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Information Meeting on Polivy

June 3, 2021

Event Summary

[Company Name]	CHUGAI PHARMACEUTICAL CO., LTD.
[Company ID]	4519-QCODE
[Event Language]	JPN
[Event Type]	Special Announcement
[Event Name]	Information Meeting on Polivy
[Fiscal Period]	
[Date]	June 3, 2021
[Number of Pages]	46
[Time]	13:30 – 14:49 (Total: 79 minutes, Presentation: 56 minutes, Q&A: 23 minutes)
[Venue]	Dial-in
[Venue Size]	
[Participants]	
[Number of Speakers]	2

Takaki Koga	Polivy Lifecycle Leader
Koji Izutsu	Department of Hematology, National Cancer Center Hospital

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Shinichiro Muraoka	Morgan Stanley MUFG Securities Co., Ltd.
Hidemaru Yamaguchi	Citigroup Global Markets Japan Inc.
Fumiyoshi Sakai	Credit Suisse Securities (Japan) Limited
George Zhou	Goldman Sachs Japan Ltd.

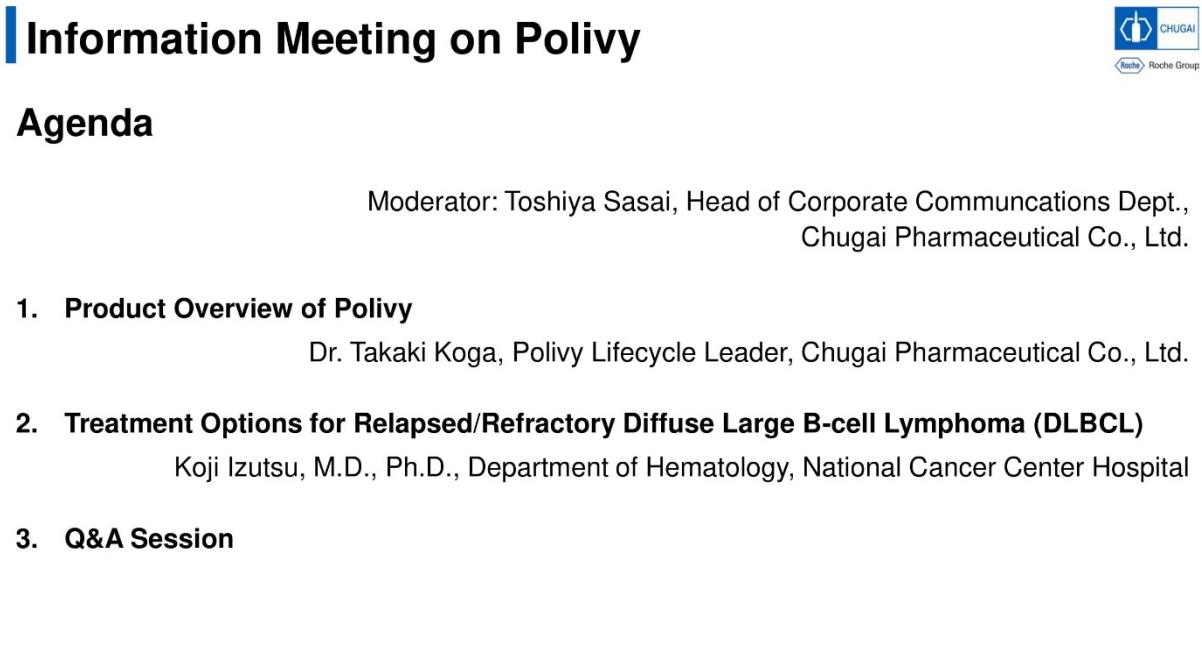
*Analysts that SCRIPTS Asia was able to identify from the audio who spoke during Q&A.

Presentation

Sasai: Thank you for attending today despite your busy schedule. I am Sasai of the Corporate Communications Department, and I will be the moderator for today's session. Thank you for your cooperation.

The anti-cancer agent Polivy received approval from the Japanese Ministry of Health, Labour, and Welfare on March 23 as a new treatment for relapsed or refractory diffuse large B-cell lymphoma, or DLBCL. This is a first-in-class antibody-drug conjugate, or ADC, that targets the CD79b protein, which is specifically expressed in many B cells. The therapy consists of a humanized anti-CD79b monoclonal antibody, and a tubulin polymerization inhibitor linked together.

In order to prevent the spread of coronavirus infection, today's session will be conducted in the form of a conference call.

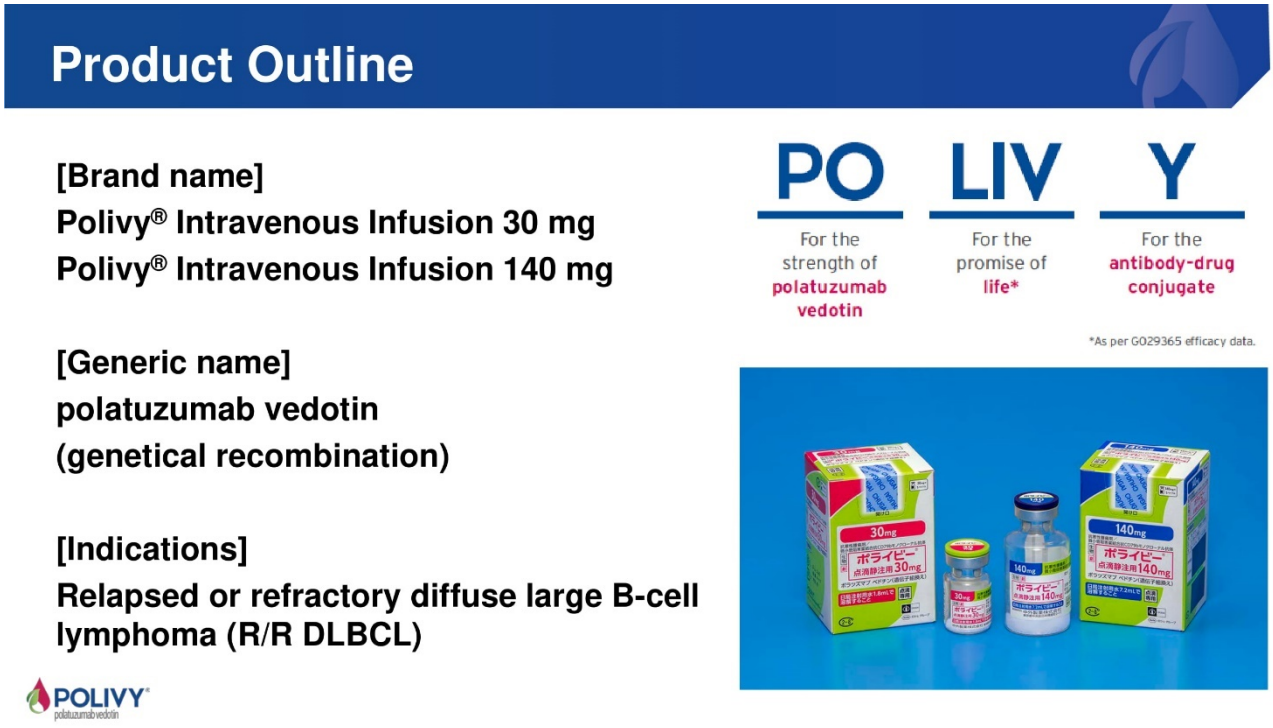


The agenda for today's meeting can be found on the web screen and on the first page of the presentation materials. The presentation will proceed according to this agenda.

Today, we have invited Dr. Koji Izutsu from the Department of Hematology at the National Cancer Center Hospital as a special lecturer. I would like to skip Dr. Izutsu's biography here, as it is included in the presentation materials for today.

Questions will be taken collectively after all presentations have been completed.

First of all, I would like to start with an explanation by Dr. Koga.



Koga: I'm Koga, Chugai's Polivy Lifecycle Leader. Thank you.

Today, I would like to give you an overview of what kind of therapy Polivy is. After that, we will hear from Dr. Izutsu.

Polivy is marketed as a 30-milligram or 140-milligram intravenous infusion. The generic name is polatuzumab vedotin, genetical recombination. It is indicated for the treatment of relapsed or refractory diffuse large B-cell lymphoma, also known as DLBCL.

The name "Polivy" comes from the PO part of the generic name polatuzumab vedotin. “Liv,” as you know, comes from the word “Life.” The "Y" represents the antibody part of this antibody-drug conjugate.

Development History

Mar. 2011	Global phase I study started by Roche
Jul. 2014	Phase I study started in Japan
Oct. 2014	Global phase Ib/II study started in patients with R/R FL and DLBCL (GO29365)
Jun. 2017	PRIME designation (Europe)
Sep. 2017	Breakthrough Therapy designation (US)
Oct. 2018	Phase II study (P-DRIVE) started in patients with R/R DLBCL in Japan
Jun. 2019	Accelerated approval in the US
Nov. 2019	Orphan drug designation in Japan
Jan. 2020	Approved in Europe
Jun. 2020	Application for approval in Japan (R/R DLBCL)
Mar. 2021	Approved in Japan (33rd in the world)

POLIVY polatuzumab vedotin

FL: Follicular lymphoma
DLBCL: Diffuse large B-cell lymphoma
PRIME: Priority Medicines

Cited from the interview form of Polivy intravenous infusion 30 mg/140 mg [prepared in May 2021 (Ver.3)]

4

This slide outlines the development process.

Development began overseas at Roche in 2011. In Japan, we started Phase I in 2014. In 2014, the same year, a second-line study was started overseas for patients with relapsed or refractory lymphoma, including patients with DLBCL.

This study was called GO29365, and it is the most important major trial. As Dr. Izutsu will talk about later, the results of this study showed very high efficacy and safety, and applications have been submitted, on the basis of Phase II results, both to the FDA and the EU.

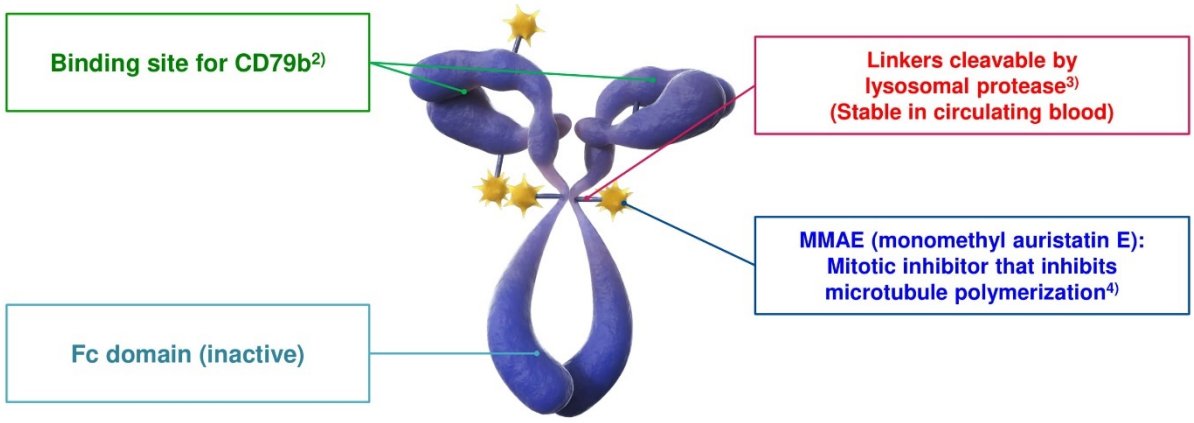
In response to this, we had originally expected to conduct a Phase III trial in Japan, but when we heard that an overseas application would be filed in Phase II, we immediately planned a bridging trial in Japan. That was in 2018, when we conceived of the P-DRIVE trial. This is the second major trial in this application.

Approval was granted in the US in 2019. Approval in Europe followed in January 2020. In June of last year, we filed an application in Japan and received orphan drug designation. In March of this year, we received approval, 9 months after our application. As a result, the lag period was less than 2 years: 1 year and 9 months after approval in the US, and 1 year and 2 months after approval in Europe.

We have been working hard to achieve this.

