In addition, the second cycle should be administered in the same manner with 60 mm.

The possibility of CRS occurring at this time is high, so we have decided to admit patients to hospital on Day 15 as instructed by the authorities.

After the third cycle, we will enter the base dose phase of Lunsumio, in which we will administer 30 mm. For those who have confirmed CR up to eight cycles, administration ends here. The treatment is completed in approximately six months. Patients with PR or SD will receive up to 17 additional cycles, at which point the treatment will be terminated.

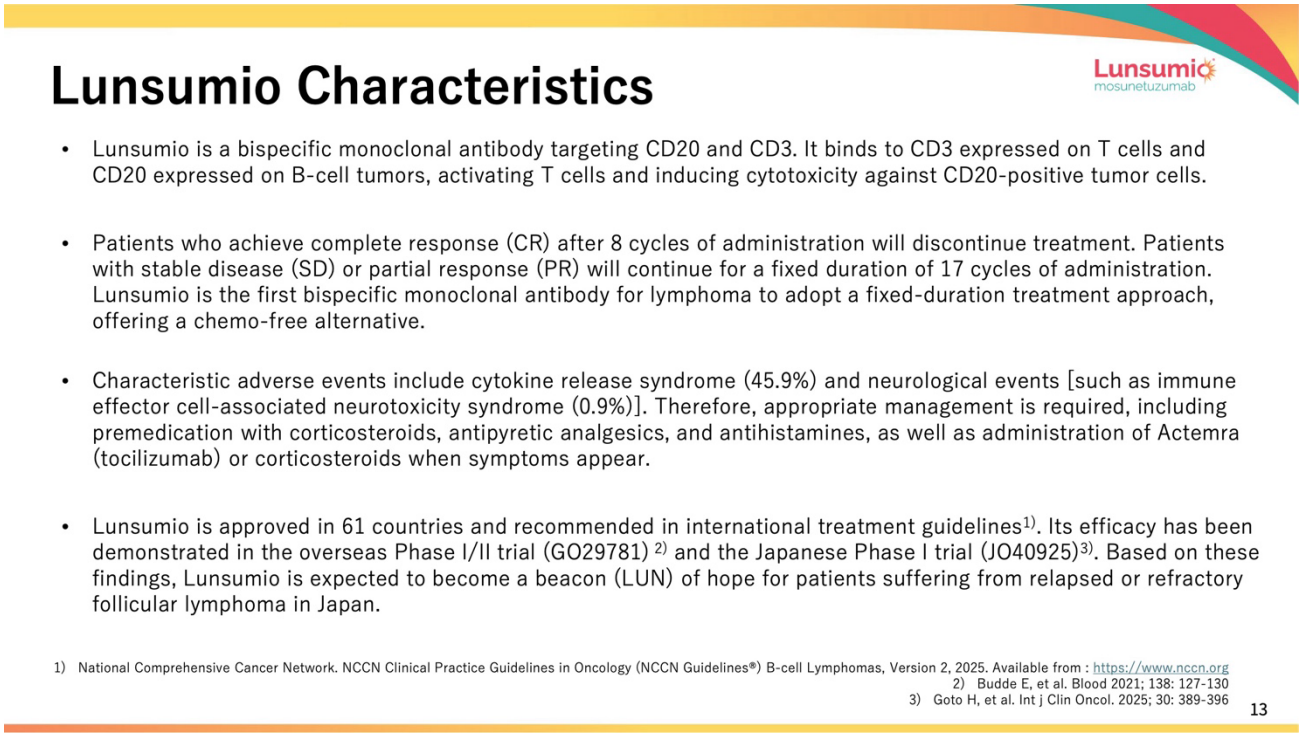


The approval we have acquired this time is for the single-agent Lunsumio, which is listed at the bottom of the page, for use in the third line and beyond for follicular lymphoma.

However, this is not the end of administration of Lunsumio. As you can see here, we are currently conducting Phase III international joint clinical trials for follicular second-line and first-line treatments, and we are also conducting international joint clinical trials for the combination of Lunsumio and Polivy in aggressive Non-Hodgkin's lymphoma.

In addition to Lunsumio, Chugai and the Roche Group also have a similar bispecific antibody called glofitamab. Regarding this, a clinical trial is currently underway using a combination of many drugs, including the first-line drugs glofitamab, Polivy, and R-CHP.

In this way, Chugai, and the Roche Group, hopes to provide new value in this area of lymphoma while offering therapeutic drugs that will become a weapon for patients and doctors alike.



Last but not least, I would like to reiterate the features of this Lunsumio. Lunsumio, a bispecific monoclonal antibody against CD20 and CD3, has generated evidence to date based on the fixed duration I mentioned earlier. Therefore, the main focus of this clinical trial was whether or not the therapeutic effect could be maintained at this fixed duration.

On the other hand, this drug has already been approved in 61 countries and is one of the drugs recommended in foreign guidelines. This is due to the fact that the drug has a high response rate despite its fixed duration, as well as three- and four-year follow-up data, which is supported by the fact that the drug has been approved by doctors in many countries.

Dr. Maruyama will later introduce these data, especially the follow-up data, which we expect to be the most important feature of the next Lunsumio.

As the video mentioned earlier shows, Chugai's hope is that Lunsumio is a drug like a beacon of hope that illuminates' patients, their partners, and their families so that they can stay together forever. This is the end of a product overview from me. Thank you.

Miyata: Thank you for your attention. Dr. Dai Maruyama will continue with an explanation of the clinical positioning of Lunsumio. There will be a short pause at the beginning, so if you would like to take a screen capture, please use this opportunity. Thank you for your cooperation.

A New Treatment Option for Third-line and Beyond for Relapsed or Refractory Follicular Lymphoma

– Lunsumio –

Dai Maruyama, M.D., Ph.D.

Department of Hematology Oncology,
Cancer Institute Hospital,
Japanese Foundation for Cancer Research

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Maruyama: Hello, everyone. Thank you for your cooperation. My name is Maruyama from Cancer Institute Hospital.

I will talk about the clinical trials that formed the basis for the approval of this drug, Lunsumio, or mosunetuzumab, as well as the current situation regarding the treatment of relapsed and refractory follicular lymphoma, including a little about first-line treatment. I will also talk about the issues and current situation regarding the treatment of follicular lymphoma, and how this new drug is positioned and expected to be used. Thank you for your cooperation.

COI Disclosure

Dai Maruyama

Honoraria: Chugai, Mundipharma, Janssen Pharma, Takeda, Eisai, Celgene, Kyowa Kirin, Ono Pharmaceutical, Nippon Shinyaku, Zenyaku Kogyo, BMS, MSD, AstraZeneca, Sanofi, AbbVie, Genmab

Research funding: Chugai, Ono Pharmaceutical, Celgene, Janssen Pharma, Mundipharma, Takeda, BMS, MSD, Otsuka, Novartis, Sanofi, Astellas Pharma, Amgen Astellas BioPharma, AbbVie, Eisai, Genmab

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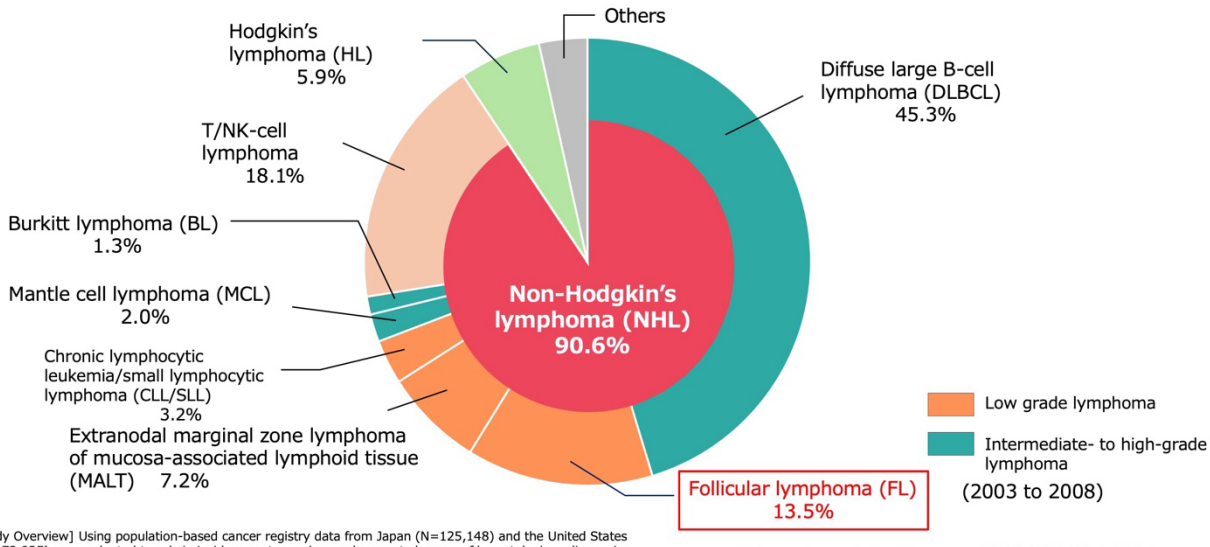
This is COI.

Types of Lymphoma and Proportion of Follicular Lymphoma



[Study Overview] Using population-based cancer registry data from Japan (N=125,148) and the United States (N=172,925), we evaluated trends in incidence rates and annual percent changes of hematologic malignancies (analysis period: 1993-2008).

Chihara D, et al. Br J Haematol 164: 536-545, 2014

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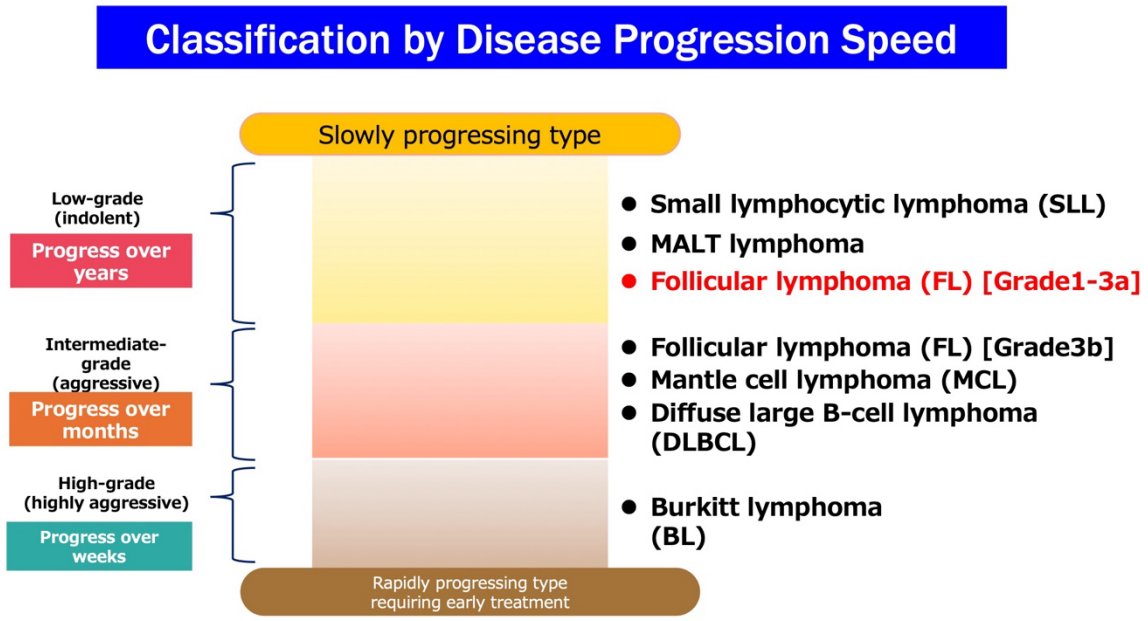
This is the types of lymphoma and the proportion of follicular lymphoma. The disease of lymphoma is divided into several types. B-cell lymphoma accounts for about two-thirds of all lymphomas, but there are several types of B-cell lymphoma, the most frequently occurring being diffuse large B-cell lymphoma, followed by follicular lymphoma. Follicular lymphoma is the second most common type of lymphoma but still accounts for more than 10% of all cases.



Adapted from the Japanese Society of Hematology Clinical Practice Guidelines for Hematologic Malignancy 2024 Edition. Kanehara & Co., Ltd, 2024. http://www.jshem.or.jp/gui-hemali/table.html (Japanese only)(Accessed on March 2025) 18

Lymphoma has a classification by malignancy. There are three main classifications: low grade, intermediate grade, and high grade. This is a rather rough and rough division in the natural death of lymphoma, divided by how fast the disease progresses or advances. It can be divided into low grade, which progresses on a yearly basis, then highly aggressive or high grade, which gets bigger and bigger on a weekly or daily basis for those who are really fast, and in between, aggressive, which progresses on a monthly basis.

The most common type of lymphoma, diffuse large B-cell lymphoma, as I mentioned earlier, is the aggressive lymphoma of intermediate grade, and follicular lymphoma, which I will discuss here, is also divided into grade 1 to grade 3b, of which grade 1 to 3a are treated as low grade.

Grade 3b is a type of follicular lymphoma, but it is treated as a medium-grade lymphoma and is included in the development of medium-grade lymphomas, so when we refer to follicular lymphoma this time, we are referring to grades 1 to 3a. Please be aware that this is a low-grade indolent lymphoma that progresses over years.

Clinical Characteristics of Follicular Lymphoma

- Accounts for approximately 20% of adult lymphomas, with a higher prevalence in individuals in their 60s.
- A representative type of indolent lymphoma, characterized by slow progression.
- While some patients present with large abdominal masses at diagnosis, many remain asymptomatic.
- At diagnosis, about 80% of patients are in Stage III or higher.
- Additionally, 50% to 60% of patients have bone marrow involvement (Stage IV).
- Primarily involves lymph node lesions, but in some cases, it is confined to the gastrointestinal tract (especially the duodenum).
- B symptoms* and elevated LDH levels are uncommon (≤20%).
- The median survival exceeds 15 years, but curative treatment is challenging in advanced stages.

Prepared by the presenter.

* B symptoms: fever, weight loss, and night sweats (profuse sweating during sleep) that appear as systemic symptoms of lymphoma.

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The clinical features of follicular lymphoma are shown in this one slide. The frequency of lymphoma in adults is 20%, or 13% as I mentioned earlier, but it varies from 10% to 20% depending on the report, but it is roughly less than 20%. There are characteristics that are common in people in their 60s.

As I mentioned earlier, this is the typical form of low-grade lymphoma and shows slow progression. Because it progresses slowly, there are often few subjective symptoms at first, unless the superficial lymph nodes are swollen, so there are many cases where it is referred to as being swollen lymph nodes in the abdomen, for example, in a full physical examination, a health checkup, or a CT or abdominal echo. It is relatively typical for them to be asymptomatic, even when they are of a reasonable size at such times.

Therefore, when we take care of patients who are referred to us, there are no symptoms in spite of the size of the lymph nodes, or there are no major abnormalities in blood tests. In such cases, even if it is lymphoma, it is probably low-grade. If the disease is low-grade, the most frequent diagnosis is probably follicular lymphoma, and to some extent, we are trying to guess this by clinical diagnosis.

Clinical characteristics are that many are at stage 3 or more advanced, and bone marrow involvement is not at all uncommon, so it is usually at an advanced stage. Furthermore, it is not uncommon for the disease to involve the bone marrow, and these are the clinical characteristics.

Follicular lymphoma, a lymphoma, is typically a disease of swollen lymph nodes, but there is also a subtype of follicular lymphoma of the gastrointestinal tract with lesions only in the gastrointestinal tract, particularly in the duodenum. They are known to have a more gradual course and progress more slowly than the typical follicular lymphoma with main involvement of the lymph nodes. These patients, too, may be treated a little differently than the typical follicular lymphoma with normal lymph nodes. What I am going to talk about today is basically patients who need to be treated, mainly in the lymph nodes.