Structure of Polivy (conceptual image)

Polivy is an antibody-drug conjugate (ADC) targeting CD79b[1)].



POLIVY polatuzumab vedotin

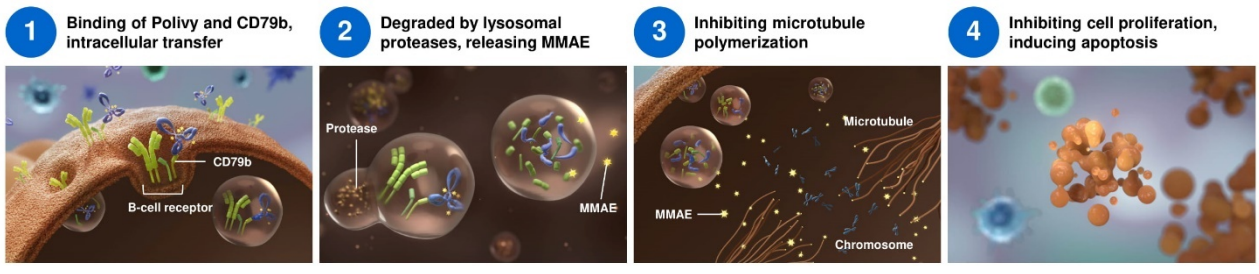
1)Li D, et al. Br J Pharmacol. 2019; 176(19): 3805-3818.
2)Polson AG, et al. Expert Opin Investig Drugs. 2011; 20(1): 75-85.
3)Dornan D, et al. Blood. 2009; 114(13): 2721-2729.
4)Doronina SO, et al. Nat Biotechnol. 2003; 21(7): 778-784.
[COI: The literature 1, 2) includes the employees of Genentech.
The literature 3) includes the employees of Genentech and the authors funded by Genentech.]

5

The structure of Polivy is a little more complicated than that of ordinary antibodies.

The antibody part is designed to recognize CD79b, which is located on the surface of B cells. The antibodies are attached to stable linkers which are degraded in a cell, at the end of which is attached a toxin called MMAE, which causes cell death. This structure is called an antibody-drug conjugate.

Mode of Action (conceptual image)



- Polatuzumab vedotin binds to CD79b expressed on the cell membrane of tumor cells and is taken up by cells[1-3)].
- The linker is cleaved by proteases, and MMAE is released into cells[4)].
- Released MMAE is considered to inhibit tumor growth by binding to microtubules, inhibiting cell division, and inducing apoptosis[5-7)].

MMAE: Monomethyl auristatin E

POLIVY polatuzumab vedotin

1) Pfeifer M, et al. Leukemia. 2015; 29(7): 1578-1586.
2) Polson AG, et al. Blood. 2007; 110(2): 616-623.
3) Polson AG, et al. Cancer Res. 2009; 69(6): 2358-2364.
4) Sutherland MSK, et al. J Biol Chem. 2006; 281(15): 10540-10547.
5) Bai R, et al. J Biol Chem. 1990; 265(28): 17141-17149.
6) Doronina SO, et al. Nat Biotechnol. 2003; 21(7): 778-784.
7) Francisco JA, et al. Blood. 2003; 102(4): 1458-1465.
[COI: The literature 3) includes the employees of Genentech.
The literature 1, 2) includes the employees of Genentech and the authors funded by Genentech.]

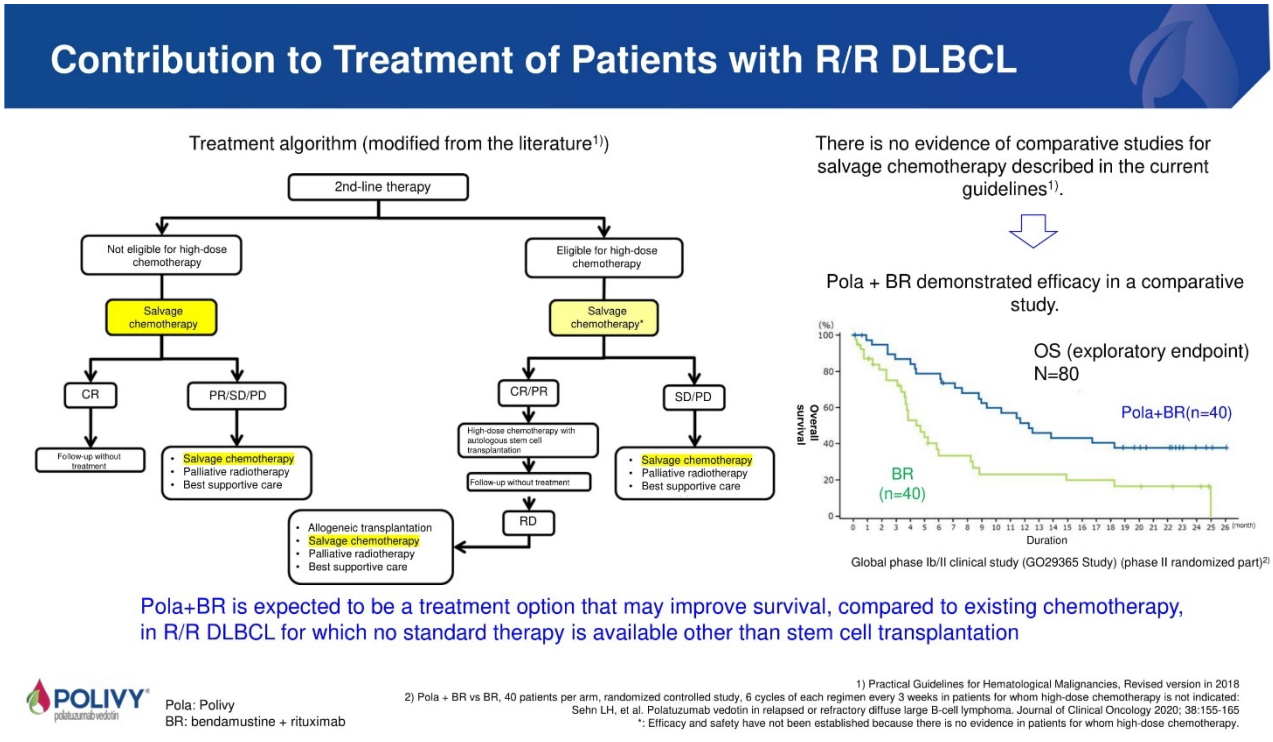
6

Here's how it works.

When Polivy binds CD79b on the B-cell surface, it is transported inside the cell. At that time, the linker binding the drug part is cleaved by protease, and the drug, MMAE, is released into the cell.

MMAE inhibits the action of microtubules, a cellular apparatus necessary for cell division and proliferation. If this happens, cancer cells will not be able to divide and will undergo apoptosis, or cell death.

Compared to general chemotherapy, Polivy, which is treated in combination with bendamustine, and rituximab, has a very high cell specificity, so it is designed to enter the necessary cells and act on them from the inside.



This slide describes therapeutic positioning.

Patients with DLBCL do unfortunately experience relapses, and patients who have relapsed or become refractory after the first treatment are moved to stem cell transplantation if they are young and have some reserve. If not, rescue chemotherapy is generally given. Patients who have failed transplantation may be given another round of rescue chemotherapy.

In this figure, the area shown in yellow is for relapsed or refractory DLBCL, and Pola-BR represents Polivy.

One thing I'd like to add is this part. As for the rescue chemotherapy for transplant recipients, Pola-BR is in a trial for transplant-ineligible patients, so we have no evidence of efficacy and safety at this point, although we have obtained the indication for this part of the trial.

One thing that is unique about second-line, relapsed/refractory DLBCL is that in national and international guidelines, until now, there has been no standard therapy other than stem cell transplantation that can be used as a definitive standard therapy.

Even if a therapy is listed in the guidelines, we have checked all the guidelines in Japan and abroad, but there are no proper comparative studies, so I think we can say that the GO29365 study was the first regimen to show a clear drug effect in a comparative study.

As you can see here, the OS, or overall survival of Pola-BR is significantly better than that of the control group.

Characteristics of Polivy

Brand name	Polivy intravenous infusion 30 mg	Polivy intravenous infusion 140 mg
Dosage form	Injection (vial)	
Description	White to off-white mass	
pH[Note1)]	5.0 to 5.6	
Osmotic pressure ratio[Note 1), Note 2)]	Approximately 0.5	

Note 1) Upon reconstitution with water for injection (for IV Infusion 30 mg: 1.8 mL; 140 mg: 7.2 mL)
Note 2) Ratio to physiological saline

POLIVY
polatuzumab vedotin

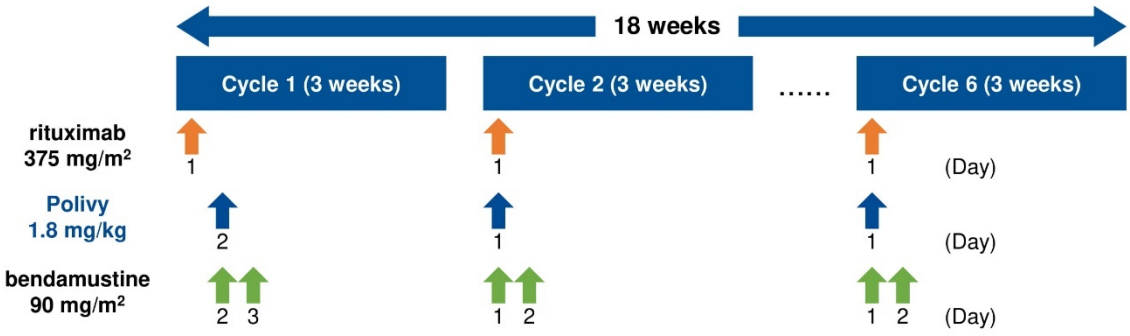
Cited from the interview form of Polivy intravenous infusion 30 mg/140 mg [prepared in May 2021 (Ver.3)]

8

It is sold as a freeze-dried product and is to be dissolved with an injectable solution when needed.

Dosage and Administration

The recommended adult dosage is 1.8 mg/kg (body weight) of polatuzumab vedotin (genetical recombination) administered by intravenous drip infusion once every 3 weeks for 6 doses in combination with bendamustine hydrochloride and rituximab (genetical recombination). The first infusion should be administered over 90 minutes, and if well tolerated, the duration of subsequent infusions may be shortened up to 30 minutes. The dose should be appropriately reduced according to the patient's condition.



POLIVY
polatuzumab vedotin

Prepared based on the package insert revised in May 2021 (Version 3)

9

This slide shows dosage and administration.

Polivy is administered with rituximab and bendamustine for one cycle, and then for up to 6 cycles. Doses are spaced 3 weeks apart. It is administered for a total of 18 weeks.

For safety reasons, rituximab is administered only as part of the first cycle.

Conditions for Approval

1. A risk management plan should be formulated and implemented appropriately.
2. Given the very limited sample sizes in clinical trials in Japan, a post-marketing all-patient drug use surveillance required until data on a certain number of patients has been collected to determine the background information of the patients using the product and to, in the near term, collect data on the safety and efficacy of the product, implementing necessary measures to ensure the appropriate use of the product.

POLIVY polatuzumab vedotin

Prepared based on the package insert revised in May 2021 (Version 3)

10

This slide details conditions of approval.

A drug risk management plan, or RMP, should be developed and implemented. Also, the number of cases in clinical trials in Japan is extremely limited. In fact, there were 35 patients in the P-DRIVE study, so until more data are collected, we will conduct result surveying of all patients. There are conditions attached, such as additional collection of efficacy and safety data.

Overview of Risk Management Plan (RMP) for Polivy

Safety Specification

[Important identified risks] Bone marrow depression (neutropenia, thrombocytopenia, anemia) Peripheral neuropathy Infection Infusion reaction	[Important potential risks] Progressive multifocal leukoencephalopathy (PML) Tumor lysis syndrome Reproductive toxicity Hepatic function disorder
[Important missing information] None	

	Pharmacovigilance Plan	Risk minimization Plan
Usual	• Collecting and evaluating individual cases • Research report: Collecting and evaluating literature • Report on measures taken overseas: Collecting and evaluating information on measures taken overseas • Signal detection and evaluation by the data mining method, etc. for adverse events (including death)	• Preparing (revising) package insert • Drug guide for patients
Addition	• Collecting information by Early Post-marketing Phase Vigilance • General Drug Use-Results Survey (all-case surveillance) • Post-marketing clinical study continued from phase II clinical study	• Providing information by Early Post-marketing Phase Vigilance • Providing information to healthcare professionals (guide for proper use) • Providing information to patients (patient handbook) • Explanation in advance / providing information via website (Early Post-marketing Phase Vigilance FB, number of adverse reactions, number of serious adverse reactions, etc.)

Company's voluntary activities

POLIVY polatuzumab vedotin

Source: Risk Management Plan for Polivy intravenous infusion 30 mg, 140 mg

11

This slide is the Polivy risk management plan.

As for safety considerations, myelosuppression, peripheral neuropathy, infections, infusion reactions, PML, tumor lysis syndrome, reproductive toxicity, and hepatic dysfunction are identified as important specific risks in the drug safety monitoring plan and risk minimization plan.

The safety monitoring plan will be in addition to the usual actions as an extension of the clinical trial in order to collect information through post-marketing surveillance, and all-case surveillance.

In the risk minimization plan, we create a prescribing information for the drug, then provide information for post-marketing surveillance, and then develop a guide for proper use.

We will also act within the framework of voluntary activities, such as with the provision of information through patient handbooks, websites, prior explanations, and so on.

This concludes my presentation. Thank you very much.

Sasai: Next, we will move on to a lecture by Dr. Izutsu, Chief of the Division of Hematology, National Cancer Center Hospital. Dr. Izutsu, please go ahead.

Izutsu: Hello, everyone. I am Koji Izutsu from the Department of Hematology, National Cancer Center Hospital. In the Department of Hematology, as a hematologist, I am in charge of treating patients with malignant lymphoma and have been involved in clinical development trials for polatuzumab vedotin, or Polivy.

The title of my talk is "Treatment Options for Relapsed/Refractory DLBCL."

COI disclosure

Presenter: Koji Izutsu

■ The companies that the presenter has COI relationships to be disclosed are as follows:

(1) Advisor, etc.:	None
(2) Stock ownership / profit:	None
(3) Patent royalty:	None
(4) Lecture fee:	Janssen Pharmaceutical, Ono Pharmaceutical
(5) Manuscript fee:	None
(6) Contract/joint research expenses:	AbbVie, Insight, Celgene, Novartis, Chugai Pharmaceutical, Janssen Pharmaceutical, Yakult Honsha, Daiichi Sankyo, Beigene
(7) Scholarship donation:	None
(8) Affiliation to endowed courses:	None
(9) Rewards including gifts, etc.:	None
(10) Employed by a company or profit organization:	None
(11) Provision of samples, drugs, etc.:	None
(12) Off-label use:	None

13

This is my COI.

Therapeutic Strategies for Relapsed/Refractory (R/R) DLBCL

- Epidemiology and treatment of DLBCL
- What is R/R DLBCL?
- 2nd-line treatment of patients who are eligible for autologous transplantation
- Challenging Situations
  - 2nd-line refractoriness
  - Post-autotransplant relapse
  - Elderly patients who are ineligible for autotransplantation
    - Pola-BR

DLBCL: diffuse large B-cell lymphoma
BR: bendamustine+rituximab

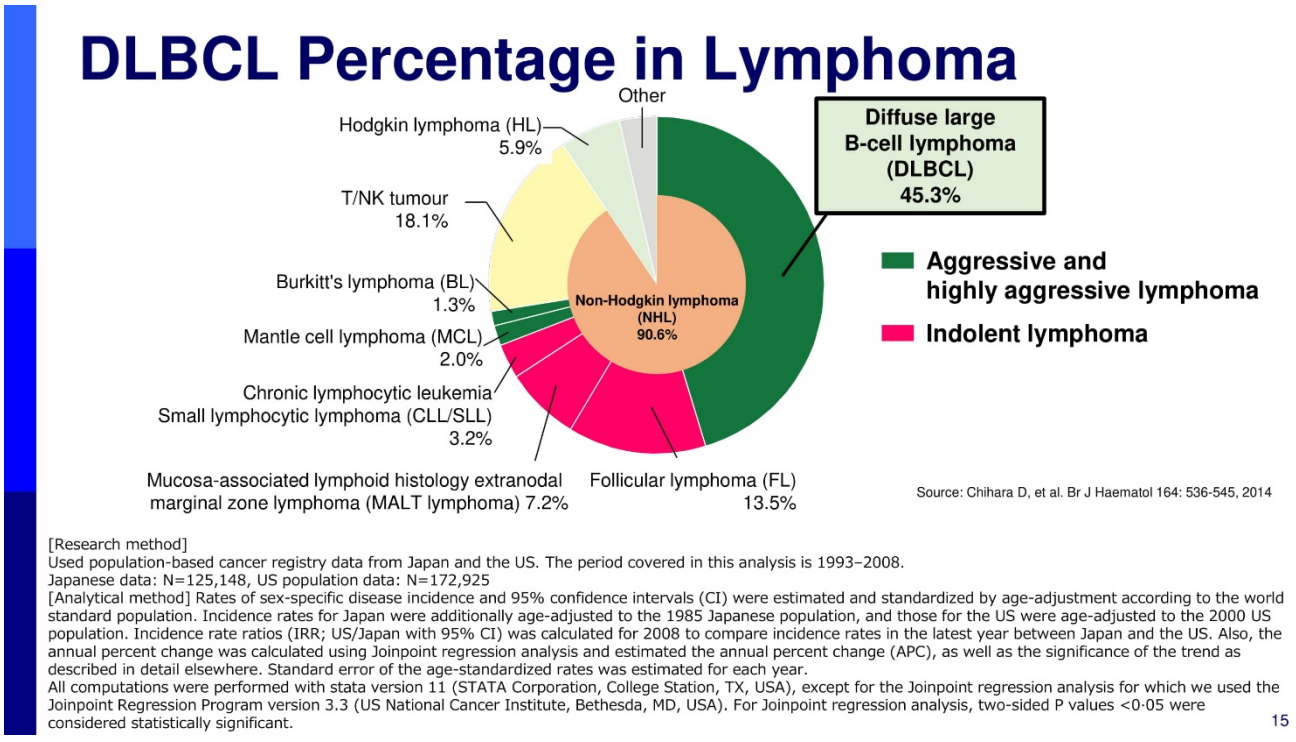
14

Today, I would like to touch on the following areas in my talk.

First of all, what is diffuse large B-cell lymphoma, or DLBCL, what is its position among malignant lymphomas, and how many patients are there? Next, I will talk about the situation with relapsed and refractory DLBCL.

Then I will talk about the flow of treatment for relapsed and refractory DLBCL so far, including the standard secondary treatment in young patients with no organ damage who are eligible for autologous transplantation. After that, I will talk about some situations when such standard secondary treatment does not work.

I would like to talk about the clinical results of Pola-BR, which is a combination of polatuzumab vedotin and BR therapy, for the second line or later treatment options of patients who are not eligible for autologous transplantation, such as the elderly.



First of all, what kind of disease is malignant lymphoma? I will talk about the position of DLBCL in this context.

Malignant lymphoma is a malignant tumor that originates from lymphocytes. It is a cancer that originates from lymphocytes. It is estimated that 30,000 to 35,000 patients are diagnosed with malignant lymphoma per year in Japan, and DLBCL is the most common form of the disease.

The trend is the same in every country of the world.

As shown in this data based on cancer registries, DLBCL is said to be present in 45% of patients diagnosed with malignant lymphoma.

Classification according to Symptom Progression

[Classification of non-Hodgkin lymphoma (NHL) according to grade]

Grade	Prediction of progression (without treatment)	Type of non-Hodgkin lymphoma (NHL)
Low grade (Indolent lymphoma)	In years	Follicular lymphoma (FL) (Grade 1, 2) Mucosa-associated lymphoid tissue lymphoma (MALT lymphoma) Lymphoplasmacytic lymphoma (LPL) Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) Mycosis fungoides (MF) Sézary syndrome (SS), etc.
Intermediate grade (Aggressive lymphoma)	Monthly basis	Follicular lymphoma (FL) (grade 3) Mantle cell lymphoma (MCL) Diffuse large B-cell lymphoma (DLBCL) Peripheral T-cell lymphoma (PTCL) Extranodal nasal type NK/T cell lymphoma (ENKL) etc.
High grade (Highly aggressive lymphoma)	In weeks	Burkitt's lymphoma (BL) etc.

Source: National Cancer Research Center Cancer Information Service malignant lymphoma https://ganjoho.jp/public/cancer/ML/index.html (accessed May 2021) 16

Malignant lymphoma is classified into 3 grades according to the speed of progression: low-grade, intermediate-grade, and high-grade.

Among these, DLBCL belongs to the category known as intermediate-grade or aggressive lymphoma, where the lesions grow in size, on a monthly basis, in the untreated, pre-treatment situation.

Clinical Features of DLBCL

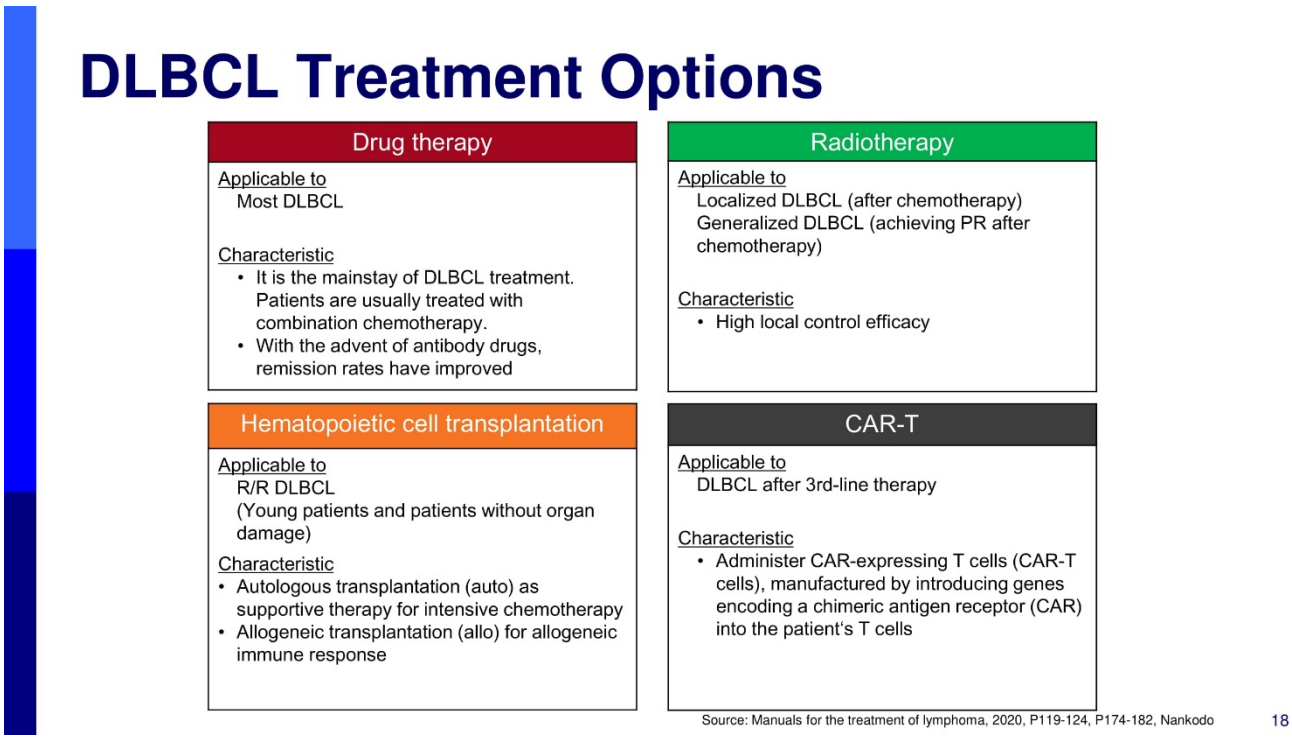
Clinical features of DLBCL	
Clinical classification	'Aggressive' B-cell lymphoma progressing in months
Incidence	Approximately 45% of malignant lymphomas. The most common type of the disease.
Age at onset	Prevalent in middle-aged and elderly people, mainly in their 60s and 70s.
Symptoms	Lymphadenopathy is common. Other symptoms may occur depending on the site of onset and organs involved.
Lesion	Both segmental and extranodal. DLBCL can start almost anywhere in the body (particularly the gastrointestinal tract, skin, central nervous system, bone, and testis)
Prognostic model	International Prognostic Index (IPI); age-adjusted IPI; NCCI-IPI

Source: Lymphoma Seminars for Level Up, Minami-Edo, p140-141, 2014
Easy-to-understand Lymphoma lecture, tabulated from MEDICAL VIEW, p. 76, 2015 17

The characteristics of DLBCL are, again, typical of aggressive B-cell lymphoma, which accounts for 45% of all malignant lymphomas. The median age of onset is between 60 and 70 years old, and males tend to be slightly more common.