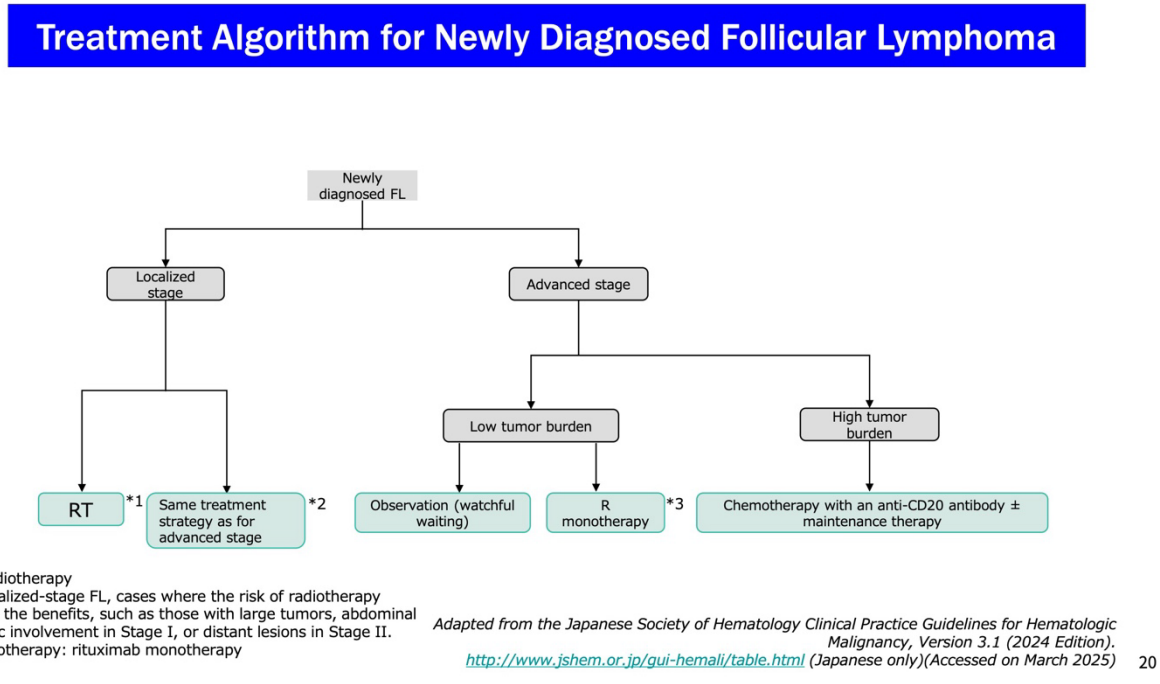
As I have said, since the disease progresses slowly and many are asymptomatic, they have a textbook symptom of lymphoma, which is called B symptom. More specifically, symptoms such as night sweats, weight loss, and unexplained fevers are referred to as B symptoms, and as these symptoms reflect the inflammatory

findings of lymphoma, or manifest as symptoms of exhaustion, they are rarely seen in cases of follicular lymphoma or low-grade lymphoma.

On the other hand, if these symptoms are present at the time of initial diagnosis or at the time of recurrence, it is necessary to suspect that a histological transformation from low-grade to intermediate-grade or high-grade has occurred, and to take further measures such as performing a repeat biopsy.

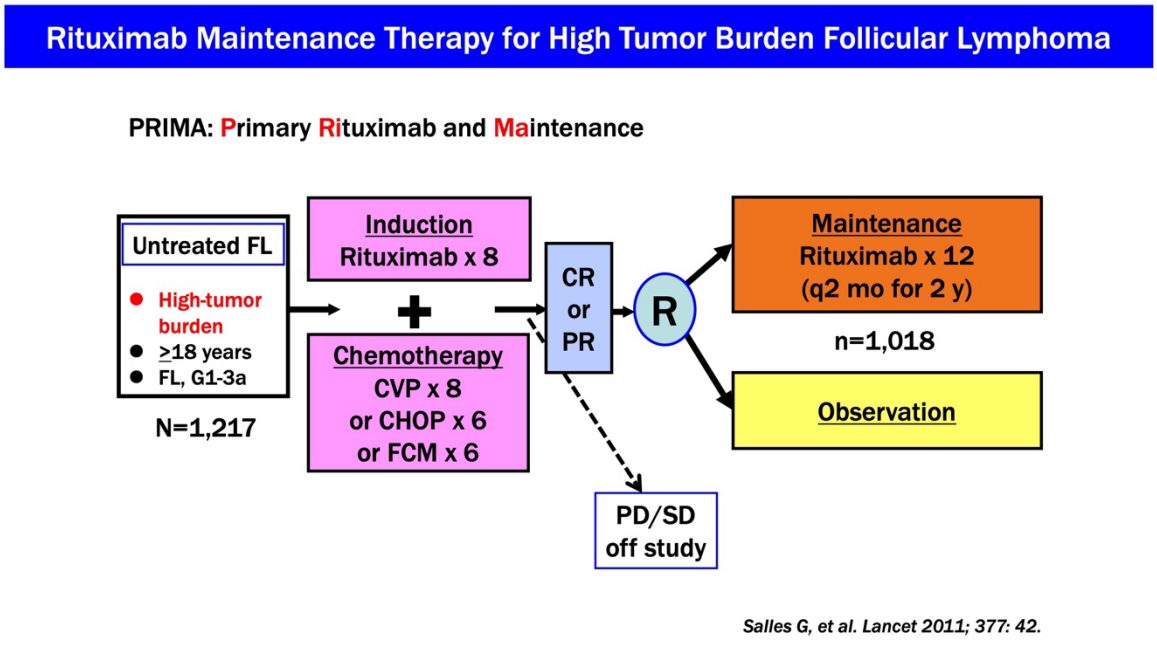
Because it is a disease that progresses slowly, and in many cases the symptoms are also poor, or because treatment development is being actively carried out, the survival period is definitely increasing. In particular, since the advent of antibody drugs such as rituximab, survival rates have increased, and the median survival rate is now probably over 20 years, but unfortunately in reality, the fact that it is still a disease that is difficult to cure is a very important keyword when considering the treatment policy for follicular lymphoma.

In other words, the symptoms as a whole are slow. Just because a disease has appeared, it does not necessarily mean that immediate and prompt treatment is required. However, even with therapeutic intervention, cure will be difficult in many cases. As a treatment policy for patients with follicular lymphoma, we always have to consider that we must avoid causing excessive toxicity to the patient. Or avoid unnecessary interventions as much as possible. Such is a very important concept for a treatment plan.



Based on this way of thinking, the treatment algorithm for initial follicular lymphoma is, for example, in the case of low tumor volume in the advanced stage, which makes up the majority of cases, the latest version of the Japanese Society of Practical Guidelines for Hematological Malignancies, the 2024 edition, recommends treatment interventions that do not cause as much toxicity as possible, such as observation without treatment or rituximab monotherapy.

If you have a high tumor load or a large tumor volume, you will still need some kind of treatment, but in such cases, single-agent therapy, antibody drugs alone, are still weak. For such patients, maintenance therapy in combination with chemotherapy is also listed in the guidelines as the standard of care.



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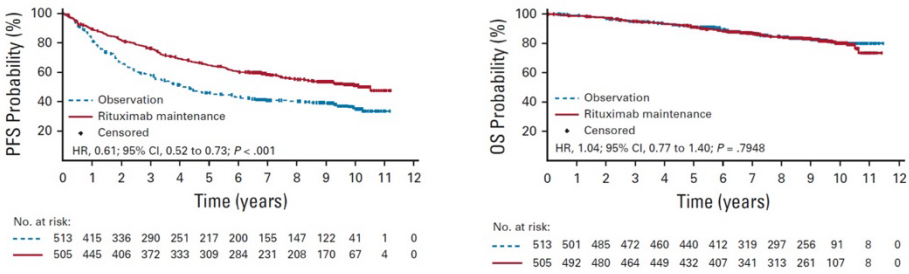
Here is a brief introduction to the development of treatments for follicular lymphoma with a high tumor load. First of all, the introduction of this Anti-CD20 antibody, a monoclonal antibody called rituximab, has greatly improved the treatment system and treatment outcomes for B-cell lymphomas, including follicular lymphoma. After rituximab was incorporated into the initial chemotherapy, the PRIMA study was conducted to compare whether or not maintenance therapy should be performed.

9-Year Follow-up Data from the PRIMA Study



- **Median PFS: 10.5 years in the maintenance therapy group vs. 4.1 years in the observation group (HR 0.61, 95% CI 0.52–0.73, P < 0.001)**
- **Median OS: Not reached in either group, with no significant difference. 10-year OS: 80% in both groups.**
- **Serious AE (maintenance therapy group: 21.2%, observation group: 13.4%)**

Bachy E, et al. J Clin Oncol. 2019; 37: 2815.

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As a result, it was found that the maintenance therapy with rituximab, which is also limited to a two-year period, clearly improved the primary endpoint of progression-free survival compared to the observation group that did not receive maintenance therapy. However, since there is a long survival period of 15 to 20 years, it is extremely difficult to make a difference in the OS , and there was no difference even in the maintenance therapy.

Obinutuzumab vs Rituximab: GALLIUM Study

Rituximab	Obinutuzumab
■ Type I antibody	■ Type II antibody
■ Mechanism of action	■ Mechanism of action
➢ Induces complement-dependent cytotoxicity	➢ Weak complement activation
➢ Induces antibody-dependent cytotoxicity	➢ Strongly induces antibody-dependent cytotoxicity
➢ Direct effect on cells leading to apoptosis	➢ Induces non-apoptotic direct cell death

Sehn LH, et al. J Clin Oncol. 2015; 33: 3467.

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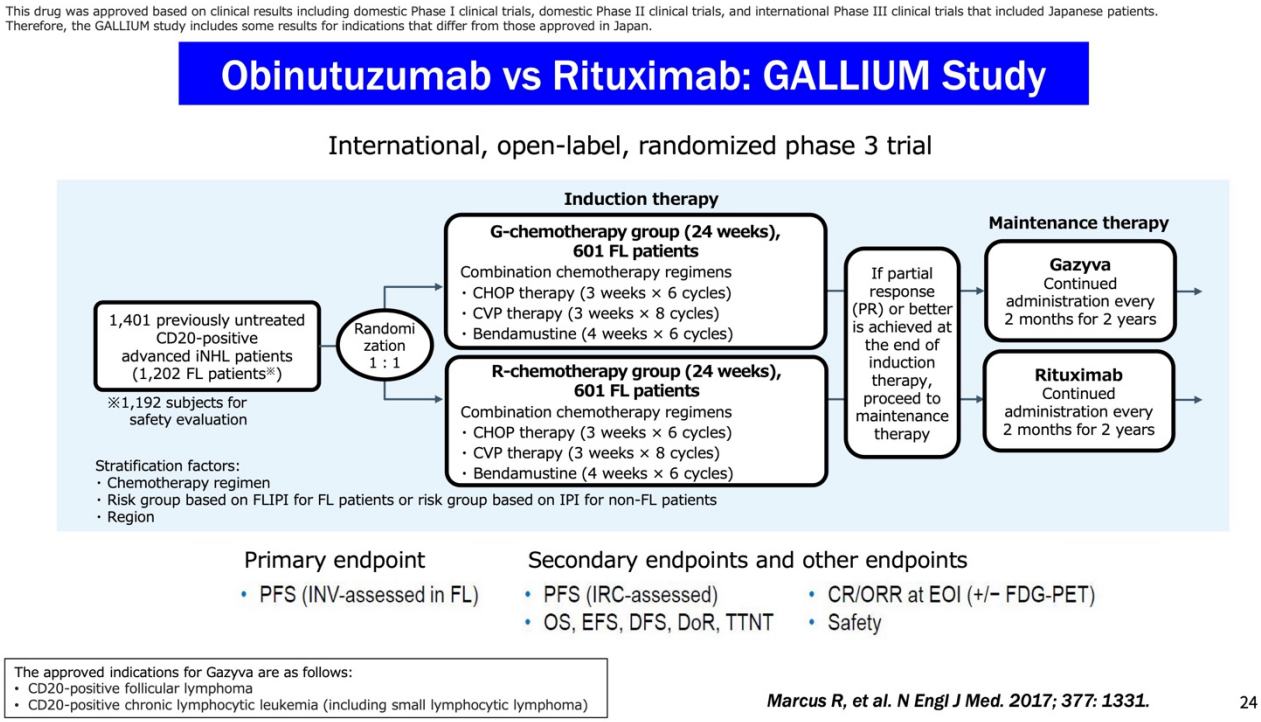
I have mentioned many times that the introduction of rituximab has improved treatment outcomes, and obinutuzumab was developed as a novel anti-CD20 monoclonal antibody to rituximab. Several anti-CD20

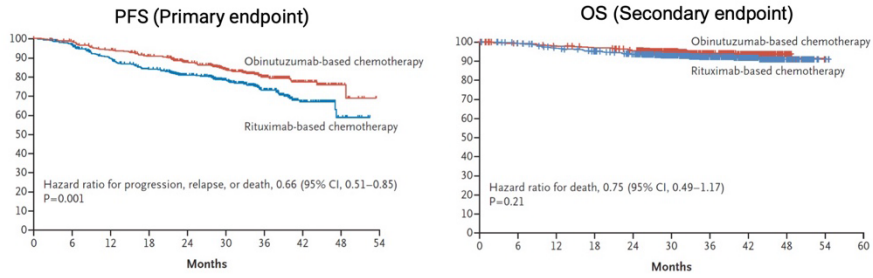
antibodies have been developed that should be considered post rituximab. Although several drugs have been developed, obinutuzumab is the only drug currently available for use in actual clinical practice.

Obinutuzumab is a type 2 antibody, which means that its mechanism of action is somewhat different from that of rituximab. It is said that there are differences such as antibody-dependent cell cytotoxicity being more powerful, and non-apoptotic, antibody-induced direct cell death being stronger, and it is a drug that has been developed with the expectation that it will have a higher therapeutic effect than rituximab.



The GALLIUM study is a Phase III clinical study to verify this. Rituximab combination chemotherapy, plus rituximab maintenance therapy. This is the standard treatment that was established through the PRIMA study I mentioned earlier, but this is a head-to-head, one-on-one comparison study that uses obinutuzumab in combination with chemotherapy against the standard arm and incorporates obinutuzumab maintenance therapy.

Obinutuzumab vs Rituximab: GALLIUM Study

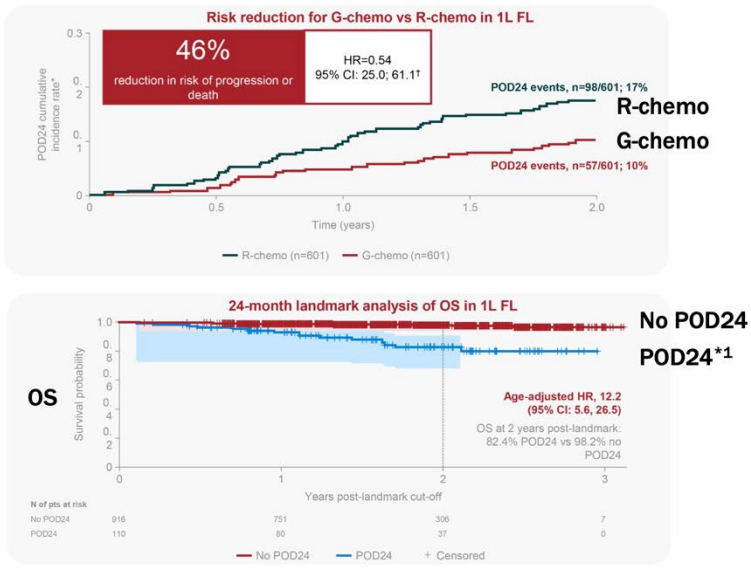


- **Median follow-up: 34.5 months**
- **Overall response rate (obinutuzumab: 88.5% vs. rituximab: 86.9%)**
- **3-year PFS (planned interim analysis): Obinutuzumab: 80% vs. rituximab: 73.3% (HR 0.66; 95%CI 0.51-0.85; P=0.001).**
- **3-year OS (obinutuzumab: 94% vs. rituximab: 92.4%): No significant difference**
- **Grade 3–5 AEs (obinutuzumab: 74.6% vs. rituximab: 67.8%)**

Marcus R, et al. N Engl J Med. 2017; 377: 1331. 26

The results showed that the obinutuzumab group was significantly superior to the rituximab group in the primary endpoint, Progression-Free Survival. However, there was still no difference in OS. This is why obinutuzumab has become one of the standard of care as combination chemotherapy for high tumor volume follicular lymphoma.

Disease Progression at 24 Months (GALLIUM Study)



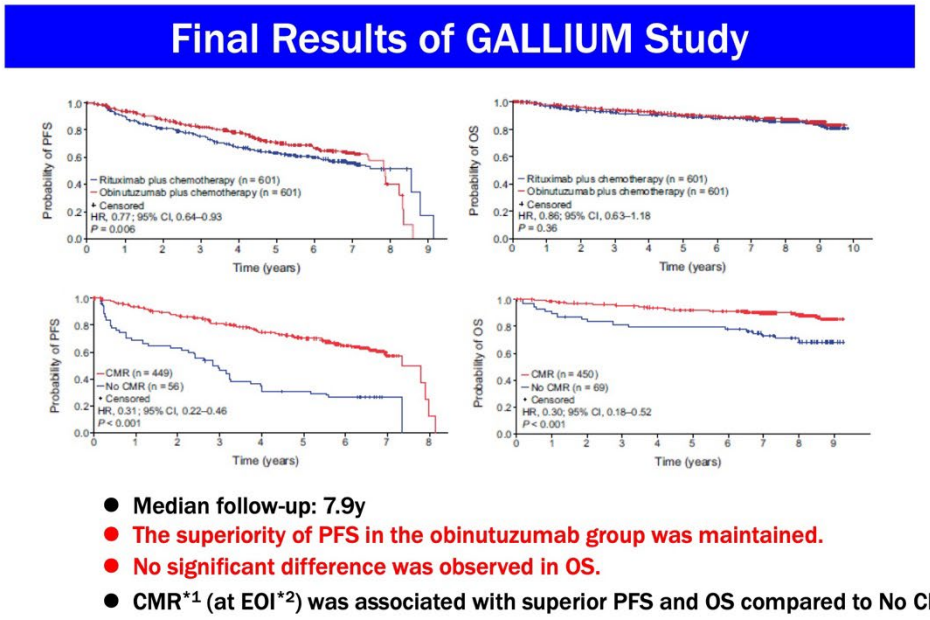
*1 POD24: Progression of disease within 24 months from randomization, or death due to disease progression

Seymour JF, et al. Haematologica. 2019; 104: 1202. 27

The GALLIUM trial included several subgroup and secondary analyses, the most notable of which looked at disease progression by group at 24 months. The impact on survival has been analyzed by the presence or absence of disease progression at 24 months.