The lesions can occur not only in the lymph nodes, the superficial lymph nodes but lymph nodes in the mediastinum or abdomen, as well as in various other organs other than the lymph nodes, such as the stomach and colon.

There are several known prognostic models, such as the International Prognostic Index, or IPI, shown here, and other similar prognostic models.



Various treatment options are being used for DLBCL.

To name a few, there is drug therapy, radiation therapy, hematopoietic stem cell transplantation, and the recently introduced CAR-T cell therapy.

The mainstay of treatment in this context is drug therapy. Drug therapy is the mainstay of treatment for DLBCL, usually using multi-drug chemotherapy, both for initial treatment and for treatment after relapse.

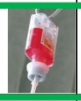
As I will show you later, R-CHOP therapy is used as the first-line treatment for DLBCL, and the remission rate and survival rate of DLBCL patients have improved since before the introduction of the "R," the anti-CD20 antibody rituximab.

Radiation therapy may be used in combination with chemotherapy, medication, or later for symptom relief.

Hematopoietic stem cell transplantation is a curative treatment for patients who have failed to respond adequately to drug therapy, and CAR-T cell therapy has a similar position.

We will talk about these treatments in more detail later.

R-CHOP Regimen

rituximab	375 mg/m^2	Day 1	May be given on separate days from the other drugs
cyclophosphamide	750 mg/m^2	Day 1	6 to 8 cycles of treatment, spaced 3 weeks apart Outpatient treatment
doxorubicin 	50 mg/m^2	Day 1	
vincristine	1.4 mg/m^2 (max 2)	Day 1	
prednisolone	100 mg (or 40 mg/m2)	Day 1-5	

Source: Manuals for the treatment of lymphoma, 2020, P249-253, Nankodo 19

This is the typical initial treatment for DLBCL.

This multi-drug chemotherapy called R-CHOP is used. Cyclophosphamide, doxorubicin, vincristine, and prednisolone, these 4 drugs have been used as CHOP therapy for a long time, for 40 years now.

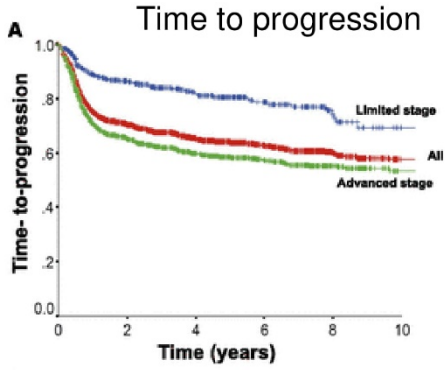
About 20 years ago, rituximab was developed, and CHOP or R-CHOP therapy combined with rituximab became the standard treatment for DLBCL.

Specifically, this treatment involves the use of these 5 drugs by intravenous infusion every 3 weeks, with the last in the list, prednisolone, being the only oral drug and the others being intravenous drugs.

Although there are times when patients are hospitalized for the introduction of treatment, the treatment can essentially be done on an outpatient basis, and is repeated for 6 or 8 courses, so the treatment can be completed in about 5 or 6 months.

R-CHOP in Previously Untreated DLBCL Patients

- British Colombia, Canada
  - N=1,660, diagnosed between 2001-2013
  - Localized stage n=433, advanced stage n=1,227



Source: Sehn L et al. Blood 2015; 125:22

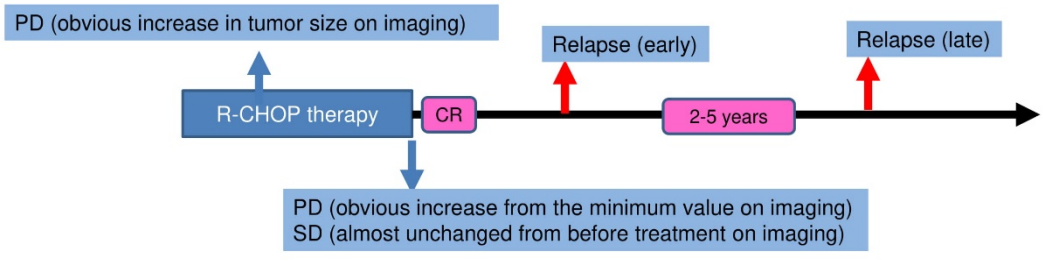
20

It is said that this kind of treatment can cure about 60% or a little more than 60% of all patients with DLBCL.

This is the data from Canada, where treatment is mainly based on R-CHOP therapy. As you can see, the progression-free period curve flattens out at roughly 60%, indicating that the disease can be cured by chemotherapy.

What is R/R (treatment-resistant) DLBCL?

Ex. Relapse or refractory after 1st-line treatment



CR: complete response
PR: partial response
SD: stable disease
PD: progressive disease
R-CHOP: rituximab + cyclophosphamide, doxorubicin, vincristine, prednisolone
Source: Japanese Society of Hematology. Practical Guidelines for Hematological Malignancies, 2018,

21

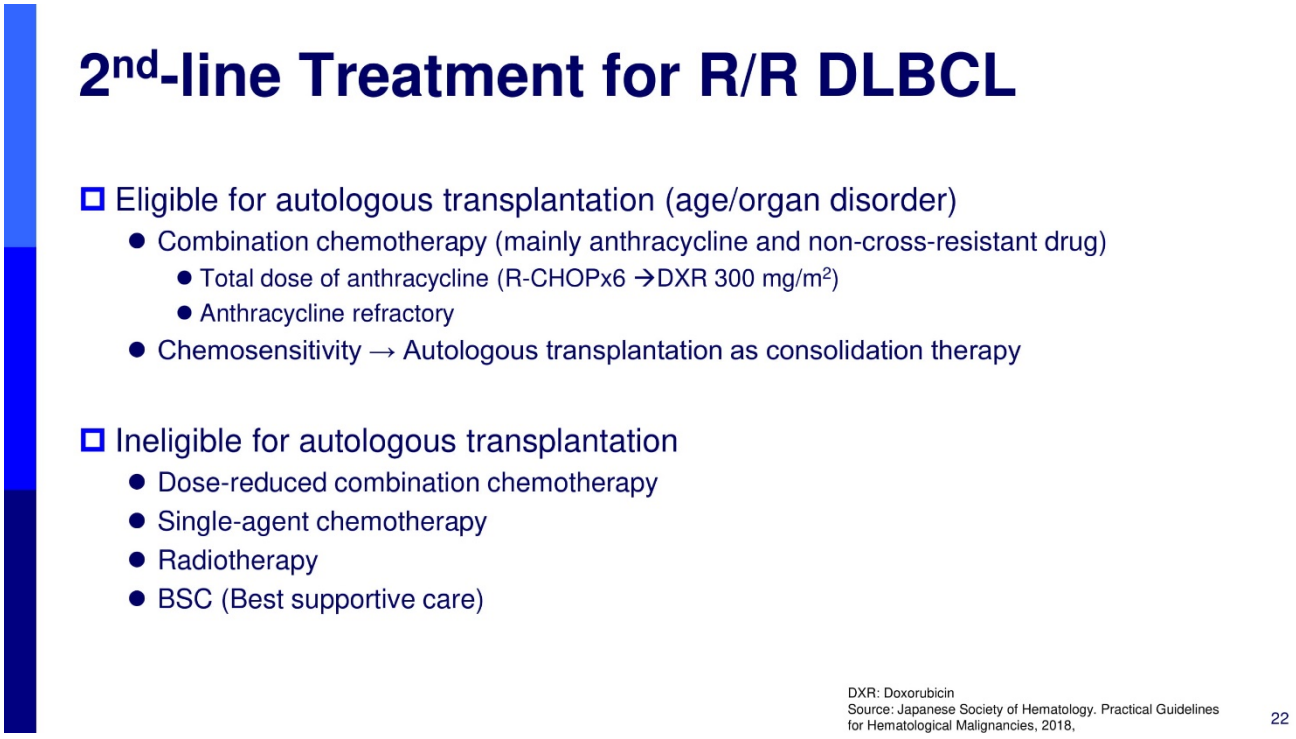
However, unfortunately, some patients do not respond to R-CHOP therapy, or once they have a complete response to R-CHOP therapy, the lesions disappear, but then recur.

With R-CHOP therapy, the first thing we aim for is a complete response, or CR, which, according to the current standard, means that there are no more positive lesions on imaging tests, especially PET-CT.

In most cases, patients with CR can be expected to be cured without any recurrence, but recurrence may occur early or late in the course of treatment, after 2 to 5 years.

Some patients may develop disease progression during or after R-CHOP therapy, or the treatment may not be sufficiently effective, resulting in a mass that is almost unchanged on imaging from before treatment.

During and after this type of treatment, patients who are initially SD or PD, and relapse after CR are called relapse/refractory, and secondary treatment is indicated for these patients.



This slide concerns choice of secondary treatment for relapsed and refractory DLBCL.

First of all, depending on the patient's age, organ damage, and comorbidities, the direction of treatment will change in terms of whether an autologous transplant is possible or not.

For patients who are eligible for autologous transplantation, the general flow of treatment is to give them a high-intensity multi-drug chemotherapy regimen. If it results in tumor shrinkage, then treatment proceeds to high-dose chemotherapy with autologous hematopoietic stem cell transplantation (SCT).

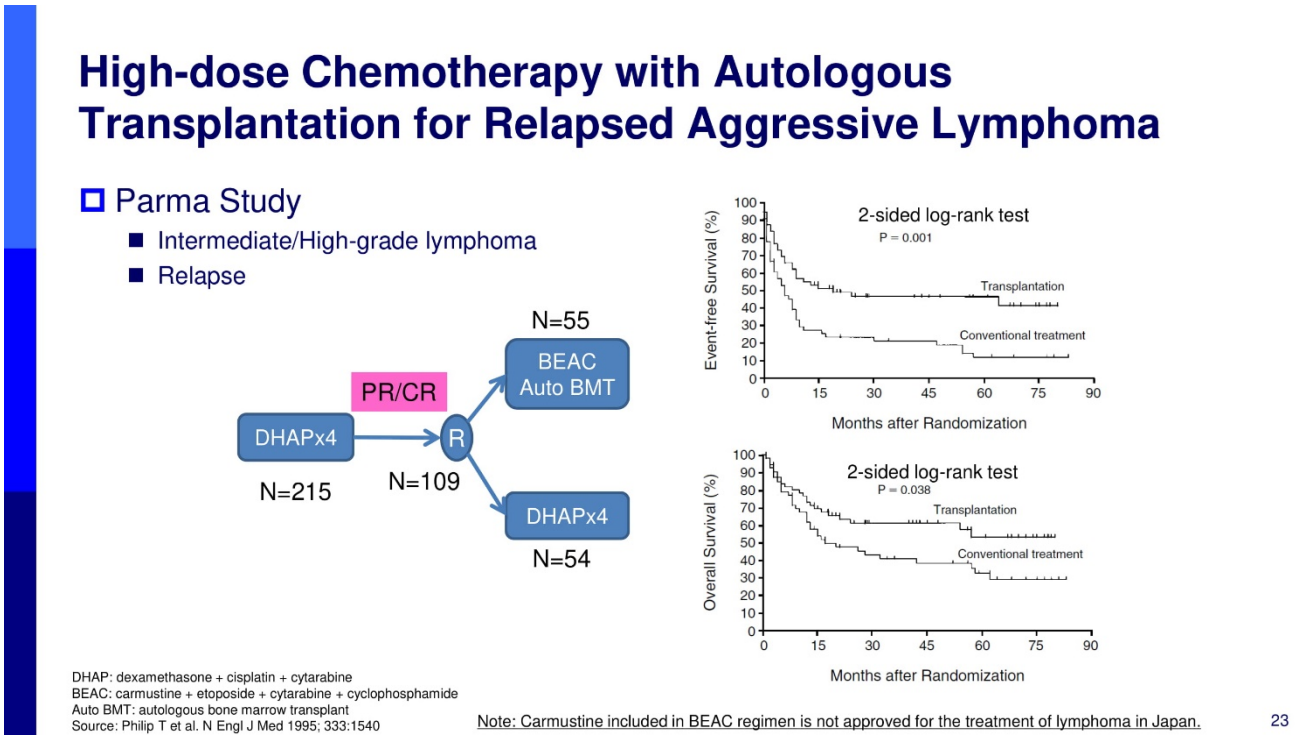
As for the multi-drug chemotherapy used here, the main reason is that the patient is refractory to R-CHOP therapy, which means that we do not use anthracyclines such as doxorubicin, which is a key drug for R-CHOP therapy. Instead, we choose drugs that are not cross-resistant to anthracyclines.