It was reported that, compared to the standard arm of rituximab-based chemotherapy, obinutuzumab-based chemotherapy reduced the risk of disease progression at 24 months, known as POD24, by 46%.

Furthermore, it was shown that patients who experienced a POD24 event, regardless of group, had a poorer prognosis in terms of OS than patients who did not experience a POD24 event, and it was hoped that the long-term follow-up data might show that the obinutuzumab group had an OS and survival advantage over the rituximab group. At the time of this 2019 report.

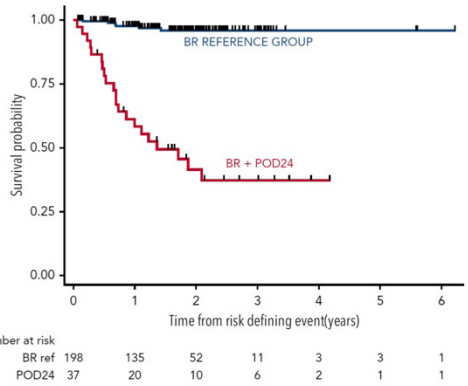


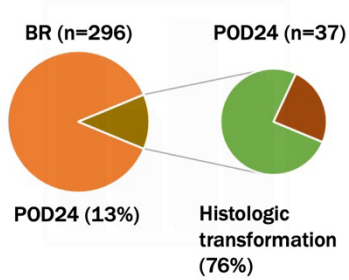
However, the final results of the GALLIUM trial were reported in 2024, and although obinutuzumab continues to be superior in terms of PFS, the OS unfortunately completely overlaps. This difference in POD24 did not directly translate into improved OS in the GALLIUM follow-up data.

For this reason, obinutuzumab is listed as one of the standard treatments, but since there was no difference in OS with rituximab combination chemotherapy, it is still listed as one of the standard treatments. In short, it is against this background that both obinutuzumab and rituximab are listed together.

Disease Progression at 24 Months (BR ± R Maintenance Therapy)

Retrospective study at BCCA*2





- **Early disease progression within 24 months on BR*1 therapy was associated with poor prognosis.**
- **The majority (76%) of cases involved histologic transformation.**
- **The only identified risk factor for POD24 was elevated baseline serum LDH.**

*1 BR : Bendamustine and Rituximab
*2 BCCA : British Columbia Cancer Agency

Freeman CL, et al. Blood. 2019, 134: 761. 29

In this follicular lymphoma treatment, progression of the disease at 24 months, POD24, is recognized as an important clinical event that also affects OS, as I mentioned earlier, and it depends on the treatment content, etc. Until then, the data from R-CHOP was the first thing that was said, but there are not many data that have been prospectively verified to see how bendamustine, which is now often used as the first-line treatment for follicular lymphoma, works.

This is a retrospective study by the British Columbia Cancer Center in Canada, but it seems that patients who experienced POD24 after BR therapy, bendamustine and rituximab, had a worse prognosis than those who did not experience POD24. Furthermore, it was reported that the majority of these cases were due to histological transformation, with transformation from low-grade to higher-grade lymphoma types.

Relapse or Progression Within 24 Months after Initial Chemotherapy (POD24)

Key Summary Points

Multiple studies have shown increased mortality risk in patients with follicular lymphoma (FL) who have progression of disease within 24 months of initial treatment (POD24) versus those who do not have POD24.

In clinical practice, it is not currently possible to identify individuals who are at increased risk for POD24. Improved tools for risk assessment are needed.

G-chemotherapy appears to reduce the risk of POD24 relative to R-chemotherapy in patients with previously untreated FL, but the impact on overall survival remains unclear.

Treatment strategies for the management of patients with POD24 are not well established. Well-designed studies are needed to determine the role of standard and emerging therapies.

In the absence of treatment standards, reducing the risk of POD24 with effective first-line therapies remains a priority.

Rodgers TD, et al. Oncol Ther 2021; 9: 329.

	High risk FLIPI, %	High risk m7-FLIPI, %	High risk POD24-PI, %
Sensitivity	70-78	43-61	61-78
Specificity	56-58	79-86	67-73

Casulo C, et al. Blood 2019; 133: 1540.

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So, how to predict the risk of POD24 or what effective treatment options are available for patients who develop POD24. Such is still an important clinical question in the treatment of this follicular lymphoma.

There have been several review articles on POD24, two of which I have brought to your attention, but unfortunately, at this point in actual clinical practice, there are basically no tools yet to predict whether or not an individual patient will develop POD24. Attempts have been made to predict that.

There have been reports that have examined the sensitivity and specificity of the FLIPI, which is a prognostic score for follicular lymphoma, and the m7-FLIPI, which is a combination of seven genes, in determining whether POD24 has occurred. In each case, this varies from one thing to another, but this is 70%. This is 40% to 60%, the sensitivity to begin with. This is 60% or 70%. The specificity is also 50% or even 70% or 60% at the highest, which makes this very difficult to use in clinical practice.

The most important reason why it cannot be used in clinical practice is because it is a target to avoid unnecessary intervention, which I mentioned at the beginning. So, if you identify a patient with a poor prognosis and try to change the treatment in anticipation of a poor prognosis, it will naturally be stronger than the existing treatment. Stronger treatments naturally result in more exposure to treatment toxicity to the patient.

In such a situation, where the sensitivity and specificity are low, it is not possible to strengthen the treatment intervention at the outset, because there is a possibility that it may cause POD24, and so it is not possible to intervene with such a strong treatment without any evidence to expose it.

Obinutuzumab, as I mentioned earlier, reduces the risk of POD24, but it is just not translating to OS. The fact that there is no established management for patients with POD24 is cited as a problem in the treatment of follicular lymphoma at present.

Summary: Newly Diagnosed Follicular Lymphoma

- **The standard treatment for previously untreated high tumor burden FL is chemotherapy with an anti-CD20 monoclonal antibody. While long-term disease control is achievable for many patients, FL remains an incurable disease.**
- **In some patients, POD24 occurs and is recognized as a prognostic factor, particularly affecting OS. However, a first-line treatment that reduces POD24 risk and improves prognosis has not yet been established.**

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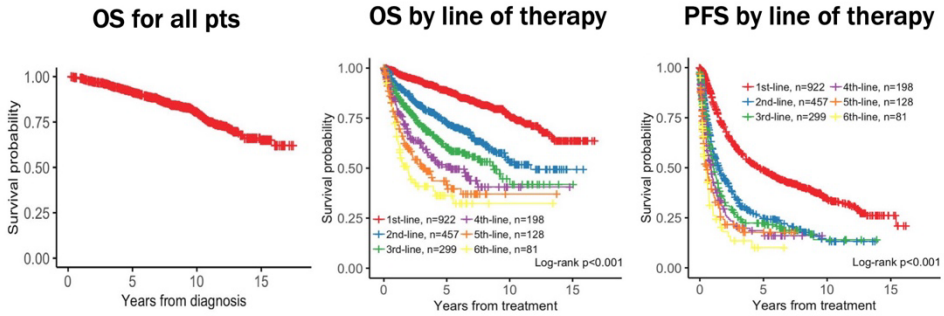
A summary on first-time, first-episode follicular lymphoma is shown on this slide.

Prognosis of Follicular Lymphoma

FL, G1-3a in MSKCC (1998-2009, N=1088)



- **OS: 92% at 5y, 80% at 10y, 65% at 15y.**
- **Despite an increasing number of treatment options for FL, patient prognosis continues to decline with each successive line of therapy (a major challenge in the treatment of R/R FL).**

R/R FL: relapsed/refractory follicular lymphoma

Batlevi C, et al. Blood Cancer J. 2020; 10: 74.

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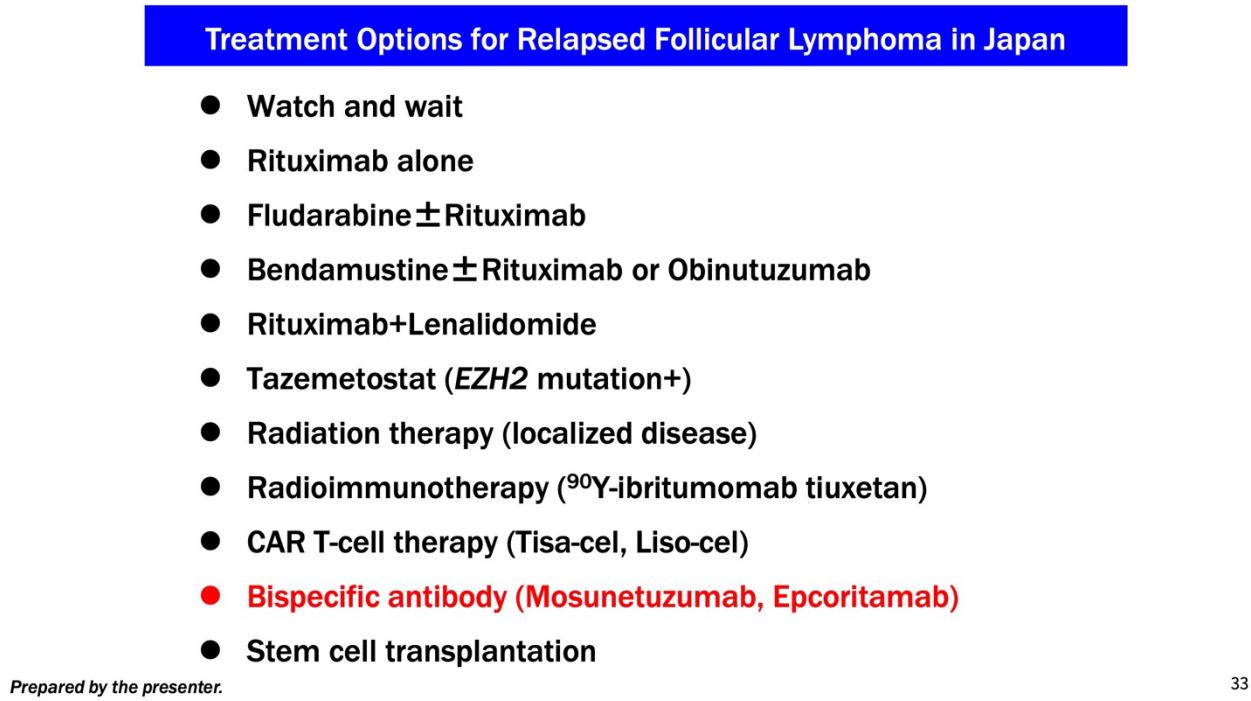
We will now move on to today's main topic, relapsed follicular lymphoma. This is data from over 1,000 patients at the Memorial Sloan Kettering Cancer Center in the United States, covering the prognosis of follicular lymphoma treatment and patients with grades 1 to 3a follicular lymphoma. This is from 1998 to 2009, so it is just before or after the introduction of rituximab, but the overall OS is 50% here and 15 years here, so the median is over 15 years. Both OS and PFS have improved since the introduction of antibody drugs such as rituximab. As the line progresses from second line to third line, the curve here will inevitably fall as recurrences are repeated.

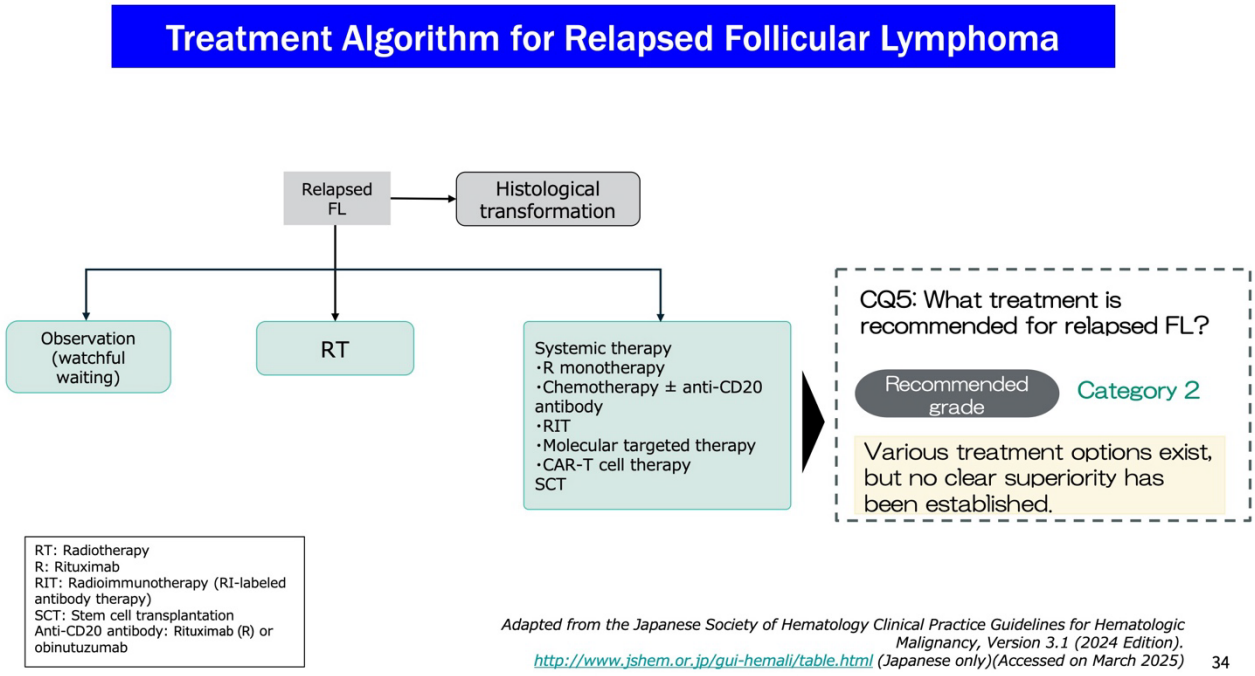
The overall prognosis is improving, and there are more treatment options available, but the decline in each treatment line means that it is important to develop treatments that do not cause this curve to decline at an earlier stage, but as I have been saying, this is a disease that is difficult to cure, so even if the treatment line progresses after a relapse, it is strongly suggested by these data that it is necessary to develop new treatments that will lift this curve. They are one of the major clinical challenges in relapsed or refractory follicular lymphoma.



Currently, there are multiple treatment options for relapsed or refractory follicular lymphoma in Japan. I've listed some of the typical ones, but just because it has recurred doesn't mean that treatment is necessary immediately, so there is also follow-up observation, or we also use rituximab alone, or in combination with bendamustine, obinutuzumab, and lenalidomide.

Tazemetostat, an EZH2 inhibitor, although it is limited to those with EZH2 mutation positive after the third line. Alternatively, if it is localized, radiation therapy or CAR-T cell therapy has recently been approved, and depending on the person, there is also the option of a transplantation.

Among these, bispecific antibodies such as mosunetuzumab and, epcoritamab which have recently been approved, have entered this category of options..

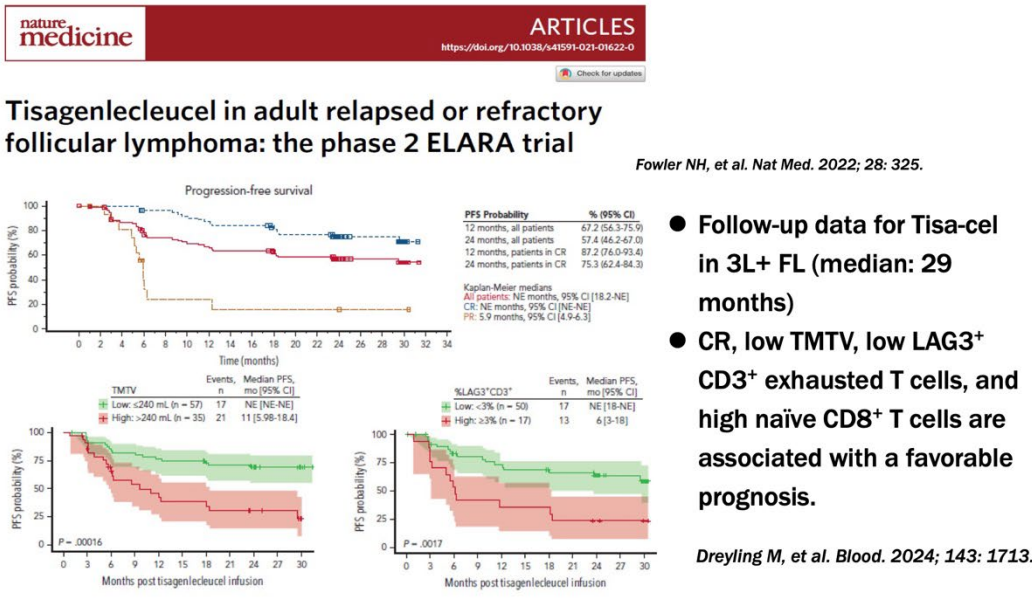


Here is an excerpt from the recurrence section of the Hematology Clinical Practice Guidelines for Hematologic Malignancy I showed you earlier.

As written here, it is necessary to first rule out the possibility of transformation in the case of relapsed follicular lymphoma, and in the case of treating it as follicular lymphoma, systemic chemotherapy or transplantation. There are multiple items in this list, and although bispecific antibodies are not yet listed here, it is thought that they will be added in the next revision.

The point is here. Various treatment options are available, but their superiority is not clear. This is because there have been few comparative studies between relapse treatments.

CAR-T Cell Therapy for Relapsed or Refractory Follicular Lymphoma



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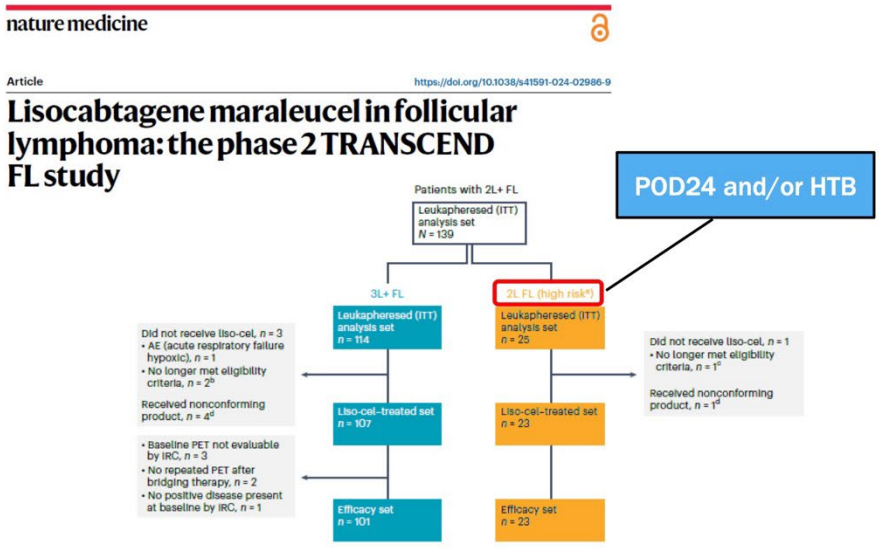
One of the most focused areas recently is cellular immunotherapy, including CAR-T cell therapy and bispecific antibodies. CAR-T cell therapy was pioneered and approved for relapsed diffuse large cell lymphoma and is now available for diffuse large cell lymphoma from second line therapy in some patients. Multiple formulations are available.

The ELARA trial, a Phase II study of Tisa-cel, the first pioneer of CAR-T cell therapy, has been reported and follow-up data are available, and the prognosis for patients who achieve a rapid complete response to CAR-T cell therapy is very good, or there are fewer exhausted T cells.

The tumor volume before the infusion of CAR-T cell therapy, which is determined by PETCT or FDG-PET, called metabolic Tumor Volume, is low. There has also been analysis of the factors that are good or bad prognosis.

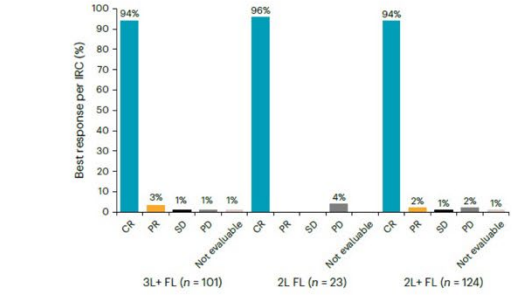
CAR-T Cell Therapy for Relapsed or Refractory Follicular Lymphoma



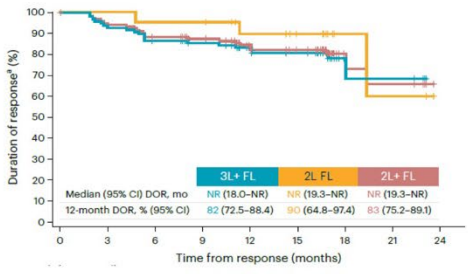
Morschhauser F, et al. Nat Med. 2024; 30: 2199.

In addition to this Tisa-cel, there is also a clinical trial of a CAR-T cell therapy called Liso-cel for relapsed follicular lymphoma. This is not just for follicular lymphoma in the third line, but also for patients who have had events such as POD24, which I have been talking about, in the second line, and trials are also being conducted for these patients.

CAR-T Cell Therapy for Relapsed or Refractory Follicular Lymphoma



	ORR	CR rate
3L+ FL (*n* = 101)	97% (95% CI: 91.6–99.4) *P* < 0.0001[a]	94% (95% CI: 87.5–97.8) *P* < 0.0001[a]
2L FL (*n* = 23)	96% (95% CI: 78.1–99.9) *P* < 0.0001[b]	96% (95% CI: 78.1–99.9) *P* < 0.0001[b]
2L+ FL (*n* = 124)	97% (95% CI: 91.9–99.1)[c]	94% (95% CI: 88.7–97.7)[c]

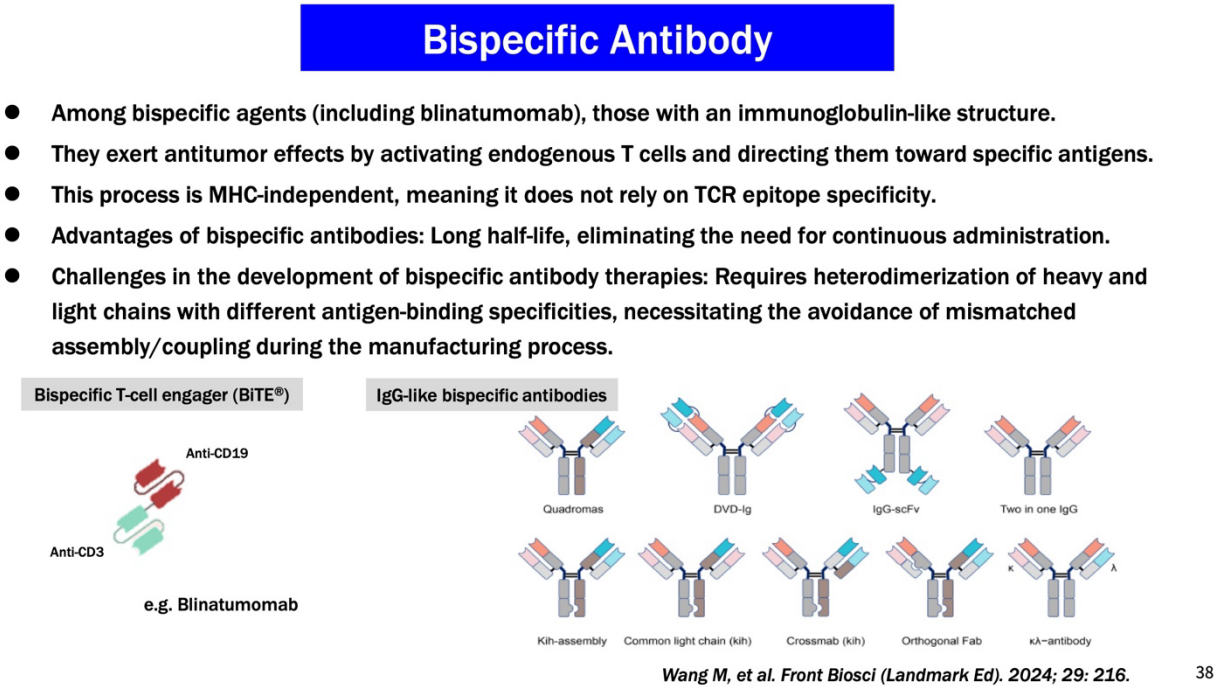


- **Liso-cel demonstrated a high response rate and durable responses in 2L+ FL, including POD24.**

Morschhauser F, et al. Nat Med. 2024; 30: 2199.

By and large, if you look at the results of the pivotal trials that are the basis for the approval of CAR-T cell therapy, the results of treatment for follicular lymphoma are very good. In Liso-cel, the bars are all standing high, even in the third line, then the second line, and then the second line and third line combined, but this is CR, complete response. So, regardless of the patient's condition or the number of lines, a CR rate of over 90%

are obtained. Furthermore, the prognosis, Duration of Response, is reported to be very good for the duration of response in patients who have achieved CR.



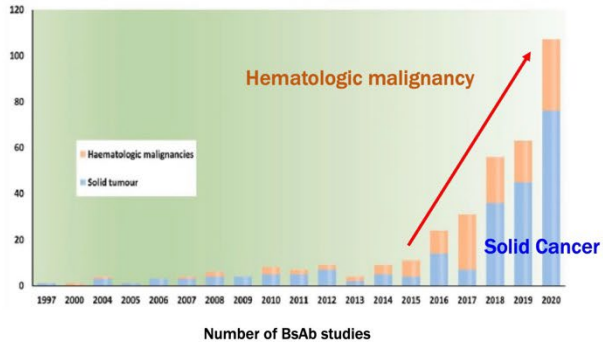
In this context, another new bispecific antibody has emerged. As for bispecific antibodies, there is a drug that was previously approved in Japan for relapsed or refractory diffuse large B-cell lymphoma.

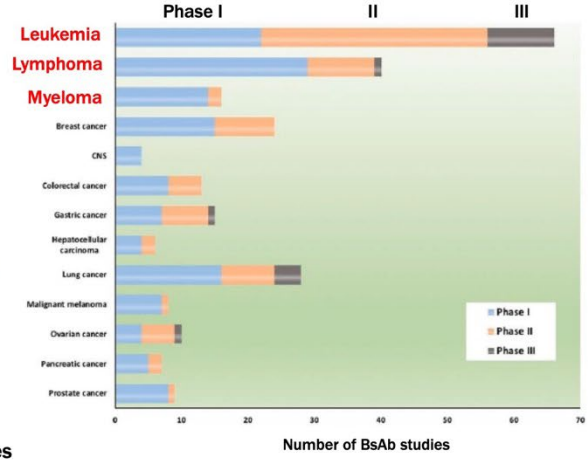
This time, mosunetuzumab is the first drug to be approved in Japan for the treatment of relapsed follicular lymphoma, but a bispecific antibody has already been approved in Japan even before a bispecific antibody targeting lymphoma appeared. That is the drug blinatumomab, which was approved for the relapsed B-cell acute lymphoblastic leukemia. This is connected by a single strand.

The major structural difference between this and a bispecific antibody is that it has an antibody structure, and this has the major clinical benefit of increasing the half-life and eliminating the need for continuous administration.

However, I have heard that there were many cases in the development stage where strange combinations were formed or the desired combination was not achieved because the heavy and light chains, which have the ability to bind to different antigens, had to be polymerized, but I understand that the development of a technology, which can polymerize the desired antigen and antibody parts as desired, has greatly and rapidly advanced the development of bispecific antibodies.

Development of Bispecific Antibodies





- Clinical trials of bispecific antibodies have rapidly increased.
- Development is notable not only in hematologic malignancies but also in solid tumors.
- As of 2020, the majority of trials were in early-phase (Phase I/II) studies.

Lim SM et al. Cancer Treat Rev. 2021; 99: 102240.

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This is actually a 2021 review paper, so the data is up to 2020, so it is already four or five years ago. It was already half a decade ago, but this shows that the number of clinical trials for this bispecific antibody has been rapidly increasing since late 2010, around 2016, 2017, 2018, and so on.

The orange shows hematologic malignancies, and the light blue shows solid tumors, but in recent years in particular, the number of trials for solid tumors has increased dramatically. In parallel, we see an increasing number of developments for hematologic malignancies. Overall, this means that there has been a significant and rapid increase.

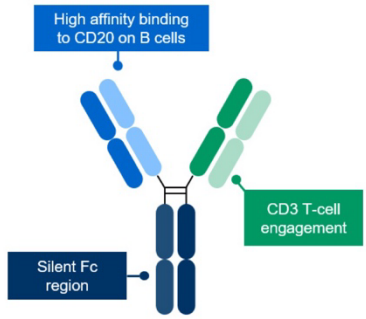
This is a breakdown of the types of clinical trials being conducted at the time, but as you can see, the majority of trials were in the early phases, Phase I and Phase II, for Leukemia, Lymphoma, and Myeloma about five years ago.

However, many of these drugs have already progressed to Phase III trials, and in addition, Phase III trials for the first-line treatment of B-cell lymphoma and follicular lymphoma have already begun using this bispecific antibody as a combination therapy, so I think that the current development status of bispecific antibodies represents an extremely competitive landscape.

LUNSUMIO (Mosunetuzumab)

- Lunsumio: bispecific monoclonal antibody targeting CD20 and CD3
- Binds to CD3 on T cells and CD20 on B-cell tumors, activating T cells and believed to damage CD20-positive tumor cells[4]
- Off-the-shelf and fixed-duration treatment[4,5]
- Phase I experience (NCT02500407)[5,6]
  - encouraging efficacy and manageable safety in patients with R/R FL and ≥2 prior therapies, including POD24 and double refractory[6]
  - effective CRS mitigation with cycle 1 step-up dosing[6]

Mosunetuzumab:
CD20xCD3 bispecific antibody[4]



1. Rivas-Delgado et al. Br J Haematol 2019;184:753–9、2. Bachy et al. Blood Adv 2021;5:1729–32
3. Seymour et al. Haematologica 2019;104:1202–8、4. Sun et al. Sci Transl Med 2015;7:287ra70
5. NCT02500407、6. Budde LE, et al. Lancet Oncol. 2021; 40（5）: 481-4915

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Against this backdrop, mosunetuzumab was approved for the first time in Japan for the treatment of relapsed or refractory follicular lymphoma. Dr. Aoki has just explained about this drug, so I will not go into details here, but please check this slide.

This drug was approved based on the results of the GO29781 and JO40295 studies, which included cohorts conducted outside the approved indications, dosage, and administration. In this presentation, we will show the cohorts conducted under the approved indications, dosage, and administration.

GO29781: Study Design

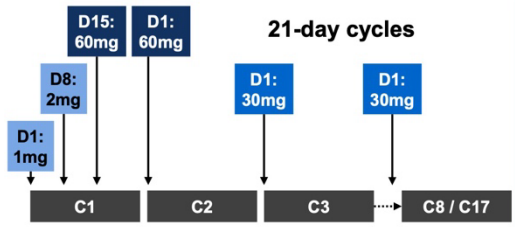
Single-arm, pivotal Phase II expansion in patients with R/R FL and ≥2 prior therapies

Key inclusion criteria

- FL (Grade 1–3a)
- ECOG PS 0–1
- ≥2 prior regimens, including
  - ≥1 anti-CD20 Ab
  - ≥1 alkylating agent

Administration method

- Intravenous infusion
- Step-up dosing (CRS mitigation)
- Fixed-duration (fixed treatment period)
  - At the 8-cycle point (approximately 6 months):
    CR: End of treatment
    PR/SD: Continue up to 17 cycles
- No mandatory hospitalization period



Endpoints

- Primary: CRR [as assessed by Independent Review Facility (IRF)]* – 14% set as threshold CRR based on historical control[1]
- Secondary: ORR, DoR, PFS, safety and tolerability

* Assessment conducted using CT and PET-CT, based on Cheson 2007 criteria2

The approved indication and dosage for Lunsumio are as follows:
- Indications: relapsed or refractory follicular lymphoma
- Dosage and administration:
  For adults, the usual dosage of mosunetuzumab (genetically modified) is administered as an intravenous infusion in 21-day cycles as follows:
  Cycle 1: 1 mg on Day 1, 2 mg on Day 8, and 60 mg on Day 15
  Cycle 2: 60 mg on Day 1
  Cycles 3-8: 30 mg on Day 1 of each cycle
  After 8 cycles, treatment should be discontinued for patients who achieve a complete response. For patients with stable disease or partial response, treatment may be continued for up to a total of 17 cycles.

Dreyling et al. J Clin Oncol 2017;35:3898–905
Cheson et al. J Clin Oncol 2007;25:579–86
Budde LE, et al. Lancet Oncol. 2022; 23 (8):1055-1065.
This study was conducted with the support of F. Hoffmann-La Roche Ltd. and Genentech, Inc.
This publication includes authors who are employees of or have received funding from F. Hoffmann-La Roche Ltd. and Genentech, Inc.

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This study design is an overseas pivotal trial, which is a single arm, overseas Phase I/II trial for third line, or relapsed or refractory follicular lymphoma with at least two prior treatment regimens. Targets are follicular lymphomas of grades 1 to 3a. As for pre-treatment regimens, I repeat, at least two regimens of anti-CD20 antibodies, which are considered the standard of care, such as rituximab or blinatumomab. Then there are alkylating agents, which are mainly bendamustine, or cyclophosphamide.

For patients with this type of treatment history, the cycle portion will be Day 1, 8, 15, which means every week with a double step-up dose method, and the drug will be in a three-week cycle from the second cycle. If a complete response is achieved after eight cycles, the treatment ends there, and if not, the treatment is fixed for a maximum of 17 cycles, or one year.

As Dr. Aoki mentioned earlier, I think the fixed duration is a very significant feature of the mosunetuzumab treatment schedule.