Generally speaking, the upper limit of age for autologous transplantation is between 65 and 70 years old. The idea of the upper limit differs from institution to institution, country to country, and hematologist to hematologist, but in general, the hurdle for eligibility for autologous transplantation is high for elderly patients.

For patients who are not eligible for autologous transplantation, the following options are currently available for second-line treatment.

For patients who are not eligible for autologous transplantation, we use multidrug chemotherapy for those patients who can bear high-intensity treatment. Since multidrug chemotherapy can be very toxic, it may be necessary to use a slightly reduced dose compared to that used for younger patients.

Unfortunately, if we do not use autologous transplantation, we cannot aim for cure after relapse, so we have to maintain the patient's QOL as much as possible. It is also common to choose single-agent chemotherapy or radiation therapy that can be performed on an outpatient basis, or to provide best supportive care without direct treatment for cancer.



For patients who are eligible for autologous transplantation, the treatment rationale is based on the results of a Phase III study published in 1995, which was a very long time ago. In this case, treatment including autologous transplantation should be used as a second-line treatment after relapse.

This is a clinical trial for patients with relapsed or refractory lymphoma, relapsed cases of intermediate or high-grade lymphoma, and patients who have relapsed after once being in CR. This trial was conducted before the advent of rituximab.

Patients who have achieved a response to so-called DHAP salvage chemotherapy as second-line therapy are treated with BEAC, although one of the drugs, carmustine, is not available in Japan.

This is a randomized trial to compare PFS and OS between high-dose chemotherapy and autologous hematopoietic stem cell transplantation, or HSCT, and DHAP therapy with response up to a total of 8 cycles.

Thus, not only event-free survival but also overall survival is prolonged with autologous transplantation. The data supports the idea that in patients who are eligible for autologous transplantation, it is better to proceed to autologous transplantation if there is a response to salvage chemotherapy or a partial response or better.

Salvage Chemotherapy (2nd-line treatment) for DLBCL

Typical regimens used in Japan

	Rit	High-dose araC	GEM	Platinum-based drug	ETP	Alkylating agent	Steroid	Other
R-ESHAP	○	○	-	CDDP	○	-	mPSL	-
R-DHAP	○	○	-	CDDP	-	-	Dexa	-
CHASER	○	○	-	-	○	CY	Dexa	-
R-ICE	○	-	-	CBDCA	○	IFM	-	-
R-DeVIC	○	-	-	CBDCA	○	IFM	Dexa	-
R-GDP	○	-	○	CDDP	-	-	Dexa	-
R-GCD	○	-	○	CBDCA	-	-	Dexa	-
DA-EPOCH-R	○	-		-	○	CY	PSL	DXR
								Continuous infusion

R-ESHAP: methylprednisolone, etoposide, cytarabine, cisplatin + rituximab
CHASER: cyclophosphamide, cytarabine, dexamethasone, etoposide + rituximab
R-ICE: ifosfamide, carboplatin, etoposide + rituximab
R-DeVIC: dexamethasone, etoposide, ifosfamide, carboplatin + rituximab
R-GDP: gemcitabine, dexamethasone, cisplatin + rituximab
R-GCD: gemcitabine, dexamethasone, cisplatin + rituximab
DA-EPOCH-R: Dose adjusted EPOCH-R (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin + rituximab)
CDDP: cisplatin
CBDCA: carboplatin
CY: cyclophosphamide
IFM: ifosfamide
mPSL: methylprednisolone
Dexa: dexamethasone
Rit: rituximab
araC: cytarabine
GEM: gemcitabine
ETP: etoposide

Table: Prepared by the presenter

*Mostly platinum-based regimen
*cytarabine (araC)-containing vs non-cytarabine

24

There are a variety of second-line treatments in patients eligible for autologous transplantation. This is a list of typical regimens that are used in Japan and have been used in the past.

Second-line therapy is often combined with rituximab, an anti-CD20 antibody, as in R-CHOP regimen. There are various regimens, such as R-ESHAP, R-DHAP, CHASER, R-ICE, R-DeVIC, R-GDP, R-GCD, et cetera. Those with the Japanese flag mark here are combination chemotherapies developed in Japan.

Many of both regimens use platinum drugs such as cisplatin or carboplatin. This classification can be broadly divided into regimens that include cytarabine, and those that do not. The regimens that do not include cytarabine can be divided according to whether they use the drug gemcitabine or not.

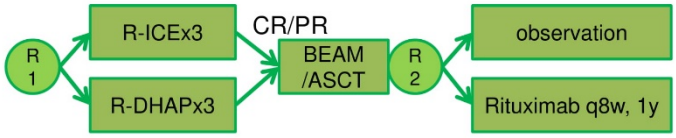
However, each regimen is a combination of multiple drugs, so per cycle, it's not just a one-day infusion like R-CHOP regimen.

Most of the regimens require hospitalization due to the need for continuous infusion for several days, and some drugs require continuous infusion for 24 hours, even while sleeping, as well as strong myelosuppression. This causes some of the most common side effects of anti-cancer drugs.

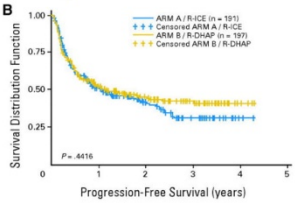
In the past, these regimens were the only way to treat patients, and in the elderly, these regimens were used at reduced doses.

R-ICE vs R-DHAP for R/R DLBCL

- CORAL Study N=396
  - R/R DLBCL



- Response rate: R-ICE 63.5% vs R-DHAP 62.8%
- Mobilization-adjusted response rate: R-ICE 52.3% vs R-DHAP 54.5%
- Autologous transplantation rate: R-ICE 51% vs R-DHAP 55%



AEs	R-ICE vs R-DHAP
Plt transfusion	35% vs 54%
Infection with neutropenia (G3/4)	17% vs 16%
Renal (G3/4)	1% vs 6%

Plt: platelet
ASCT: autologous stem cell transplantation
Source: Gisselbrecht C et al. J Clin Oncol 2010; 28:4184

25

Among the various second-line treatments, several comparative studies have been conducted to determine which treatment is better, but the results of these comparative studies have not shown which treatment is superior.

A representative study compared R-ICE, a regimen that does not include high-dose cytarabine, with R-DHAP, a regimen that includes high-dose cytarabine, in patients with relapsed or refractory DLBCL.

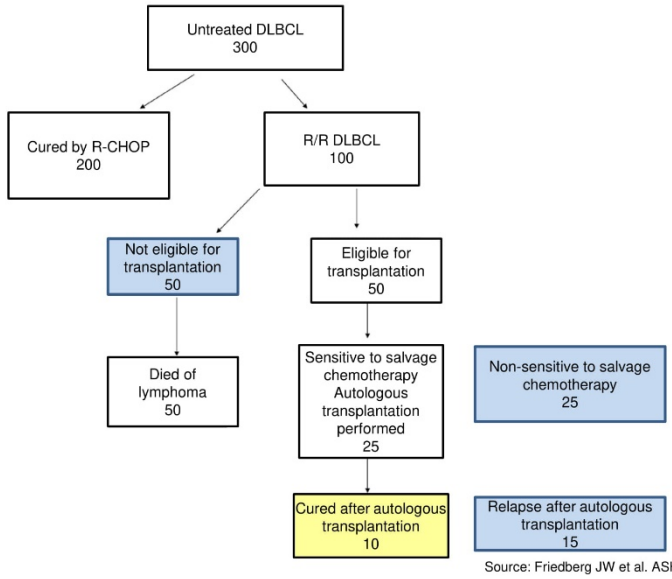
This trial was for patients with relapsed or refractory DLBCL. If patients achieve partial response or better after these salvage chemotherapies, they would proceed to autologous transplantation according to the study settings. The response rate to these salvage chemotherapies was about 60%, and about 50% were able to proceed to autologous transplantation.

What is unfortunate, though, is that if we look at event-free survival, starting from the point where we start this salvage chemotherapy, the results are not very different whether we choose R-ICE or R-DHAP.

The ratio of those who remain relapse-free beyond two-three years is just about 30%. Unfortunately, only a small percentage of patients with relapsed or refractory DLBCL can be cured by second-line salvage chemotherapy followed by autologous transplantation.

Even in these patients eligible for autologous transplantation based on their age or organ disorder, myelosuppression is quite strong, and 30% to 50% of patients require platelet transfusions, or develop infections such as febrile neutropenia after chemotherapy, and other adverse events.

Limited Number of Patients with R/R DLBCL Can Achieve Cure by Autologous Transplantation



Source: Friedberg JW et al. ASH Education Book 2011; 498-505 26

If there are 100 untreated patients with DLBCL, fortunately, nearly 60% of them can be cured by R-CHOP therapy.

If there are 100 patients with relapsed or refractory DLBCL, half of these patients are ineligible for autologous transplantation due to their age or other reasons. Even if patients are determined to be eligible for an autologous transplantation, they will not be able to proceed to autologous transplant if second-line treatments are not successful.

Even among patients who proceed to autologous transplantation, only a little less than one-half can maintain long-term survival without relapse after autologous transplantation, and if there are 100 patients with relapsed or refractory DLBCL, only one-tenth of them can be expected to be cured after salvage chemotherapy and autologous transplantation.

This means that the remaining 90% of the cases, which are bracketed in blue, cannot be cured by autologous transplantation, and are considered to be cases where treatment is not successful.

These cases can be summarized as “Challenging Situations.”

Once again, there are young patients who are eligible for autologous transplantation but cannot proceed to autologous transplantation due to lack of response to second-line therapy. There are also cases where autologous transplants are performed, but then the disease recurs.

Another reason is that there have been no good treatment options for patients who are not eligible for autologous transplantation, due to older age or other reasons.

First of all, for younger patients, if the second-line treatment does not work, one of the multiple-drug chemotherapy options used as the second-line treatment can be selected as the third-line treatment. If it works, one approach that has been taken is to proceed to a hematopoietic stem cell transplant.

Allo SCT after 3rd-line Salvage Chemotherapy

- CORAL study
  - Failed to proceed to BEAM+ASCT (n=203)
  - ORR to 3rd-line chemo (ITT): 39%
  - 31.5% eventually transplanted (ASCT 56, allo SCT 8)

Allo SCT: allogenic stem cell transplantation
BEAM: carmustine (not approved in Japan), etoposide, cytarabine+melphalan
CR: complete response, CRu: complete response unconfirmed
Source: Van Den Neste, E et al. Bone Marrow Transplant 2016; 51:51

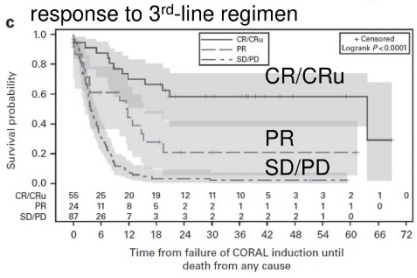
2nd line (CORAL)	3rd line	ORR to 3rd line
R-DHAP (n=94)	ICE-like (n=23)	45.3%
R-ICE (n=109)	DHAP (n=26)	42.3%

Table 2. Breakdown of response to third-line regimen according to disease status at CORAL removal

Response to third-line regimen	*Response to second-line regimen*				
	CR/CRu (N = 26)	*PR (N = 30)*	*SD/PD (N = 135)*	*UNKN (N = 12)*	*Overall (N = 203)*
CR/CRu	14	11	27	3	55
PR	1	5	16	2	24
SD/PD	7	11	69	0	87
NE/NA	4	3	23	7	37

2nd-line: SD/PD
→ 3rd-line CR/PR 32% (43/135)

OS from failure of CORAL according to response to 3rd-line regimen



29

This slide is about the CORAL trial, a Phase III trial comparing second-line treatment for DLBCL, which I mentioned earlier, with patients who did not respond to second-line treatment.

For example, in patients who did not respond to R-DHAP regimen, the type of chemotherapy was changed to R-ICE regimen, which does not contain high-dose cytarabine.

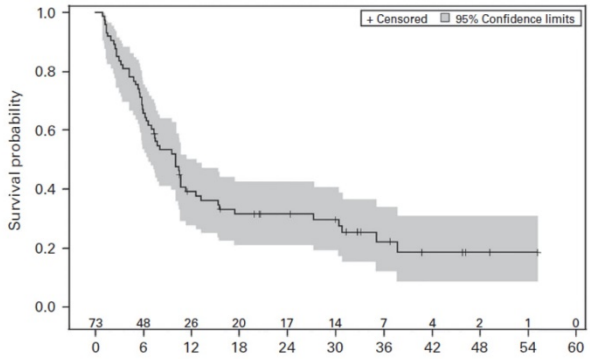
In patients who did not respond to R-ICE regimen, we tried different types of salvage chemotherapy, such as DHAP with high-dose cytarabine, as a third-line therapy, and some patients responded to it.

As you can see here, the percentage of patients who did not respond to the second-line treatment who responded to the third-line treatment was about 30%, and although PR was not sufficient, the third-line treatment worked well.

For patients who have achieved CR after third-line treatment, long-term survival can be expected in some patients through third-line treatment and subsequent hematopoietic stem cell transplantation, specifically autologous transplantation, which is performed in many patients.

Relapse after ASCT

CORAL study



N=73
Median time ASCT-PD: 7.1 mo
ORR to 3rd-line chemo 44%
Median OS 10.0 mo
13 allo SCT

Source: Van Den Neste, E et al. Bone Marrow Transplant 2017; 52:216

30

Recurrence can occur after an autograft.

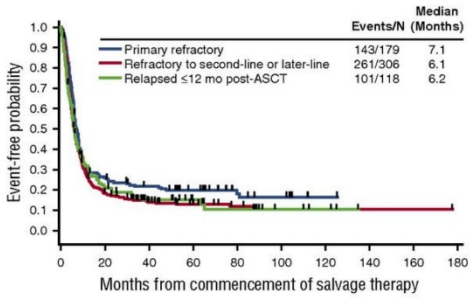
I am showing you the survival curve of a patient who had a relapse after an autologous transplant in this same Phase III trial.

As shown here, in patients who have relapsed after autologous transplantation, the response rate to third-line therapy is more than 40%, but the median survival is only 10 months.

Therefore, there is a need for treatments that can be expected to cure or control the disease in the long term in these patients.

Prognosis of Refractory DLBCL

- SCHOLAR-1 Study (retrospective study)
  - "Refractory" DLBCL
    - 1st-line therapy R-CHOP x 4→ SD/PD
    - After 2nd-line therapy →SD/PD
    - Relapse within 12 months after autologous transplantation
  - Response to the next-line therapy: Overall response rate 26%, CR rate 7%



Source: Crump M et al Blood 2017; 130:1800

31

This slide concerns patients with relapsed or refractory DLBCL, especially those who have disease progression such as SD or PD while on R-CHOP therapy, or those who had SD or PD after failure of second-line therapy. Also, patients who have undergone autologous transplantation, but had an early relapse, have a particularly poor prognosis.

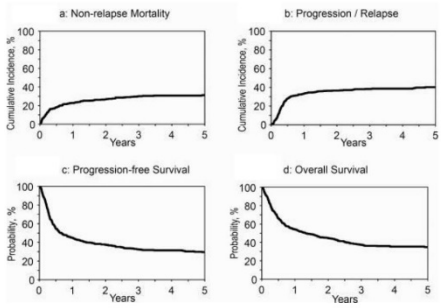
There were data that looked at the response to the next line of treatment and subsequent event-free survival in these patients after they were determined to have this kind of refractory DLBCL.

In this retrospective study, the response rate of the next line of treatment was 26%, and the possibility of CR was 7%, which means that the response to treatment was extremely poor, and the prognosis was extremely poor.

It is known that only 10% to 20% of people can survive for a long time.

Allo SCT after Failing ASCT

- CIBMTR retrospective
  - N=503
  - Status at allo SCT
    - Chemo-sensitive 74% (CR 35%, PR 39%)
    - Chemo refractory 21%
  - Graft type
    - BM 9%, PB 91%
  - Type of donor
    - HLA-identical sibling 50%
    - Unrelated well-matched 23%
    - Unrelated partially matched 26%



BM: bone marrow
PB: peripheral blood
Source: Fenske TS et al. Br J Haematol 2016; 174:235

32

In the past, another type of HSCT, different from autologous transplantation, has been used for these patients. This is an allogeneic hematopoietic stem cell transplant.

Allogeneic hematopoietic stem cell transplantation is a kind of immunotherapy in which the patient receives hematopoietic stem cells from a sibling with the same HLA, a donor from a bone marrow bank, or a donor from a cord blood bank, instead of using the patient's own hematopoietic stem cells.

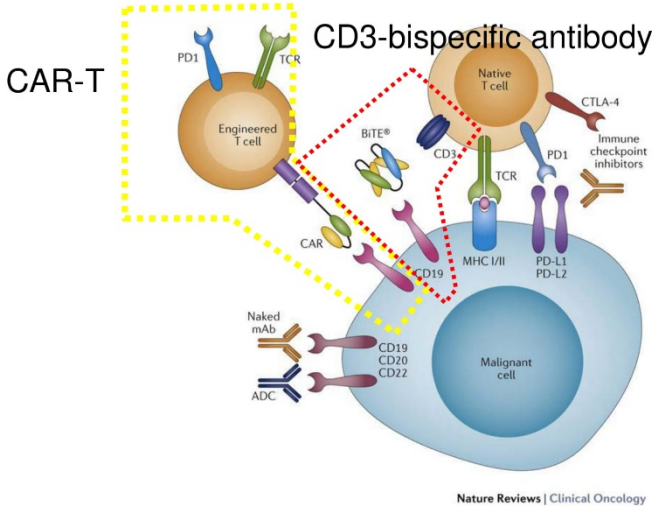
This treatment is based on the concept that malignant lymphoma cells are attacked by the allogeneic immune effect, and it has a certain effect on patients who have not responded to chemotherapy, such as relapse after autologous transplantation.

This is a compilation of data on allogeneic transplantation for patients with recurrence after autologous transplantation, based on international data on HSCT registries, mainly from the United States.

When an allogeneic transplant is performed for recurrence after an autologous transplant, the recurrence rate is 30% to 40% per year. The progression-free survival curve also flattens out around the 2-year mark, indicating that allogeneic transplantation is an effective treatment for patients with recurrence after autologous transplantation, and that long-term survival and cure can be expected.

On the other hand, the problem is that recurrence-free deaths and treatment-related deaths are at least estimated to be 20%. In addition, this data summarizes patients who have progressed to allogeneic transplantation, and in fact, three-fourths of the patients were chemotherapy-sensitive prior to allogeneic transplantation, which is the majority of patients. Since it is rather rare that chemotherapy is effective for recurrence after autologous transplantation, it can be said that the data is for fairly selected patients.

Immunotherapy Targeting CD19



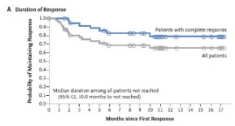
source：Batlevi CL et al. Nat Rev Clin Oncol 2016; 13:25-40

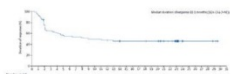
33

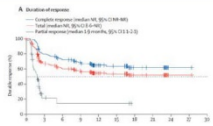
Therefore, there have been no good treatment options for these patients. CAR-T cell therapy, which has recently been introduced, has been developed as a treatment for these patients.

CD19 Targeted CAR-T Cell Therapy for R/R DLBCL

	Tisagenlecluce l (Tisa-cel)	Axicabtagen ciloucel (Axi-cel)	Lisocabtagene maralucel (Liso-cel)
Pivotal study	JULIET	ZUMA-1	TRANSCEND
Age	56 (range 22-76)	58 (IQR 51-64)	63 (range 54-70)
ORR	52%	83% (84/101)	73% (186/256)
CR rate	40%	58% (59/101)	53% (136/256)
Median follow-up	12 mo	11.1 mo	18.8 mo (apheresis)
Duration of response		11.1 mo (median)	54.7% @ 12 mo
PFS	65% @ 12 mo	44% @ 12 mo 5.9 mo (median)	44.1% @ 12 mo 6.8 mo (median)
CRS (any grade/grade ≥3)	58% / 22% (Penn scale)	93%(NEJM) /11%	42% / 2%
Neurological events (any grade/grade ≥3)	21% / 12%	64%(NEJM) / 32%	30% / 10%







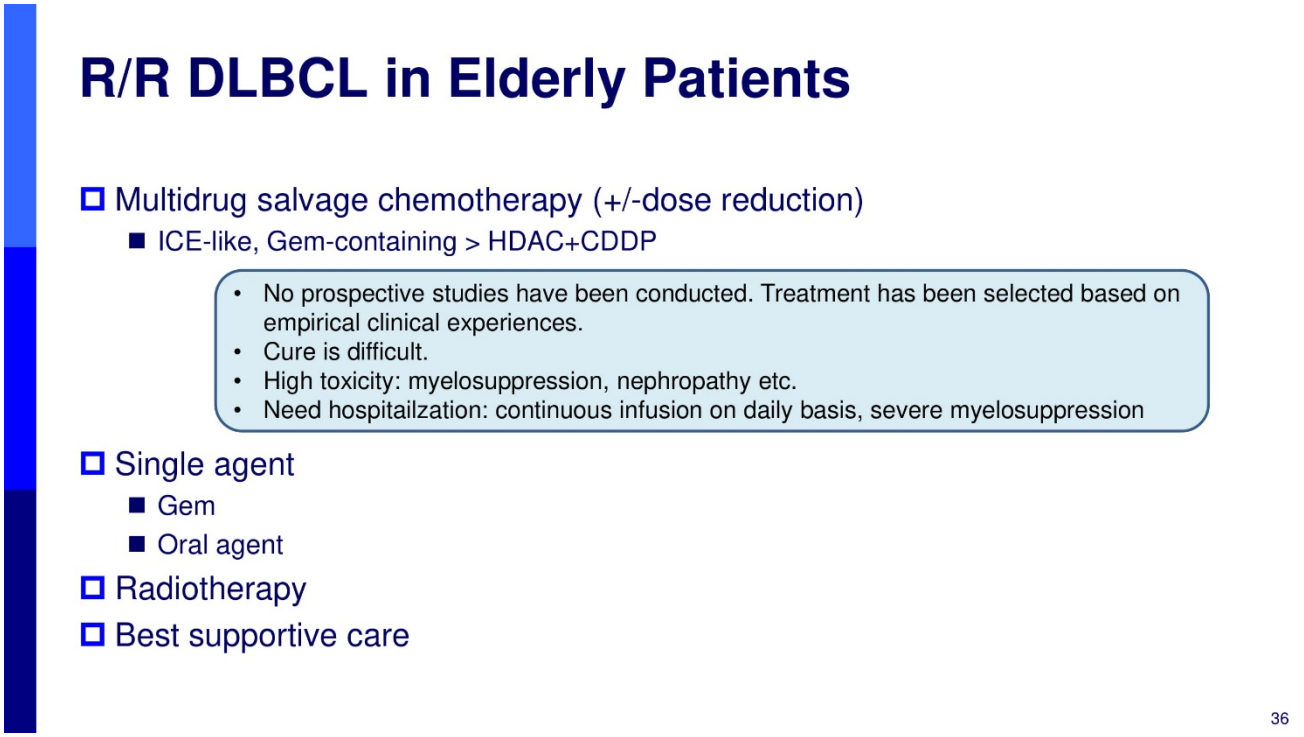
mo: month

Source: Schuster S et al. N Engl J Med 2019; 380:45-56
Locke FL et al. Lancet Oncol 2019; 20:31-42
Abramson JS et al. Lancet 2020; 396:839-852

34

In Japan, a CAR-T cell therapy called Tisagenlecleucel was approved in 2019, and this is already in clinical use. In 2021, Axi-cel and Liso-cel have been approved and will be used in medical institutions.