GO29781: Study Design

[Evaluation Items]

Primary Endpoint: Complete Response Rate (CRR) [Independent Review Facility (IRF) Assessment]

Secondary Endpoints: CRR [Investigator Assessment], Overall Response Rate (ORR) [IRF Assessment, Investigator Assessment], Duration of Response (DOR) [IRF Assessment, Investigator Assessment], Duration of Complete Response (DOCR) [IRF Assessment, Investigator Assessment], Progression-Free Survival (PFS) [IRF Assessment, Investigator Assessment], Overall Survival (OS), etc.

[Analysis Plan]

Treatment effects for each evaluation item were assessed using the revised response criteria for malignant lymphoma.
For the primary endpoint of CRR (IRF assessment), results from the ITT population were compared with historical controls using Fisher's exact test. The historical control was set at 14% CRR, based on a foreign Phase II clinical study of copanlisib monotherapy (not approved in Japan) in patients with relapsed or refractory FL1). The threshold CRR was set at 14%. With an expected CRR of 28% for Lunsumio, 80 patients were required to ensure 83% power at a two-sided significance level of 5%. The study protocol pre-specified at least one interim analysis and additional analyses.
An interim analysis was conducted with a data cutoff date of March 15, 2021. As the primary endpoint was achieved, this point was set as the main analysis timepoint, and the previously planned analysis for August 27, 2021, was conducted as an additional analysis.
The 95% CI for CRR was calculated using the Clopper-Pearson method.
The 95% CI for the secondary endpoint of CRR (investigator assessment) was also calculated using the Clopper-Pearson method.
DOR, DOCR, PFS, and OS were estimated using the Kaplan-Meier method, and the 95% CIs for median values were calculated using the Brookmeyer-Crowley method. The 6-month and 12-month DOR, DOCR, PFS, and OS rates were estimated, with 95% CIs calculated using Greenwood's formula.
Subgroup analyses for CRR (IRF assessment) were pre-specified for age, sex, BMI, ethnicity, race, ECOG PS, bulky disease, FLIPI, number of prior treatment regimens, history of R2 therapy, history of CAR-T cell therapy, refractoriness to most recent therapy, refractoriness to anti-CD20 antibodies, refractoriness to alkylating agents, refractoriness to PI3K inhibitors, time since last anti-CD20 antibody treatment, double refractory status, POD24, CD20, and EZH2 gene mutation.

1) Dreyling M, et al. J Clin Oncol. 2017; 35(35): 3898-3905. [Conflict of interest: The authors includes researchers funded by F. Hoffmann-La Roche.]

Approval evaluation data: overseas Phase I/II (GO29781), Budde LE, et al. Lancet Oncol. 2022; 23(8): 1055-1065. 42

Please refer to this slides at hand for more information on this.

Baseline Patient Characteristics

		N=90
Median age, years (range)		60 (29–90)
Male		55 (61.1%)
ECOG PS	0	53 (58.9%)
	1	37 (41.1%)
Ann Arbor stage	I–II	21 (23.3%)
	III–IV	69 (76.7%)

		N=90
Number of prior lines (range)		3 (2–10)
Prior systemic therapy	Anti-CD20 therapy	90 (100%)
	Alkylator therapy	90 (100%)
	PI3K inhibitor	17 (18.9%)
	IMiD	13 (14.4%)
	CAR-T	3 (3.3%)
Prior ASCT		19 (21.1%)
Refractory to last prior therapy		62 (68.9%)
Refractory to any prior anti-CD therapy		71 (78.9%)
Refractory to any prior anti-CD20 therapy and alkylator therapy (double refractory)		48 (53.3%)
POD24		47 (52.2%)

Cut-off date: August 27, 2021

Budde LE, et al. Lancet Oncol. 2022; 23（8）:1055-1065.

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This is the baseline patient background for patients enrolled in this study. Ninety patients were enrolled, with a median age of 60 years. The number of pre-treatment regimens is three in median. The eligibility criteria is to have both anti-CD20 antibodies and alkylating agents, but more than half of the patients have a history of resistance to these antibodies and alkylating agents.

As I have said in the past, POD24, a little more than half of the patients have a history of this type of disease, so in general, patients with follicular lymphoma who would normally have a poor prognosis according to the data to date were enrolled in the study.

Exposure and Patient Disposition

	N=90
Median duration of follow-up, months (range)	18.3 (2.0–27.5)
Patient disposition	
Completed treatment	54 (60.0%)
Discontinued treatment	36 (40.0%)
Active on retreatment	2 (2.2%)
In follow-up	76 (84.4%)
Discontinued study	12 (13.3%)

	N=90
Number of cycles received*	
<8 cycles	21 (23.3%)
8 cycles	53 (58.9%)
>8 cycles and <17 cycles	5 (5.6%)
17 cycles	11 (12.2%)

Cut-off date: August 27, 2021

Budde LE, et al. Lancet Oncol. 2022; 23（8）:1055-1065.

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The median observation period was 18.3 months, with 23% of patients receiving less than eight cycles, about a quarter of patients receiving less than eight cycles, and more than half patients receiving eight cycles, which means that the majority of patients, more than 80%, have roughly completed treatment within eight cycles.

Complete Response Rate (CRR) and Overall Response Rate (ORR)

Efficacy endpoint[1]	IRF N (%) [95% CI]	Investigator N (%) [95% CI]	Concordance IRF vs investigator
CR	**54 (60%)** [49%, 70%]	54 (60%) [49%, 70%]	93%
ORR	**72 (80%)** [70%, 88%]	70 (78%) [68%, 86%]	96%

- **60% CR rate significantly greater (p<0.0001)* than 14% historical control CR rate[2]**

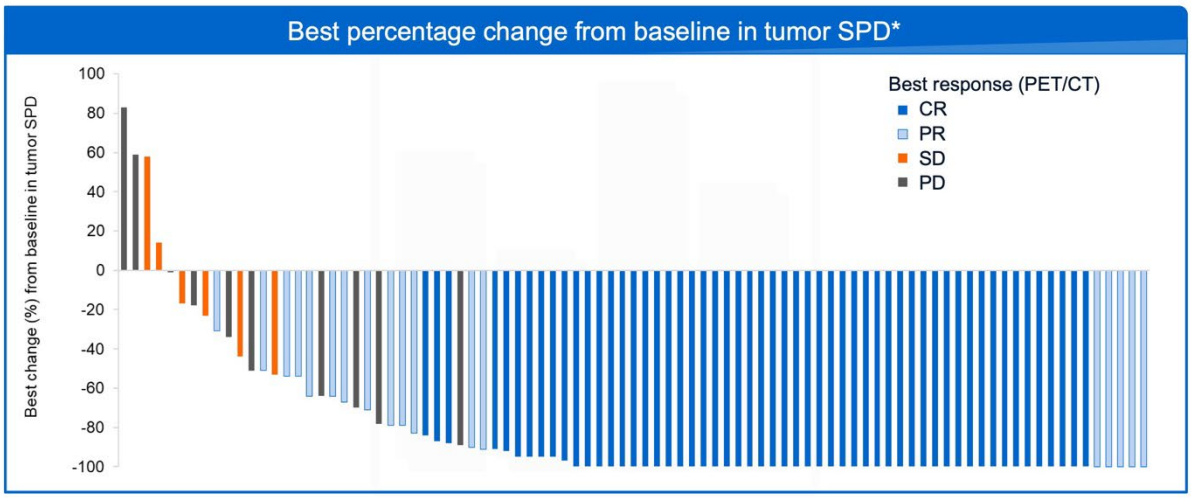
*exact binomial test with two-sided alpha level of 5%; CI, confidence interval

1. Cheson et al. J Clin Oncol 2007;25:579–86
2. Dreyling et al. J Clin Oncol 2017;35:3898–905

Budde E, et al. Blood 2021; 138: 127-130 45

The primary endpoints are the complete response rate, and then the overall response rate. This means that the response rate was 60%, and the overall response rate was 80%, so this is objectively very promising data for this single agent in this target population.

Tumor Shrinkage Effect (Waterfall plot)

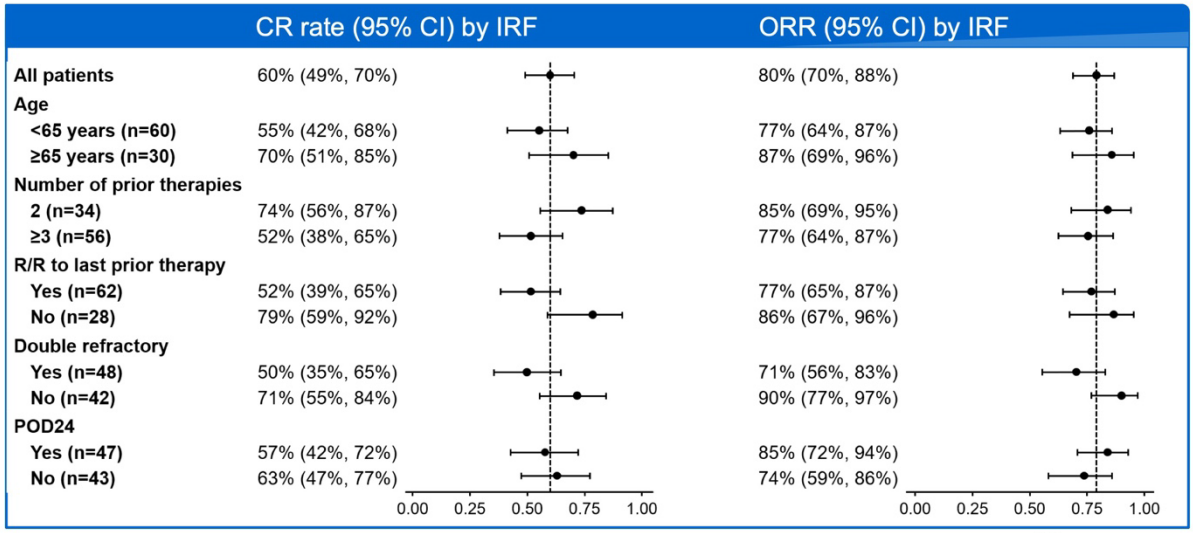


*in all patients with a baseline and ≥1 post-baseline SPD available; PD, progressive disease; SPD, sum of product diameters

Budde E, et al. Blood 2021; 138: 127-130 46

This is the waterfall plot focusing on tumor shrinkage. With the exception of a very small percentage of patients, almost all patients have achieved some kind of tumor shrinkage.

Subgroup Analysis of CRR and ORR in High-risk Populations



Budde LE, et al. Lancet Oncol. 2022; 23（8）:1055-1065.

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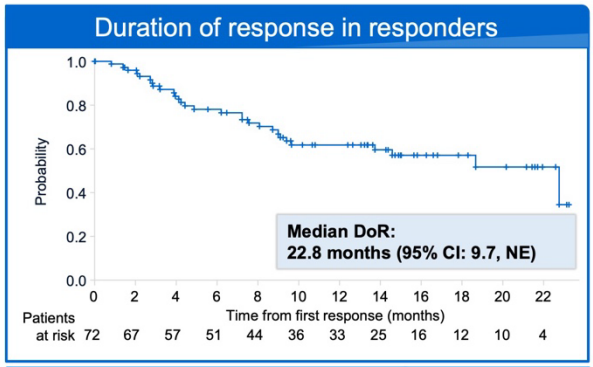
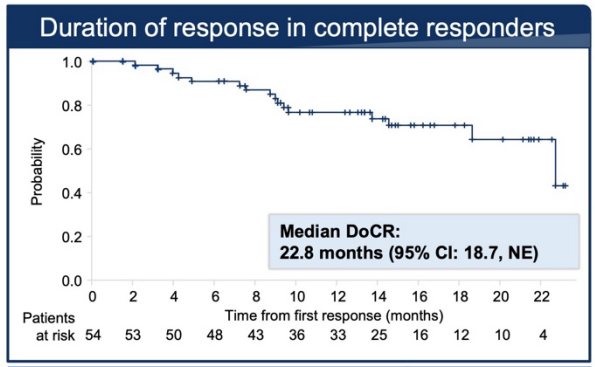
This is a subgroup analysis in the response rate, which is also the primary endpoint. Subgroup analysis does not fundamentally affect the results of the trial, but it is important as reference data to see, for example, whether there are any advantages or disadvantages to the primary endpoint or response, depending on the characteristics of the patients. In particular, if we focus on the following, we can see that for patients with poor prognoses, such as double refractory, CD20 and alkylating agents, and POD24, it is not possible to clearly say whether one is better or worse than the other if it is not more than half, but compared to those without double refractory, the response rate is slightly lower for those with double refractory, but there is no significant difference overall. Especially for this POD24, we are almost in the middle of both, so we can see that there is no difference in response to this drug alone, with or without POD24.

Duration of Response





Median time to first response, mo (range)	1.4 (1.1, 8.9)
12-month event-free rate, % (95% CI)	62% (50%, 74%)
18-month event-free rate, % (95% CI)	57% (44%, 70%)

Median time to first CR, mo (range)	3.0 (1.1, 18.9)
12-month event-free rate, % (95% CI)	76% (65%, 88%)
18-month event-free rate, % (95% CI)	70% (57%, 84%)

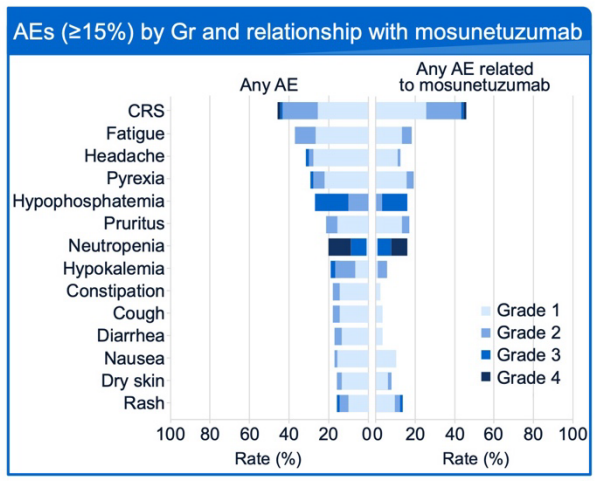
DoRC, duration of response in complete responders; mo, month; NE, not estimable

Budde E, et al. Blood 2021; 138: 127-130 48

Another thing to look at is the duration of response, especially Duration of CR. Data on how long patients who have achieved a complete response sustain CR thereafter. As I mentioned earlier, the median observation period is 18.3 months, but at that point the median is 22.8 months, so I think it would be very important data to know that the duration of CR patients is almost two years after treatment is completed.

Safety Overview

N (%)	N=90
AE	90 (100%)
Mosunetuzumab related*	83 (92.2%)
Grade 3–4 AE	63 (70.0%)
Mosunetuzumab related*	46 (51.1%)
Serious AE	42 (46.7%)
Mosunetuzumab related*	30 (33.3%)
Grade 5 (fatal) AE	2 (2.2%)†
Mosunetuzumab related*	0
AE leading to discontinuation of treatment	4 (4.4%)‡
Mosunetuzumab related*	2 (2.2%)‡

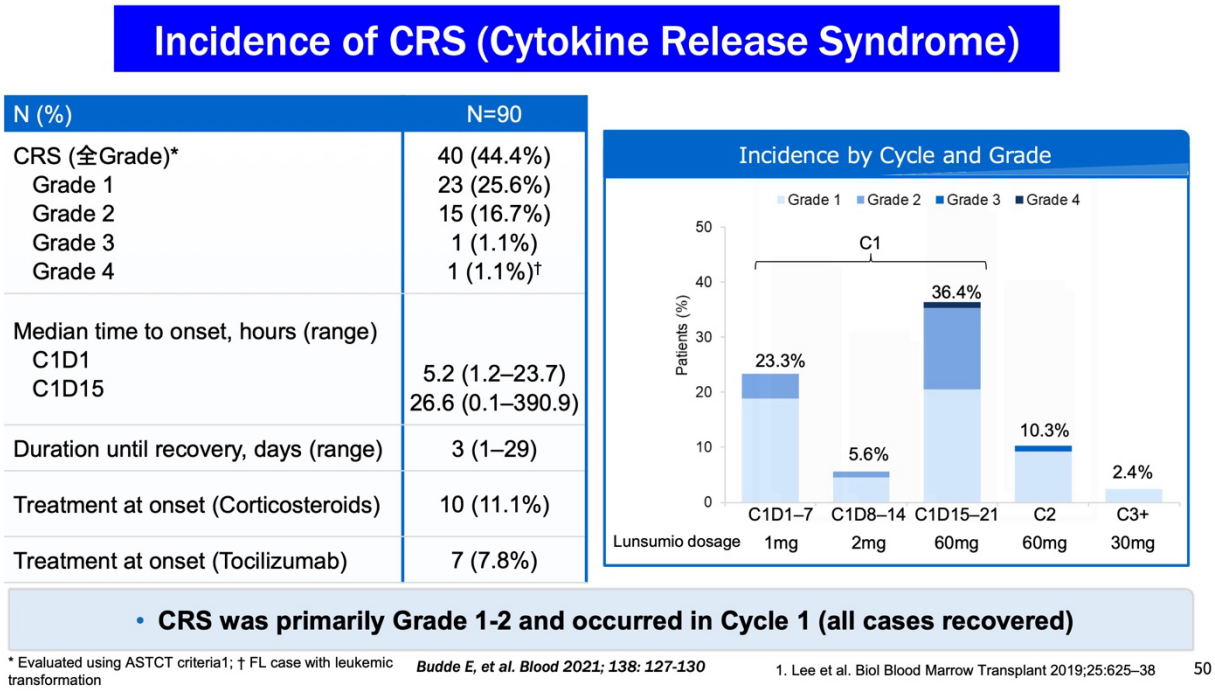


*AE considered related to treatment by the investigator; †mosunetuzumab unrelated: malignant neoplasm progression and unexplained death (1 patient each); ‡mosunetuzumab related: CRS (2 patients); mosunetuzumab unrelated: Esptein-Barr viremia and Hodgkin's disease (1 patient each); AE, adverse event; Gr, Grade

Budde E, et al. Blood 2021; 138: 127-130 49

We have been saying that we must be careful not to overtreat and that we must be very careful about toxicity. As expected for this safety data, the most frequent occurrence of this bispecific antibody, cellular

immunotherapy, is CRS, cytokine release syndrome. So, as expected, this mosunetuzumab, Lunsumio, also shows that CRS is expressed overall in just over 40% of patients.

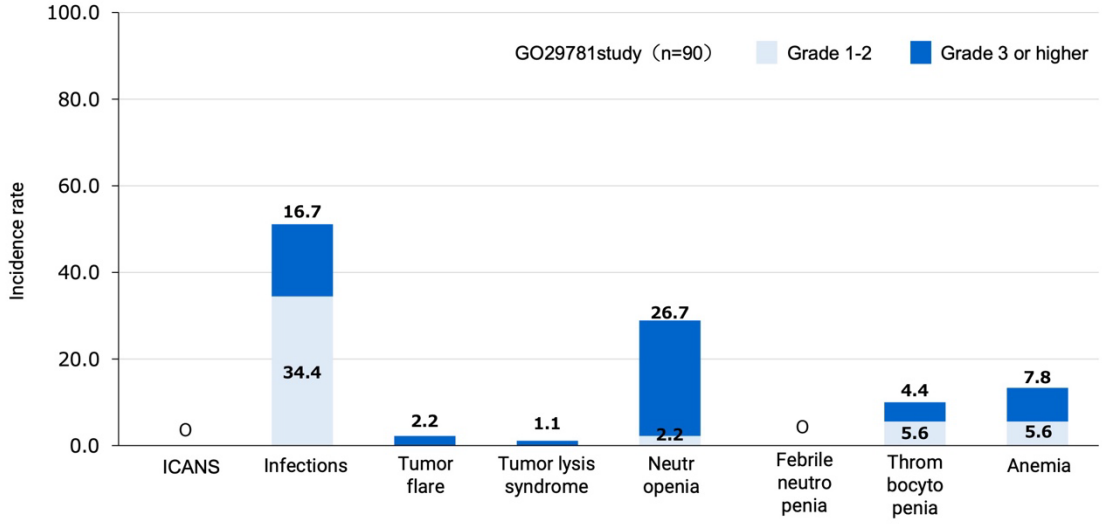


This slide shows the expression status specifically for that CRS. CRS of all grades occurs in 44.4% of cases. However, most of the cases are grade 1 or grade 2, and the frequency of so-called severe cytokine release syndrome, which is grade 3 or higher, is very low. The time it takes for this to occur is also very important data, because when the first dose is administered, it is basically done while the patient is hospitalized, and we have to pay close attention to the patient's vital signs and physical condition.

These two points are the most frequent points of CRS expression: at the first dose of this Cycle 1, Day 1, and Cycle 1, Day 15, when the first full dose of the target dose is administered. The highest frequency occurs on Cycle 1, Day 15. This is when the target dose, or first full dose, is administered.

After that, the expressions will gradually decrease, so basically, once the safety of the first full dose on Cycle 1, Day 15 has been confirmed, the patient will be discharged and the second cycle onwards will be administered as an outpatient.

Other Adverse Effects Requiring Attention



ICANS: Immune Effector Cell-Associated Neurotoxicity Syndrome

Approval evaluation data: overseas Phase I/II (GO29781)

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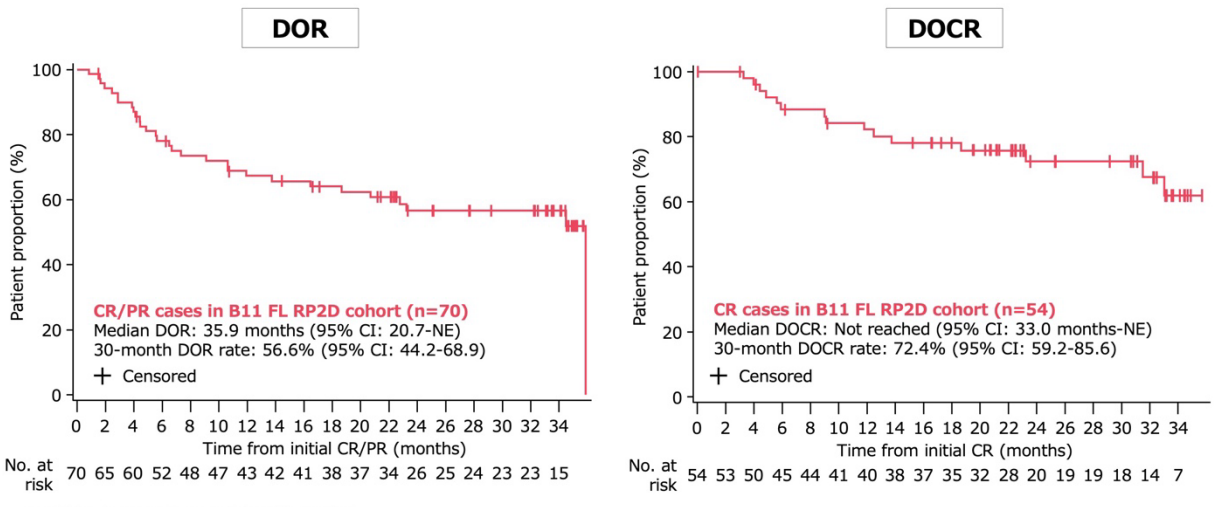
Other adverse events that should be noted are listed here. Since this is a third-line or later treatment for follicular lymphoma, it is used for patients whose immunity is naturally low, so it is necessary to be careful about infections as well among the adverse events, and this is something that should be noted for lymphoma treatment in general.

Also, this drug causes a certain frequency of neutropenia in particular, so these things need to be taken care of, and in some cases, G-CSF support or something like that. It is also necessary to monitor for the occurrence of fever due to these factors.

Mosunetuzumab in R/R FL; 3-year Follow-up Data



At additional analysis (data cutoff date: May 2, 2023),
Median observation period: 37.4 months (range: 2-48)

Sehn LH, et al. Blood. 2025; 145(7):708-719

This study was conducted with support from F. Hoffmann-La Roche Ltd. and Genentech, Inc.
This publication includes authors who are employees of F. Hoffmann-La Roche Ltd. and Genentech, Inc., or who received funding from these companies.

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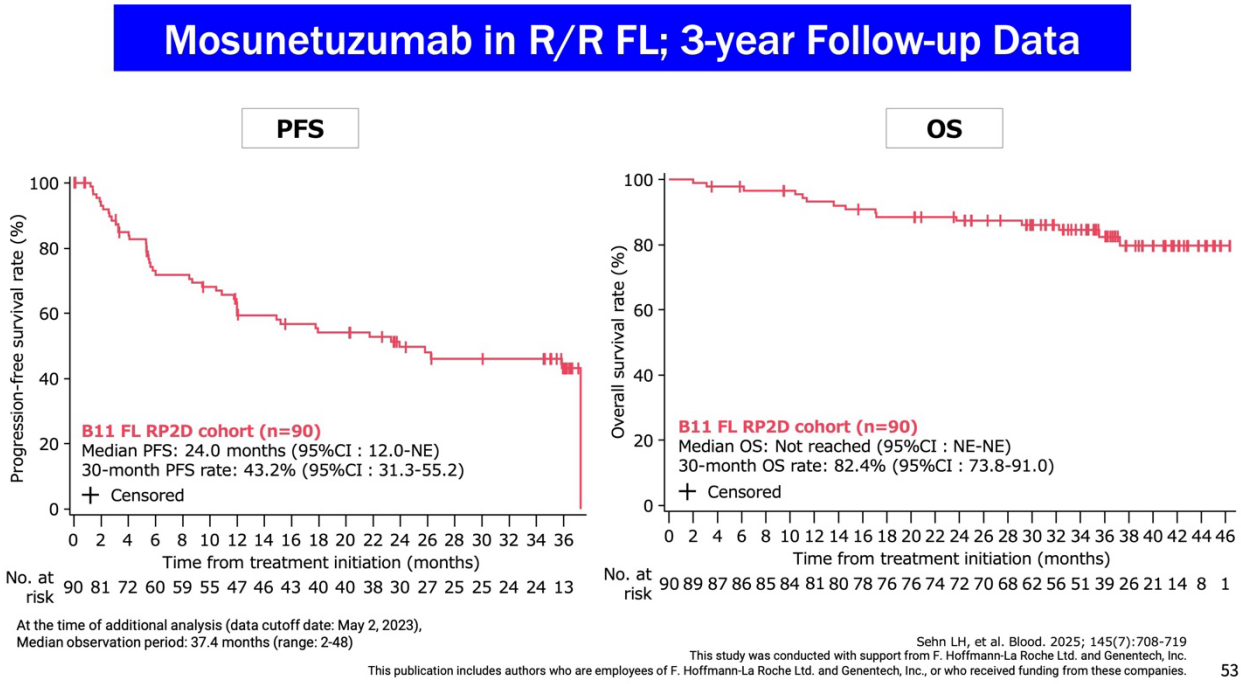
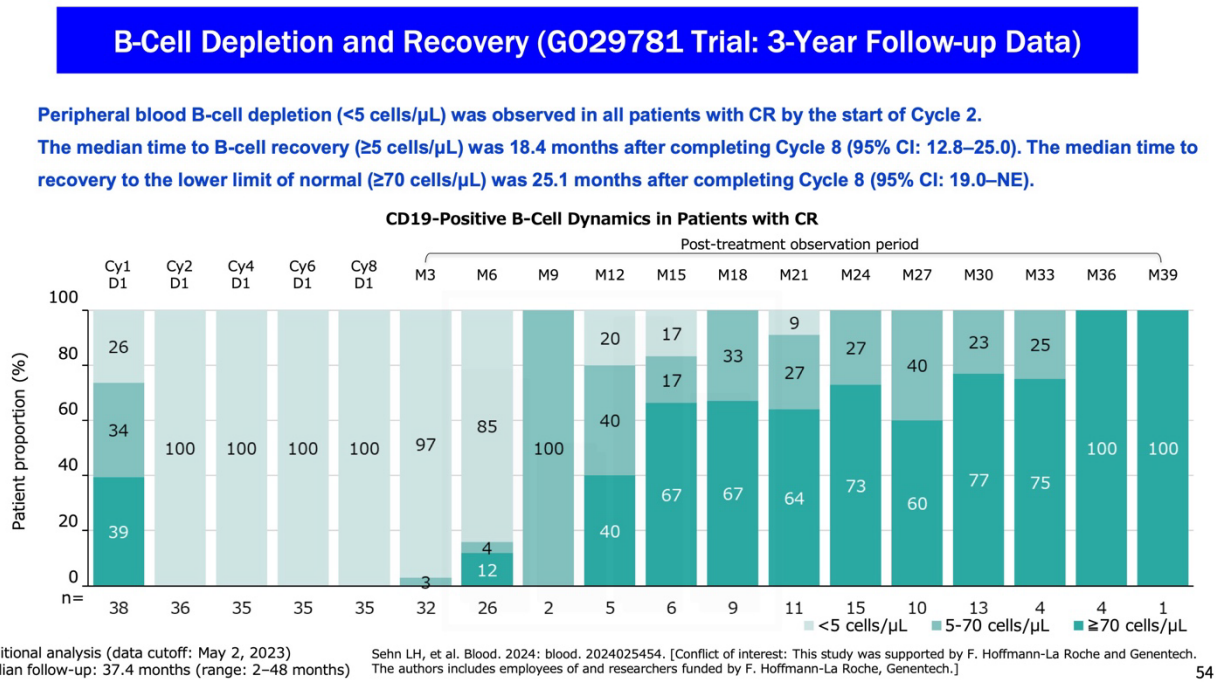
Follow-up data from the last three years are reported. The Duration of CR, as I mentioned earlier, at the time of the first report of 18.3 months, the median was 22.8 months, which was less than two years, but if we extend the observation period further, the median was not reached, and the Duration of CR at 30 months is 72%. This is very important data, as 72.4% of the patients have sustained CR at 30 months after a fixed treatment period of up to one year. This means that it is not something that relapse will suddenly occur as soon as treatment is completed.



As for PFS and OS, as you can see.

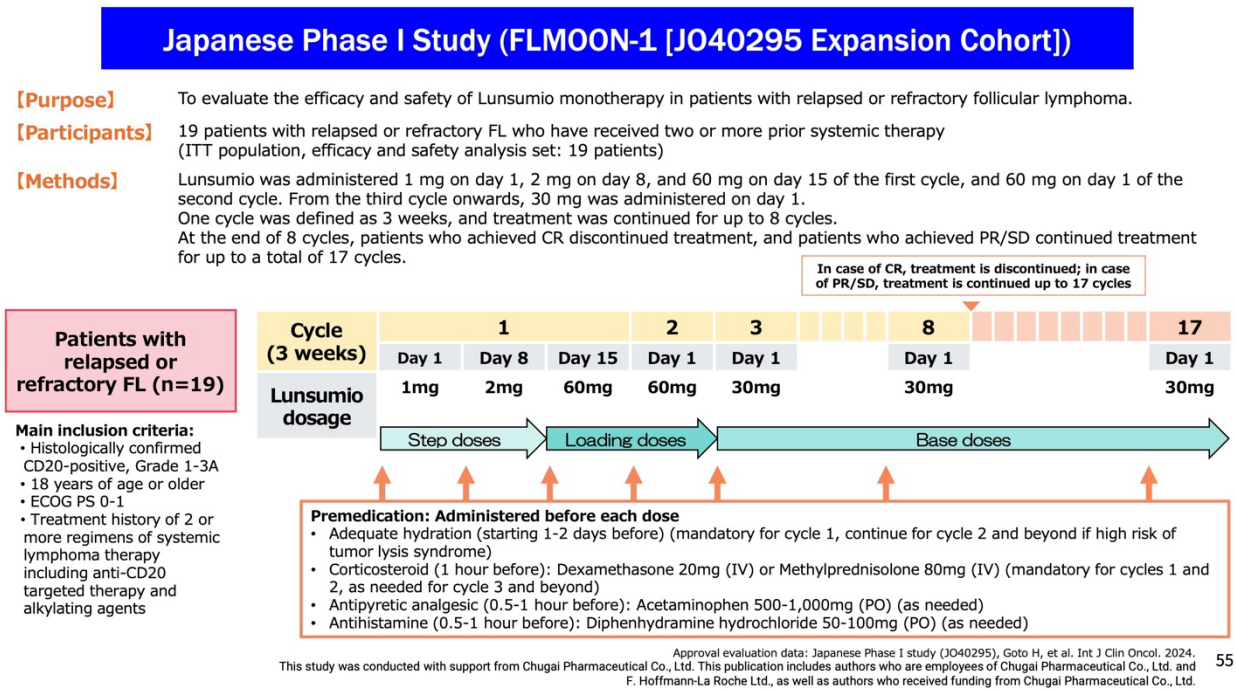


One thing to be careful of with this type of drug is that it strongly reduces B cells. It is so-called B-cell depletion therapy, so the normal ones are also reduced together, if CD20 expresses. CD20 is expressed on the majority of mature B cells, so naturally it will reduce not only lymphoma B cells, but also normal B cells.

What happens when B cells are depleted, for example, is that immunoglobulin levels, which are produced by B cells, are lowered, resulting in hypogammaglobulinemia. The concomitant decrease in liquid immunity makes it easy for infections, such as viral or bacterial infections, to occur, which are often referred to as opportunistic infections. Such things are inevitable with these types of drugs.

In the same way, this mosunetuzumab also causes a rapid depletion of B cells, and after treatment is complete, they gradually recover. So, when this treatment is being administered, when it is being reduced, and during the period of recovery, we are particularly careful to manage the toxicity by replenishing immunoglobulin as needed and being careful about infections.

This is completely my personal opinion, but because of this, the fixed treatment period is very important in terms of toxicity management, and as long as it is continued, B cells will not recover. Therefore, the point that treatment can be stopped is also expected to allow B cells to recover after recovery, so in this regard, I think the fixed treatment period has a very important message in terms of clinical perspective.



Following is a brief introduction to the domestic studies. Domestic studies are conducted in exactly the same manner as the overseas trials I mentioned earlier.