In these clinical trials of CAR-T cell therapy for relapsed or refractory DLBCL, the median age was in the late 50s to early 60s, but patients up to their early 70s were eligible. In addition, it has been shown that patients with this relapsed/refractory form of DLBCL can be expected to have long-term progression-free survival.



This is fine for these patients, but what are the options for elderly patients who are not eligible for autologous transplantation?

In older patients with relapsed or refractory DLBCL, the treatment used to be multi-drug salvage chemotherapy, often at a reduced dose, as I mentioned earlier for patients with autologous transplantation.

The reason why the dosage had to be reduced was because the elderly have a poor metabolism and are more prone to the side effects of chemotherapy, mainly myelosuppression, and also because they originally had renal disorder or renal dysfunction, which often gets worse.

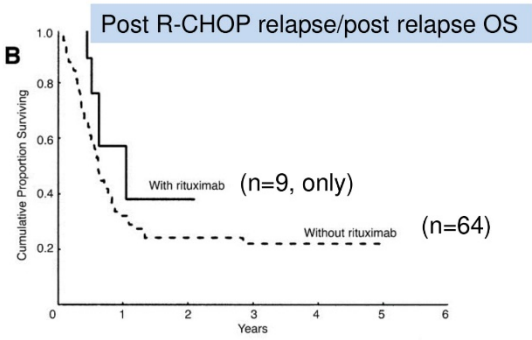
In fact, there are no well-described prospective trials in the literature on reduced-dose multi-drug chemotherapy such as ICE therapy or DHAP therapy for relapsed or refractory DLBCL in the elderly.

In fact, it is extremely rare for a patient to be cured without an autologous transplant. In addition, as I have mentioned before, many of these treatments require hospitalization, daily infusions, and a high degree of bone marrow suppression. The fact that elderly patients with difficult-to-cure diseases require long-term hospitalization is not considered to be very advantageous for their QOL.

On the other hand, several anticancer drugs are used as single-agent chemotherapy, but it is true that these drugs are not expected to be sufficiently effective, and there have been no good treatment options for elderly patients with relapsed or refractory DLBCL.

R/R DLBCL in Elderly Patients
Prognosis of Patients Relapsed after R-CHOP

- GELA LNH98-5 study (R-CHOP vs CHOP)
  - DLBCL, 60-80 years old
  - Progression after R-CHOP 77
  - Salvage chemo: DHAP, ESHAP, ICE (+ASCT, n=1)



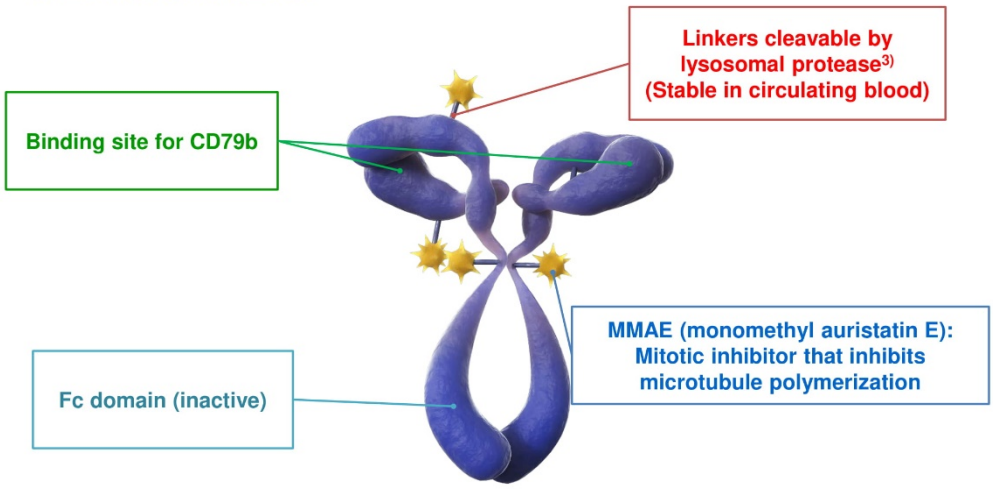
Source: Feugier P et al. J Clin Oncol 2005; 23:4117

37

This is a French study that compared R-CHOP therapy with CHOP for first-episode DLBCL.

This survival curve especially shows those who have relapsed after R-CHOP therapy. As can be seen here, more than half of the people die in one year, so the prognosis is quite bleak.

Polatuzumab vedotin (PV, Pola)
anti-CD79b ADC



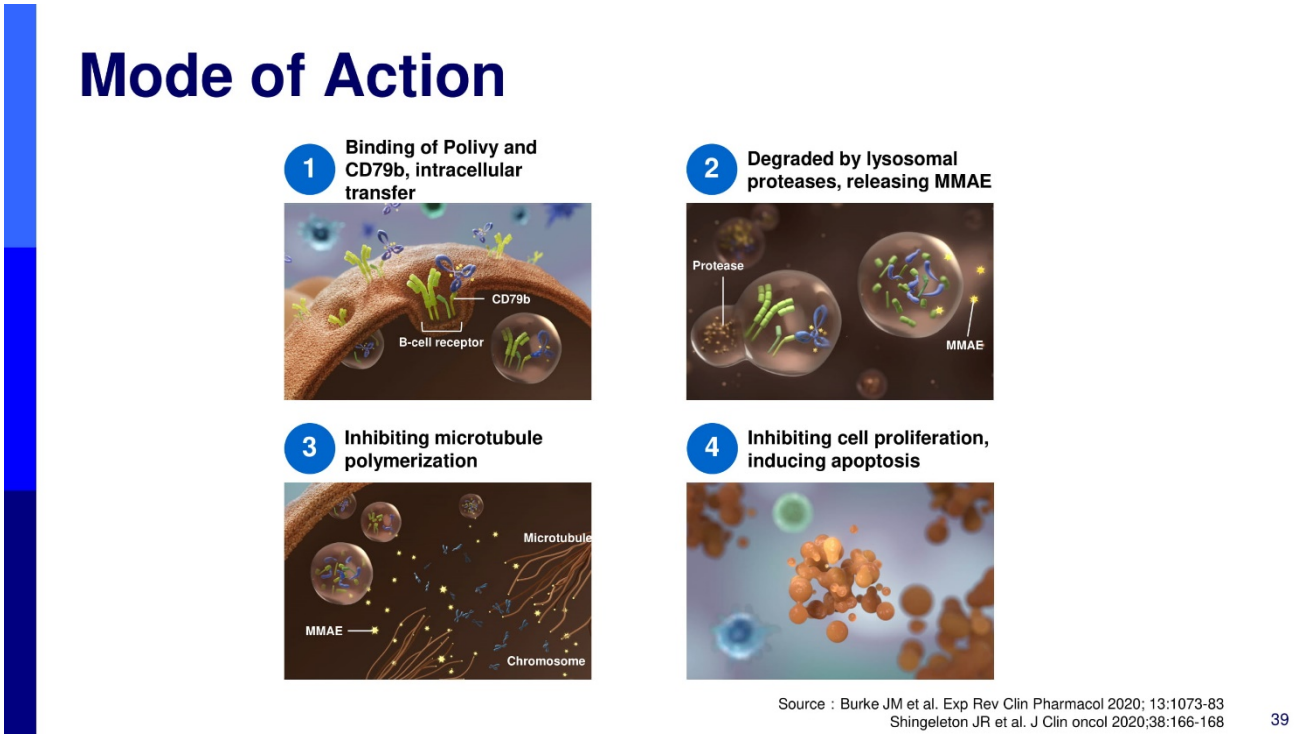
Source : Burke JM et al. Exp Rev Clin Pharmacol 2020; 13:1073-83
Shingeleton JR et al. J Clin oncol 2020;38:166-168

38

Polatuzumab vedotin was developed mainly for these patients.

Polatuzumab vedotin is an antibody-drug conjugate that combines an antibody against CD79b with a microtubule polymerization inhibitor, called monomethyl auristantin E, MMAE, as an anticancer payload.

CD79b is a cell membrane antigen that is expressed on B cells, both normal B cells and most B-cell tumors.

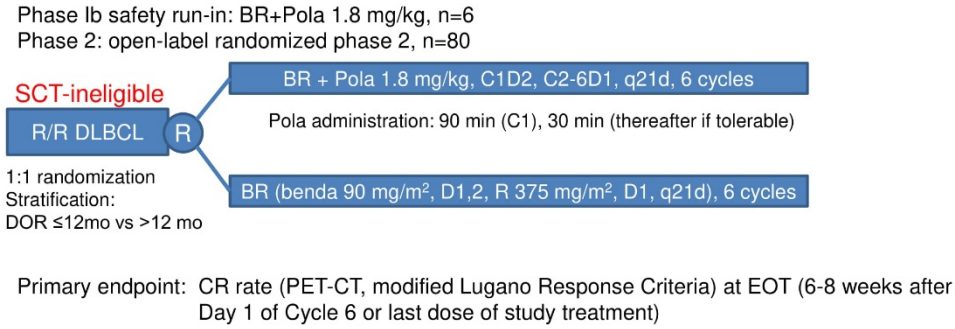


When used intravenously, polatuzumab vedotin binds to CD79b in the patient's tumor through the patient's bloodstream, and the antibody is internalized into the cell together with CD79b antigen, and in lysosomes, proteases break the bond between the antibody and its payload, MMAE, and activates the MMAE. Since MMAE is a microtubule polymerization inhibitor, it can inhibit cell proliferation, which leads to apoptosis of tumor cells.

MMAE has already been used in brentuximab vedotin, an antibody-drug conjugate targeting CD30. To date, peripheral neuropathy has been a typical adverse event.

Pola-BR vs BR in R/R DLBCL Randomized Phase 1b/2 Study (GO29365)

Study Design



Primary endpoint: CR rate (PET-CT, modified Lugano Response Criteria) at EOT (6-8 weeks after Day 1 of Cycle 6 or last dose of study treatment)

EOT: end of treatment
Source: Sehn LH et al. J Clin Oncol 2019; 38:155-165

40

This polatuzumab vedotin clinical trial, which was a randomized Phase II trial conducted overseas, compared Pola-BR and BR, and this became a pivotal trial.

BR is bendamustine and rituximab combination therapy. This study includes patients who are not eligible for autologous transplantation and who have relapsed or refractory DLBCL.

They are assigned 1:1, and in the control group, they receive a combination of bendamustine and rituximab, with 90 milligrams of bendamustine for 2 consecutive days. The usual dose of rituximab is given on Day 1. This is to be repeated 6 times at 3-week intervals.

Bendamustine has never been indicated for the treatment of DLBCL, but a 90-milligram dose of the drug will be used in combination with rituximab for indolent B-cell lymphoma and mantle cell lymphoma.

It is normal to use a 4-week interval in these conditions. Pola-BR is a regimen that is already in use and is designed to be administered once every 3 weeks, using polatuzumab vedotin on Day 2 for Cycle 1, and on Day 1 from Cycle 2 to Cycle 6.