Baseline Patient Background

		N=19
Median age [range], years		72 (58–80)
Male		9 (47.4%)
ECOG PS	0	17 (89.5%)
	1	2 (10.5%)
Ann Arbor Classification	I–II	3 (15.8%)
	III–IV	16 (84.2%)

		N=19
Number of prior treatment regimens (range)		3 (2–5)
Types of prior treatments	Anti-CD20 antibody	19 (100%)
	Alkylating agent	19 (100%)
	PI3K inhibitor	17 (18.9%)
	IMiD	1 (5.3%)
	CAR-T	1 (5.3%)
History of prior treatment with autologous stem cell transplantation		0 (0.0%)
Refractory to most recent treatment		9 (47.4%)
Refractory to any anti-CD antibody		8 (42.1%)
Refractory to anti-CD20 antibody and alkylating agent (double refractory)		8 (42.1%)
POD24		5 (26.3%)

SPD: Sum of Product of Diameters

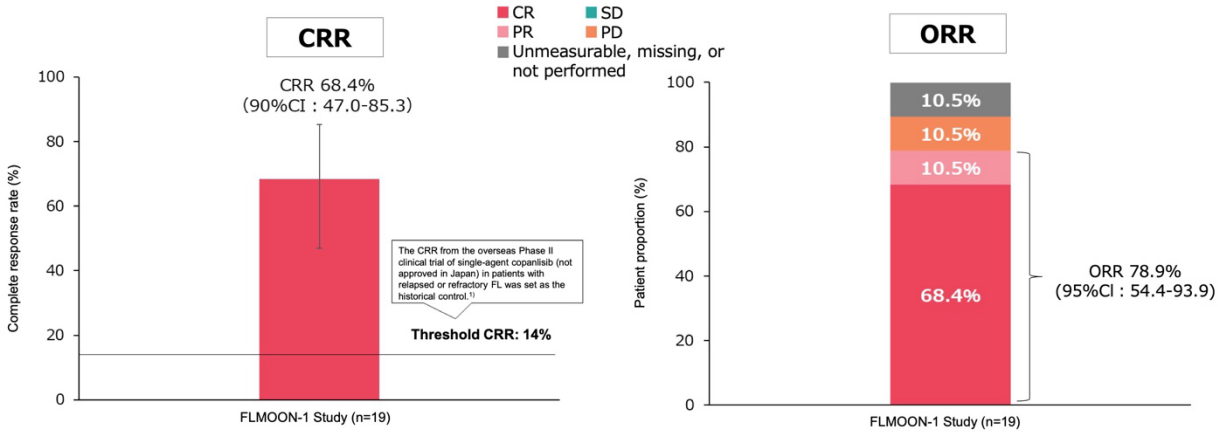
At the time of primary analysis (data cutoff: October 13, 2023)
Median follow-up: 7.95 months (range: 0.1–17.1 months)

Approval evaluation data: Japanese Phase I study (JO40295), Goto H, et al. Int J Clin Oncol. 2024. 57

However, as this is data from Japan, it is still very important, and as 19 people were enrolled, the median age of the patients was 72, so as the median age in the overseas trial mentioned earlier was 60, it can be said that the trial included patients who were older. This is true in other clinical trials as well, and there is a similar trend, but when we do it in Japan, it is relatively common to have older age groups than in other countries. Even in such cases, there is no difference in terms of safety or efficacy, and in some cases, the data is even better than overseas. This may be due to the good management of Japanese doctors, but such data has also been shown. Anyway, I think it is very important as data for looking at whether there are any extremely different toxicities in Japanese patients, whether there are any concerns about efficacy, or whether any unexpected events occur. The number of prior treatment regimens is three regimens as well. Double refractory, then POD24 is supposed to be slightly less than overseas.

CRR (IRF assessment, primary endpoint) / ORR (IRF assessment, secondary endpoint)

In the FLMOON-1 Trial, the CRR (IRF assessment) was 68.4% (90% CI: 47.0–85.3), with the lower limit of the 90% CI exceeding the threshold CRR (14%). The ORR (IRF assessment) was 78.9% (95% CI: 54.4–93.9).



At the time of primary analysis (data cutoff: October 13, 2023)
Median follow-up: 7.95 months (range: 0.1–17.1 months)

1) Dreyling M, et al. J Clin Oncol. 2017; 35(35): 3898-3905. [Conflict of interest: The authors includes researchers funded by F. Hoffmann-La Roche.]
Approval evaluation data: Japanese Phase I study (JO40295), Goto H, et al. Int J Clin Oncol. 2024.

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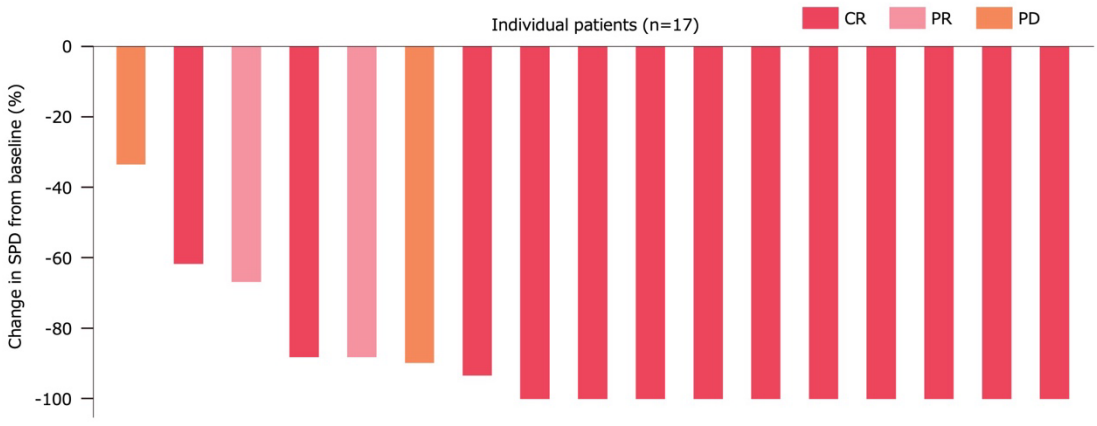
The CRR was 68.4% and the ORR was 78.9%, which are still favorable data.

Tumor Shrinkage Effect (Waterfall plot)

Tumor shrinkage was observed in all 17 patients* (100%) with available post-treatment imaging evaluations.

*Excluding 2 patients who had no tumor evaluation after baseline and no efficacy assessment.



At the time of primary analysis (data cutoff: October 13, 2023)
Median follow-up: 7.95 months (range: 0.1–17.1 months)

Approval evaluation data: Japanese Phase I study (JO40295), Goto H, et al. Int J Clin Oncol. 2024.

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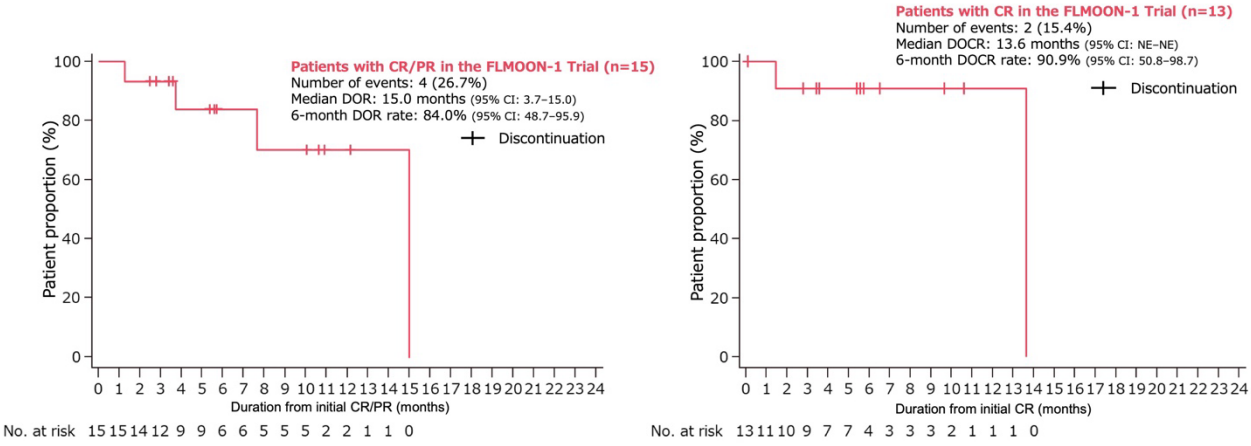
Also, this waterfall plot for tumor shrinking effect shows that all patients experienced some kind of tumor shrinkage.

DOR (IRF assessment, secondary endpoint) / DOCR (IRF assessment, secondary endpoint)

In the FLMOON-1 Trial, the median DOR (IRF assessment) was 15.0 months (95% CI: 3.7–15.0), and the 6-month DOR rate was 84.0% (95% CI: 48.7–95.9). The median DOCR (IRF assessment) was 13.6 months (95% CI: NE–NE), and the 6-month DOCR rate was 90.9% (95% CI: 50.8–98.7).



At the time of primary analysis (data cutoff: October 13, 2023)
Median follow-up: 7.95 months (range: 0.1–17.1 months)

Approval evaluation data: Japanese Phase I study (JO40295), Goto H, et al. Int J Clin Oncol. 2024.

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The duration of response and the duration of complete response are also very favorable, as they are shown here. However, since the data is based on a small number of cases, it is of course exploratory data rather than definitive data, but as you can see, the results are very good.

Main Adverse Events (≥15%)

	FLMOON-1 Trial (n=19)	
	All grades	Grade 3 or higher
Number of subjects with adverse events	18 (94.7%)	17 (89.5%)
Lymphocyte count decreased	13 (68.4%)	13 (68.4%)
Cytokine release syndrome (CRS)	9 (47.4%)	1 (5.3%)
AST increased	6 (31.6%)	2 (10.5%)
ALT increased	6 (31.6%)	2 (10.5%)
Neutrophil count decreased	5 (26.3%)	5 (26.3%)
Rash	5 (26.3%)	0
Infusion-related reaction	4 (21.1%)	2 (10.5%)
Hyperglycemia	4 (21.1%)	2 (10.5%)
Constipation	4 (21.1%)	0
Pruritus	4 (21.1%)	0
White blood cell count decreased	3 (15.8%)	3 (15.8%)
Blood bilirubin increased	3 (15.8%)	1 (5.3%)
Erythema multiforme	3 (15.8%)	1 (5.3%)
Nausea	3 (15.8%)	0
Herpes zoster	3 (15.8%)	0

At the time of primary analysis (data cutoff: October 13, 2023)
Median follow-up: 7.95 months (range: 0.1–17.1 months)

MedDRA ver. 20.1、CTCAE ver.4.03

Approval evaluation data: Japanese Phase I study (JO40295), Goto H, et al. Int J Clin Oncol. 2024.

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There is not much difference in toxicity compared to foreign data.

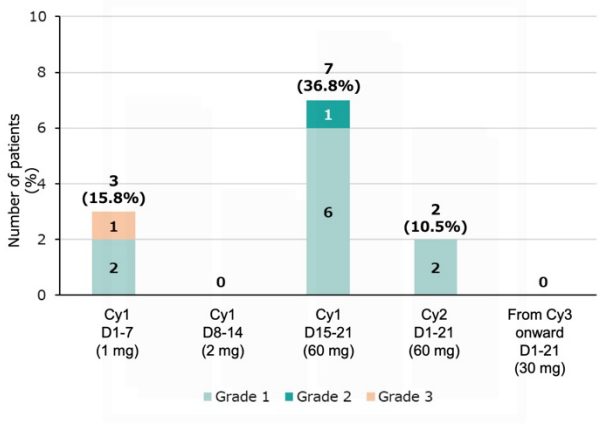
CRS Occurrence (Cytokine Release Syndrome)

In the FLMOON-1 Trial, CRS* was observed in 9/19 patients (47.4%), with 1 case (5.3%) being Grade 3 or higher, and 2 cases (10.5%) were considered serious. The median time to first occurrence of CRS was 16 days (range: 1 to 17 days). The median time to recovery from CRS was 4 days (range: 2 to 9 days).

	FLMOON-1 Trial (n=19)
CRS	9 (47.4%)
Grade 3 or higher CRS	1 (5.3%)
Serious CRS	2 (10.5%)
CRS leading to discontinuation	0
CRS leading to interruption	1 (5.3%)
Time to first occurrence Median [range], days	16 [1-17]
Time to recovery Median [range], days	4 [2-9]

*Includes events categorized under MedDRA PT as "cytokine release syndrome," "cytokine storm," "shock," "macrophage activation," "hemophagocytic lymphohistiocytosis," "capillary leak syndrome," "capillary permeability increased," "cytokine abnormal," and "cytokine test."
The grade of adverse events is in accordance with the consensus of the American Society for Transplantation and Cellular Therapy (ASTCT).

At the time of primary analysis (data cutoff: October 13, 2023)
Median follow-up: 7.95 months (range: 0.1–17.1 months)



Approved evaluation data: Japanese Phase I study (JO40295)

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As for cytokine-releasing syndrome, the overseas rate was about 44%, and the domestic rate was 47%. There is also only one severe CRS of grade 3 or higher, so there is no significant difference in the manifestations regarding occurrence. The timing of CRS occurrence is also Cycle 1, Day 1. Or Cycle 1, Day 15. Since we have observed bimodality here, the manifestation of this cytokine release syndrome has no specific difference.

Summary: Relapsed Follicular Lymphoma and Expectations for Lunsumio

- **Multiple new treatments are being developed for relapsed/refractory FL, but the treatment outcomes worsen with each subsequent line of therapy.**
- **Lunsumio, as an anti-CD20/CD3 bispecific antibody, was approved for the first time in Japan for 3L+ relapsed/refractory FL (grade 1–3A) (approved on December 27, 2024).**
- **Although it involves a fixed treatment duration, long-term durable responses were shown, regardless of the presence of POD24* events, and toxicity was manageable.**
- **Lunsumio is one of the promising treatment option for 3L+ relapsed/refractory FL.**

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This is the slide for summary. Regarding relapsed follicular lymphoma and the expectations for Lunsumio, mosunetuzumab, although multiple new treatments have been developed for relapsed refractory follicular lymphoma, the treatment outcomes have been poor as the treatment line progresses. Lunsumio is the first anti-CD20/CD3 bispecific antibody approved in Japan for third line or later relapsed follicular lymphoma, grades 1 to 3A. Although it is a fixed treatment duration, it has been shown that long-term efficacy can be sustained regardless of whether or not there is a history of POD24 events, and the toxicity is kept within manageable limits.

In this regard, I am certain that Lunsumio, mosunetuzumab is a promising treatment options for recurrent follicular lymphoma in the third line and beyond. This may have been a bit of a miscellaneous talk, but that's all I have to say. Thank you for your attention.

Question & Answer

Miyata [M]: Thank you. We are now moving onto 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, along with the presentation, will be posted on our website at a later date.

Wakao [Q]: I'm Wakao from JPMorgan. Thank you for your valuable presentation. I understand very well. I would like to ask one question to Dr. Maruyama and one to Dr. Aoki. First, I would like to ask Dr. Maruyama about the treatment options that you have listed for the third line and beyond. I think that CD20 and CAR-T are being used at this point, but I would like to know more about the current situation.

Also, looking at the data you showed us this time, it seems very promising, so I thought as an amateur that Lunsumio should be used for the third line and beyond, but is that understanding correct? If there are any hurdles to be overcome, I would like to know about them. In addition, I believe there is another drug that has recently been approved, Epkinly, I suppose. It would also be helpful if you could tell us how it compares to this one. That is my first question.

Maruyama [A]: First of all, I would like to talk about the current treatment system for follicular lymphoma, which includes some of the treatments I mentioned earlier today. As first-line treatment, chemotherapy combined with anti-CD20 antibodies is often used, and I think that bendamustine is now more commonly used, plus maintenance therapy, this is often used as standard treatment.

As for the second line after that, this varies quite a bit from facility to facility, but at least in our hospital, the second line of rituximab, plus lenalidomide, is the majority of what we do as a practice.

Then the next step would be the third line. In the case of third line, until now, there have been methods such as, for example, the re-treatment of bendamustine, or in combination with other chemotherapy.

Alternatively, a relatively recently approved oral drug called tazemetostat is available. Tazemetostat is indicated for EZH2 mutation-positive, relapsed follicular lymphoma with third-line and beyond, which works very well. Against EZH2 mutation-positive follicular lymphoma.

The problem with this, however, is that it is necessary to confirm the positive EZH2 mutation. Less than 20% of patients with follicular lymphoma are confirmed positive for this mutation. So it is a matter of checking five people and seeing if one person tests positive, so of course many will not be subject to tazemetostat.

Since mosunetuzumab is basically indicated for all cases of relapsed follicular lymphoma from the third line onwards, I think that the emergence of this drug will mean that mosunetuzumab will be chosen with a relatively high probability, because the unmet medical needs in this area from the third line onwards are extremely high.

One more thing, the last question you asked about the same type of drug, epcoritamab, which was approved for DLBCL first, and has now been expanded to include relapsed follicular lymphoma, is currently the subject of much debate. There is still no clear and settled view on which one to use under what circumstances and if so, which one to use.

There are no details to talk about epcoritamab today, but for example, the frequency of CRS occurrence or the prevention methods for CRS occurrence, it could be a co-administered drug, and the administration methods are not the same.

Also, the efficacy of mosunetuzumab alone for follicular lymphoma as a whole, or for those with increased grade of malignancy or transformed cases, is not exactly the same for both agents. Or the duration of administration is different. Because of these differences, we can only use them differently depending on the patient's situation, and I think that this is our current, rough, and unifying, though not unified, opinion.

Wakao [Q]: I understand very well. Secondly, I would like to get your comments on the marketability of this drug, if possible. I see from the MHLW data that the peak sales were JPY28.6 billion and the number of patients was 1,200, but I was wondering if you could tell me what assumptions were used in the calculation of these figures.

Aoki [A]: Thank you. Aoki will answer the question. I'm very sorry, but we cannot disclose the share of the drug currently, so we will just introduce the features of Lunsumio that I mentioned earlier, the efficacy that Dr. Maruyama also introduced, and the fact that B-cells are being revived and recovered due to the fixed duration, and we believe that Lunsumio has many advantages.

Compared to the CAR-T therapy that Dr introduced, we think that this is a drug with potential that we can expect, so we hope that you will consider that point as well and think that we have calculated it. I'm sorry.

Wakao [Q]: Then you can't tell us the number of eligible patients and the number of potential patients, can you?

Aoki [A]: The number of potential patients is also undisclosed. We are not disclosing this information because we believe that each company has different sources for their data. I'm sorry.

Wakao [M]: I understand well, thank you very much. That's all from me.

Miyata [M]: The person in front, please go ahead.

Hashiguchi [Q]: My name is Hashiguchi from Daiwa Securities. I have two questions. The first is about the extent to which the drug is likely to be actively used in the future when the indication is expanded to first-line and other indications. With the risk of CRS, how well can it be controlled? I understand that there are still big differences among medical institutions in terms of how well-equipped they are, and also among doctors in terms of their experience.

In this situation, of course, the extent to which its efficacy is demonstrated in future clinical trials will also depend on the situation, but I would like to ask Dr. Maruyama for your opinion on the extent to which this drug can be used proactively at the present time for patients in the first line, earlier stages, and of course, for patients with various other options.

Maruyama [A]: I see. At the moment, to answer your question directly, I don't know whether or not mosunetuzumab will be used in the first line, but there are multiple Phase III trials of bispecific antibodies already underway, so I think it is highly likely that bispecific antibodies will be incorporated into the standard treatment for the treatment of follicular lymphoma in the first instance.

The overall trend in therapeutic development is the development of so-called chemo-free regimens that do not include cytotoxic anticancer therapies. Whether it's the first time you're using cellular immunotherapy or you're using CAR-T cell therapy afterwards, for example, you have to think about the overall treatment sequence, not just one point, because it's a disease that is difficult to treat over the long term and that recurs repeatedly, for example, without losing the function of T cells as much as possible. The development of such chemo-free regimens is still the mainstream today.

In this context, I believe that this bispecific antibody occupies a significant position, and it is highly likely that it will be incorporated into the first line in the future. However, whether it will replace all of the current treatments for all follicular lymphoma patients, I think this will depend on the results of the clinical trials.

Hashiguchi [Q]: Thank you. Second, what dosage and administration are you developing for the subcutaneous injection formulation? If there are any differences in usage other than just the route of administration, such as step dosing or how to set the duration of administration, could you please let us know?

Aoki [A]: Thank you. I, Aoki, will explain. The subcutaneous injection formulation is currently under development, and of course the dosage and administration may differ, so I will refrain from introducing it in detail here, but to be specific, the 5 mg and 45 mg dosages, which are neither the current 1 mg nor 30 mg dosages, are currently under development. As for Lunsumio, we are currently in the late phase of development, and we expect that it will be available in Japan in the near future.

Hashiguchi [Q]: How is the concept of fixed duration different?

Aoki [A]: Regarding fixed duration, Chugai and the Roche Group are very particular about this, so we are continuing to develop this area even for subcutaneous injection formulations.

Hashiguchi [M]: Thank you very much.

Miyata [M]: Thank you. Now, the person next, please.

Yokoyama [Q]: My name is Yokoyama from Nikkei Medical. Similar to the previous person's question, the first point I would like to ask is how to use it differently from epcoritamab. Dr, you say that there is a slight difference in the results obtained from different studies, but is that all right to use under that recognition? I would like to ask that first.

Maruyama [A]: Very perceptive question, thank you. Of course, we cannot compare the efficacy or safety of a drug between different trials equally and on the same playing field. We cannot, but what I am saying is based on my own experience with mosunetuzumab, but as I showed you today, the efficacy of mosunetuzumab as a single agent in follicular lymphoma is very high.

On the other hand, although mosunetuzumab is not indicated for this indication, I believe that the results of single-agent therapy for diffuse large cell lymphoma may be somewhat lower than, for example, epcoritamab or other bispecific antibodies that are in development.

Then, I'm not going to talk about anything too scientific now, but suppose a patient is being treated for follicular lymphoma and the disease is progressing slightly more quickly than before. In other words, it is possible that an aggressive component is emerging from follicular lymphoma, or in cases where a patient is considered to be clinically more aggressive, for example, where the only diagnosis is follicular lymphoma and the patient must be treated as such, in cases where both mosunetuzumab and epcoritamab are available, epcoritamab has sufficient data as a single agent for relapsed diffuse large B-cell lymphoma, so in such cases, perhaps epcoritamab would be chosen. This is completely my opinion, but I meant it in that way, although it is a rather vague usage.

Yokoyama [Q]: Then you say that it is not yet clear how to clearly distinguish the usage.

Maruyama [A]: Not at all. How to use it differently is.

Yokoyama [Q]: Also, earlier you said that there was no difference in OS, and that rituximab and obinutuzumab were both equally effective, but when it comes to third-line and beyond, CRR is naturally the primary endpoint,

and since we only have Phase I/II data, it may be unavoidable, but I think that OS will be the deciding factor in the end. Is my understanding correct that if that comes up again, the order will eventually change?

Maruyama [A]: What do you mean the order?

Yokoyama [Q]: In what order or what kind of treatment sequence?

Maruyama [A]: You mean priorities. If there is a difference in OS, of course that priority would be at the top of the list. It just depends on what data you compared to what data, of the difference in OS.

In general, however, I think it is hard to say yet, because at present there are actually few cases where PFS differences in follicular lymphoma properly translate to OS differences. For example, compared to previous reports, it is likely that data on these new drugs and bispecific antibodies may improve OS, but since they have not been examined in comparative studies, their priority may increase, but it is unlikely that they will become established.

Yokoyama [Q]: I understand. I would like to ask one more question about sequencing. There is also the option of CAR-T cells, but in what order should you use CAR-T and bispecific antibodies? Furthermore, how should we consider the effect of using one of the drugs first on the effectiveness of the drug on the remaining side? Or else, since this is a fixed period administration, I wonder if it is possible to reintroduce it in case of an exacerbation. Please tell us about this point.

Maruyama [A]: Thank you. I think these are all very important questions. First of all, there is unfortunately no very clear basis for determining a very definite order of treatment with respect to the use of CAR-T cell therapy.

Since CAR-T cell therapy was introduced into clinical practice earlier, there are reports based on real-world data from overseas, for example, that confirm the sufficient efficacy of bispecific antibodies, including mosunetuzumab, in relapsed follicular lymphoma after CAR-T cell therapy.

Recently, there are also reports beginning to emerge that not only mosunetuzumab but also other bispecific antibodies can be done first, followed by CAR-T cell therapy, without much effect on the efficacy of CAR-T cell therapy.

From that point of view, which one should be done first, and moreover, the currently available CAR-T cell therapy and the currently available bispecific antibodies have different targets, CD20 and CD19. So I don't think there will be much conflict there.

This is also a completely personal opinion, but the question of whether CAR-T cell therapy can be expected to cure the disease is also very important in considering the order of treatment, and for diffuse large B-cell lymphoma that has recurred, a certain percentage of patients can be expected to be cured with CAR-T cell therapy.

But so far, there is a little bit of long-term follow-up data for follicular lymphoma with CAR-T cell therapy. The PFS, or Duration of Response curve doesn't flatten out. So, unfortunately, there is no consensus that CAR-T cell therapy for follicular lymphoma is still a treatment modality that can provide a cure at this time.

This can lead to more manageable toxicity or, for example, to a certain percentage of patients experiencing significant and prolonged thrombocytopenia after CAR-T cell therapy is completed, or to complications due to severe immunodeficiency. It is more frequent than bispecific antibodies. In that case, my personal opinion is that it would probably be more reasonable to use a bispecific antibody first for the treatment of follicular lymphoma relapse.

Yokoyama [M]: Thank you very much.

Miyata [M]: Thank you. For those in the venue, if you have any questions, the one in the most front, please go ahead.

Sakai [Q]: My name is Sakai from UBS Securities. I would like to ask you a follow-up question to what you just said, including a confirmation, about the options of treatment in the table on page 33. From what you're saying now, this is the third line, but is it correct to understand that there are no major changes in the basic approach to treatment for the first and second lines?

Then you mentioned the name of a product called bendamustine, which I think is quite an old product. How will this product be used in the future, and whether this can still adequately endure in the market. I would like to ask you about that perspective as well.

Maruyama [A]: Thank you. As for whether first- and second-line treatment methods will change significantly at this point, they probably will not. For example, clinical trials are currently being conducted on first-line treatment, and recently, the results of Phase III trials using a completely different class of drug for the treatment of relapsed follicular lymphoma, including second-line treatment, were published, so it is expected that such drugs will be added to second-line treatment in the near future, but I don't think that the treatment system will change significantly.

In other words, initial therapy is by chemotherapy with CD20 antibody, plus or minus maintenance therapy. I think it will probably take the form of rituximab in the second line, plus lenalidomide, plus or minus alpha.

As for the positioning of bendamustine, I think the current situation is still the same. However, bendamustine has a completely negative effect, especially when used in the early stages before the CAR-T cell therapy is administered, and when there is not much time between the treatment periods with bendamustine. In other words, bendamustine strongly reduces T cells, especially, both CD4 and CD8. We know that this would have an impact on the outcome of CAR-T cell therapy, or on the creation of it.

The positioning of the use of bendamustine, which is mainly the initial treatment, is probably still the same. However, the use of bendamustine for patients who are considering CAR-T cell therapy or bispecific antibodies in the event of relapse is still, and will continue to be, discouraged.

In particular, I mentioned POD24 earlier today, but for many patients, even if maintenance therapy is performed using both bendamustine in combination with CD20 antibodies, BR or BG, it is possible to achieve long-term, multi-year treatment, so for those patients, the impact of the initial use of bendamustine on subsequent cell-based immunotherapy probably does not need to be a major concern.

However, if the POD24 event, which is problematic and requires attention because it significantly impacts prognosis, occurs immediately after the first treatment, it is highly likely to have a negative effect on CAR-T cell therapy and bispecific antibodies. For this reason, there is also hope that combining bispecific antibodies with the first treatment will reduce POD24 events, although this may be a little off-topic from your question. To answer your question, I would like to reiterate that the situation is still the same.

Sakai [Q]: Okay, thank you. And one more thing, I believe you mentioned something about T cell's revival and recovery. In what form is this proven? I would like to check if there is some form of paper on the subject. Is that OK?

Maruyama [A]: Of the ones we talked about today, it is B, not T. I told the story of B's recovery in my slides. That data is based on the number of B cells. That is because the number of B cells in the peripheral blood, a subset of lymphocytes, will tell you if it is B or not, so that is what we are checking them.

Sakai [M]: I see. Thank you.

Saga [Q]: I am Saga, a freelance writer. I would like to confirm two points with Dr. Aoki. In terms of your commitment to fixed duration, am I correct in understanding that fixed duration also applies to the other follicular lymphoma treatment lines you are developing for Lunsumio, as well as the expanded indication for NHL?

Aoki [A]: Thank you. I think that your understanding is correct.

Saga [Q]: For example, in this case, Lunsumio would be fixed and lenalidomide only continues, is that the design what you are thinking about?

Aoki [A]: I cannot give you a specific schedule for the administration of lenalidomide, but it will be completed in a certain period of time. As I mentioned earlier, the background to this is that Chugaiand the Roche Group, as well as the study that Dr. Maruyama introduced, have been terminated after a certain period of time. The maintenance therapy was also included, but this time we heard from doctors and patients that they wanted to use the maintenance therapy as a single agent, or even as a third-line fix, and that it would be difficult to develop a treatment that would continue until the disease worsens.

Saga [Q]: I see. Also, Dr. Maruyama, regarding the sequence you mentioned earlier, if a patient relapses after using Lunsumio with fixed duration, as you mentioned CAR-T. What is the expected profile of patients for whom re-administration of Lunsumio should be considered?

Maruyama [A]: Regarding the re-administration of mosunetuzumab, there is very limited data, but there is some data on re-administration. That is part of the results of the even longer follow-up data than the three-year follow-up data I showed you earlier, which was reported in last year's ASH.

Because we have a fixed treatment period and follow-up for a long time, as a result, we have observed people who have been re-administered the drug, and although it is still only data for a few people, about five people, the response of those who have been re-administered the drug is very good.

So, after treatment with mosunetuzumab has been completed and a sufficient response has been achieved, there are no detailed data on how long the response period should be, but in general, I think that there is a high possibility of a re-response being achieved through re-administration in patients who have achieved a response duration of at least one year. There is also a lack of data on whether re-administration or CAR-T is better for such patients.

Saga [M]: I understand. Thank you very much for your attention.

Muraoka [Q]: Thank you. I am Muraoka from Morgan Stanley. I have a question for Dr Maruyama. It's a question that's like a confirmation of the previous question. I heard that CAR-T and bispecifics, I was thinking of them very simply, but from what you said earlier, in FL and DLBCL, CAR-T is used first in DLBCL, and then bispecifics are used afterwards. With FL, it's the opposite, and it's more reasonable to use bispecifics first and then CAR-T. I know it's a very rough question, but is my understanding okay?

Maruyama [A]: Thank you for your question. I think that is generally fine how you understand it. I say generally, because this is why the answer will include my personal opinions to a considerable extent, but it is correct that I said that CAR-T cell therapy has a high priority for DLBCL because a cure can be expected.

CAR-T cell therapy is the standard treatment for patients with diffuse large B-cell lymphoma who are refractory to first-line treatment or who relapse within one year. So far, it has been autologous transplantation, for the second line. In the case of patients who are refractory to initial treatment or who have early relapse,

CAR-T cell therapy has been shown to be superior to autologous transplantation in Phase III comparative trials, so since it is young patients who are eligible for autologous transplantation in particular, CAR-T cell therapy should be considered as the standard treatment for these patients as a matter of priority.

As there is no such solid Phase III data for third-line and beyond, in terms of such patients, CAR-T cell therapy and bispecific antibodies are basically on a par in terms of the evidence, but as you pointed out, there is a group of patients with DLBCL who can expect a cure with CAR-T cell therapy even in third-line and beyond. If such patients have access to CAR-T cell therapy, and if they are young, then CAR-T cell therapy is rather high on the priority list.

Therefore, I answered that the order of CAR-T and bispecifics depends on the disease. Did I answer to your question?

Muraoka [Q]: Thank you. It may not be from a scientific or medical perspective, but I have the image that CAR-T is a very troublesome or difficult treatment. Is that not a major factor in the doctors' decisions as to which to use first, which not to use, or which to use bispecifics or CAR-T? Or do you think that you will inevitably put off the difficult treatment?

Maruyama [A]: That is also a very important point, and in reality, such points have a significant impact on the implementation of CAR-T cell therapy, in the current situation. The number of facilities offering the treatment is not increasing very quickly, and this is partly due to various facility requirements, but as you say, CAR-T cell therapy is complicated, so there are cases where patients cannot wait for treatment or there is no opportunity to introduce them to CAR-T cell therapy due to access issues. That is what happens in reality. For those patients, I believe that treatment with bispecific antibodies are practically performed.

Muraoka [M]: Okay, thank you. That's all from me.

Miyata [M]: Thank you. Next, Ms. Sogi, AllianceBernstein securities. Please go ahead.

Sogi [Q]: Thank you for taking my question. You mentioned earlier that it is a commitment between your company and Roche regarding the fixed duration. To begin with, considering from the MOA, since it is a treatment for B-cell depletion, once the B-cells have been depleted, there will be no more malignant B-cells, so does it mean where continuous treatment is not necessary?

Aoki [A]: Thank you. As for what you just said, that is the story in our mind. Originally, there were many regimens that did not continue to the disease progression stage, including those for blood cancers, especially follicular, DLBCL, and the rituximab and obinutuzumab that we have. We have basically adopted this concept for this project as well and have decided to use a fixed duration.

I think the basic principle is similar to what you are thinking, but the basic history of the treatment makes it such a commitment.

Sogi [M]: I understand. Thank you.

Miyata [M]: Thank you. Does anyone have any other questions? You are welcome to join us at the venue or via Zoom webinar. Since there are no further questions, we will conclude the question-and-answer session.

This concludes the information meeting on Lunsumio of CHUGAI PHAMACEUTICAL. If you have additional questions, please contact Corporate Communications Department. The phone number and email address are provided on the last page of the presentation materials.

Please note that a survey will be available on the desk for those in the audience in the venue and on the Zoom for those participating via Zoom. We would appreciate your cooperation in this regard for future reference. Thank you for joining us today despite your busy schedule. Thank you very much.

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