Polatuzumab vedotin is administered by infusion in 90 minutes for the first infusion and 30 minutes for the second and subsequent infusions. For this study, the primary endpoint was the CR rate as seen by the PET, PET-CR, and PET criteria. At the end of treatment, the PET-CR rate is used.

Pola-BR vs BR in R/R DLBCL

Baseline Characteristics

	Pola-BR (n=40)	BR (n=40)
Median age	67 (33-86)	71 (30-84)
ECOG PS 2	15%	20%
ABC-DLBCL	47.5%	47.5%
GCB-DLBCL	37.5%	42.5%
Primary reason for transplantation ineligibility		
age	32.5%	47.5%
comorbidities	2.5%	2.5%
insufficient response to salvage therapy	30.0%	22.5%
failed prior transplantation	25.0%	15.0%
Bulky disease (>7.5 cm)	25.0%	37.5%
DOR of last treatment ≤ 12 mo	80%	82.5%
Lines of prior therapy (median)	2 (1-7)	2 (1-5)
Prior bendamustine	2.5%	0%

Source: Sehn LH et al. J Clin Oncol 2019; 38:155-165

41

This is the background of the enrolled patients.

There were 40 patients in each group, with a median age of 67 and 71 years, the majority of whom were elderly.

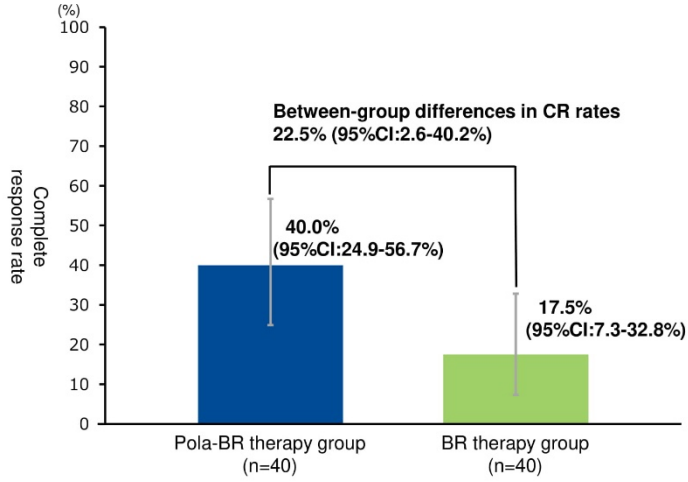
DLBCL is classified into ABC type and GCB type according to gene expression profiles, and each type comprises roughly half of all cases.

By definition, patients ineligible for transplant were included. Age, inadequate response to salvage therapy, failure of secondary therapy, or recurrence after autologous transplantation were the reasons for ineligibility for transplant.

As for the previous treatment history, the median number of previous treatment lines in each group was 2.

Pola-BR vs BR in R/R DLBCL

Efficacy (CR rate: Primary endpoint)



Source: Sehn LH et al. J Clin Oncol 2019; 38: 155-165

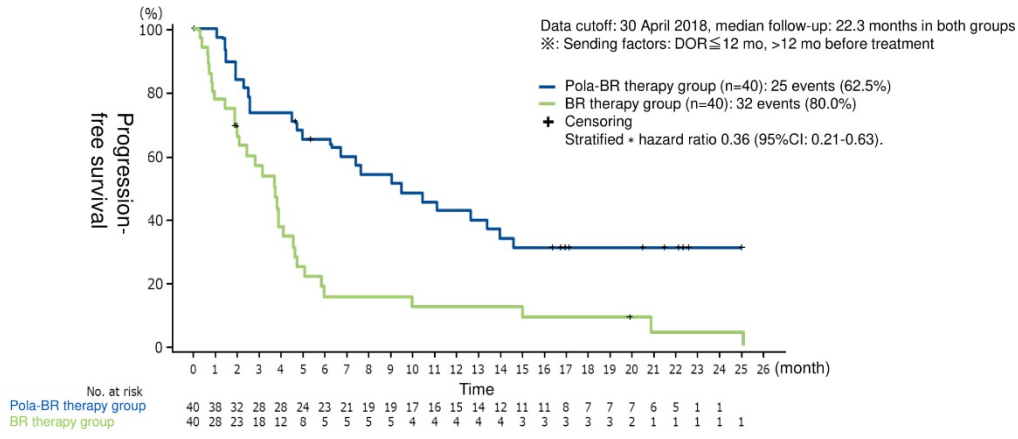
42

This is the primary endpoint, PET-CR rate at the end of treatment.

As shown here, we found that the CR rate was significantly better for Pola-BR, with the figure 40% for Pola-BR, and 17.5% for BR therapy.

Pola-BR vs BR in R/R DLBCL

Efficacy (PFS: Secondary endpoint)



Source: Sehn LH et al. J Clin Oncol 2019; 38: 155-165

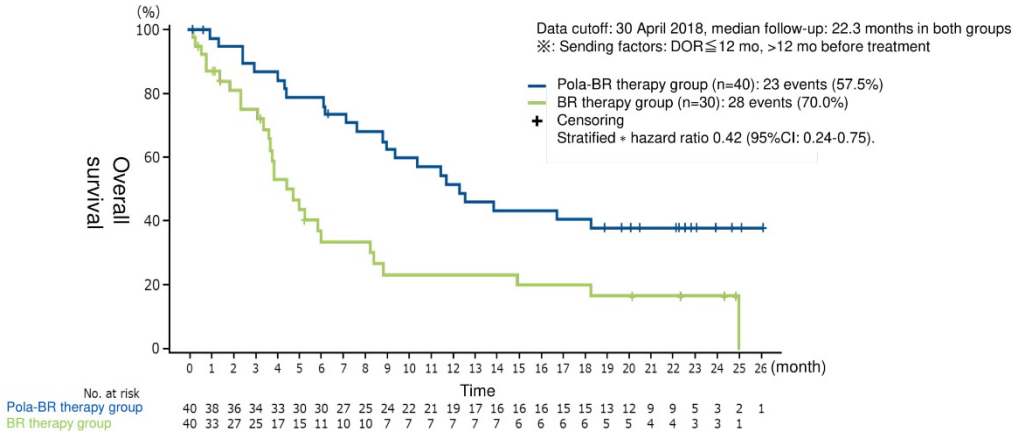
43

The secondary endpoint was progression-free survival.

Thus, we know that Pola-BR is superior, and we can expect a median PFS of almost 1 year in the Pola-BR group.

Pola-BR vs BR in R/R DLBCL

Efficacy (OS: Exploratory outcome)



Source: Sehn LH et al. J Clin Oncol 2019; 38: 155-165

44

Overall survival was also better with Pola-BR, as shown here.

Pola-BR vs BR in R/R DLBCL

Source: Sehn LH et al. J Clin Oncol 2019; 38: 155-165

Safety

No, (%)	Pola+BR (n=39)		BR (n=39)	
	ALL Grades	Grade 3-4	ALL Grades	Grade 3-4
Anemia	21 (53.8)	11 (282)	10 (25.6)	7 (17.9)
Neutropenia	21 (53.8)	18 (46.2)	15 (38.5)	13 (33.3)
Thrombocytopenia	19 (48.7)	16 (41.0)	11 (28.2)	9 (23.1)
Lymphopenia	5 (12.8)	5 (12.8)	0	0
Febrile neutropenia	4 (10.3)	4 (10.3)	5 (12.8)	5 (12.8)
Diarrhoea	15 (38.5)	1 (2.6)	11 (28.2)	1(2.6)
Nausea	12 (30.8)	0	16 (41.0)	0
Constipation	7 (17.9)	0	8 (20.5)	1 (2.6)
Malaise	14 (35.9)	1 (2.6)	14 (35.9)	1 (2.6)
Pyrexia	13 (33.3)	1 (2.6)	9 (23.1)	0
Peripheral neuropathy	17 (43.6)	0	3 (7.7)	0
Red blood cell transfusion		25.6%		20.5%
Platelet transfusion		15.4%		15.4%
G3-4 Infection		23.1%		20.5%
G-CSF		71.8%		61.5%

Serious adverse reactions were reported by 28.2% (11 of 39 subjects). Events reported included febrile neutropenia in 7.7% (3 of 39 subjects), pneumonia and pyrexia in 5.1% (2 of 39 subjects), thrombocytopenia, diarrhea, myelodysplastic syndrome, herpes virus infection, herpetic meningoencephalitis, rhinovirus infection, decreased appetite, deep vein thrombosis, pulmonary edema, and vomiting in 2.6% (1 of 39 subjects), respectively. Adverse reactions leading to discontinuation of any of the drugs were observed in 28.2% (11 of 39 subjects). Thrombocytopenia and neutropenia occurred in 10.3% (4 of 39 subjects) of subjects, respectively, and pneumonia, thrombocytopenia, neutrophil count decreased, pulmonary edema, pneumonitis, and pancytopenia occurred in 2.6% (1 of 39 subjects). Mortality occurred in 7.7% (3 of 39 patients). Pneumonia, herpetic meningoencephalitis, and pulmonary edema occurred in 2.6% (1 of 39 subjects) of the subjects, respectively. 45

In terms of adverse events and safety data, we will look at the adverse events seen in Pola-BR and Pola-free BR, both for all grades and for grades 3 and 4.

You can see that hematological toxicity, including grade 3 and any grade, is increased by concomitant use of Polivy. Neutropenia is present in 38.5% vs 53.8% of patients.

As a result, some patients needed transfusions of red blood cells and platelets. However, the percentage of patients needing blood transfusions has not necessarily increased with the use of Polivy. Similarly, the frequency of infections did not increase with the use of Polivy.

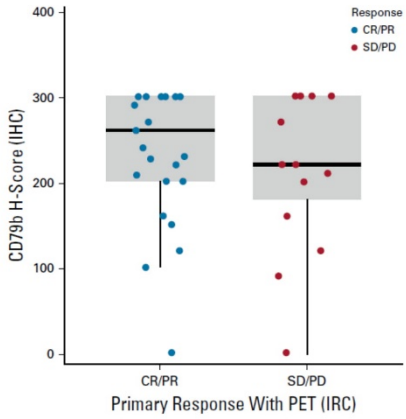
Incidentally, G-CSF was used in 70% of the patients in this study, although its use was not mandatory.

One of the most common non-hematological toxicities was peripheral neuropathy. Across all grades, the frequency of neuropathy is 7% for BR and 43% for Pola-BR, clearly indicating that the use of Polivy in combination with BR increases the frequency of neuropathy.

However, the frequency of neuropathy of grade 3 or higher was 0% in both cases.

Pola-BR vs BR in R/R DLBCL

- Efficacy by CD79b protein expression



Source: Sehn LH et al. J Clin Oncol 2019; 38:155-165

46

Since the drug targets CD79b, the relationship between the expression of CD79b and the effect of the drug is of interest, but when we looked at the correlation between the expression of CD79b protein and the effect of the drug by immunostaining, we found that there was not much of a relationship.

Therefore, although the drug targets CD79b, the presence or absence of CD79b expression was not a selection criterion in this study, and it is not necessary to check CD79b expression when the drug is used in clinical practice in the future.

Pola-BR vs BR in R/R DLBCL

Treatment exposure

Treatment exposure	Pola-BR(n=39)	BR(n=39)
Median end of treatment (range)	5(1-6)	3(1-6)
At the end of 6 cycles	18(46.2)	9(23.1)
Discontinue		
PD	6(15.4)	21(53.8)
Lack of Efficacy	1(2.6)	1(2.6)
Adverse events	13(33.3)	4(10.3)
Other	1(2.6)	4(10.3)
Dose reduction of Polivy	2(5.1)	—
Dose reduction of bendamustine	5(12.8)	4(10.3)
Delayed treatment	21(53.8)	15(38.5)
Median dose		
Polivy	93(58-109)	—
Bendamustine	91(84-98)	93(63-102)
Rituximab or obinutuzumab	91(70-103)	93(45-101)

Source: Sehn LH et al. J Clin Oncol 2019; 38: 155-165

47

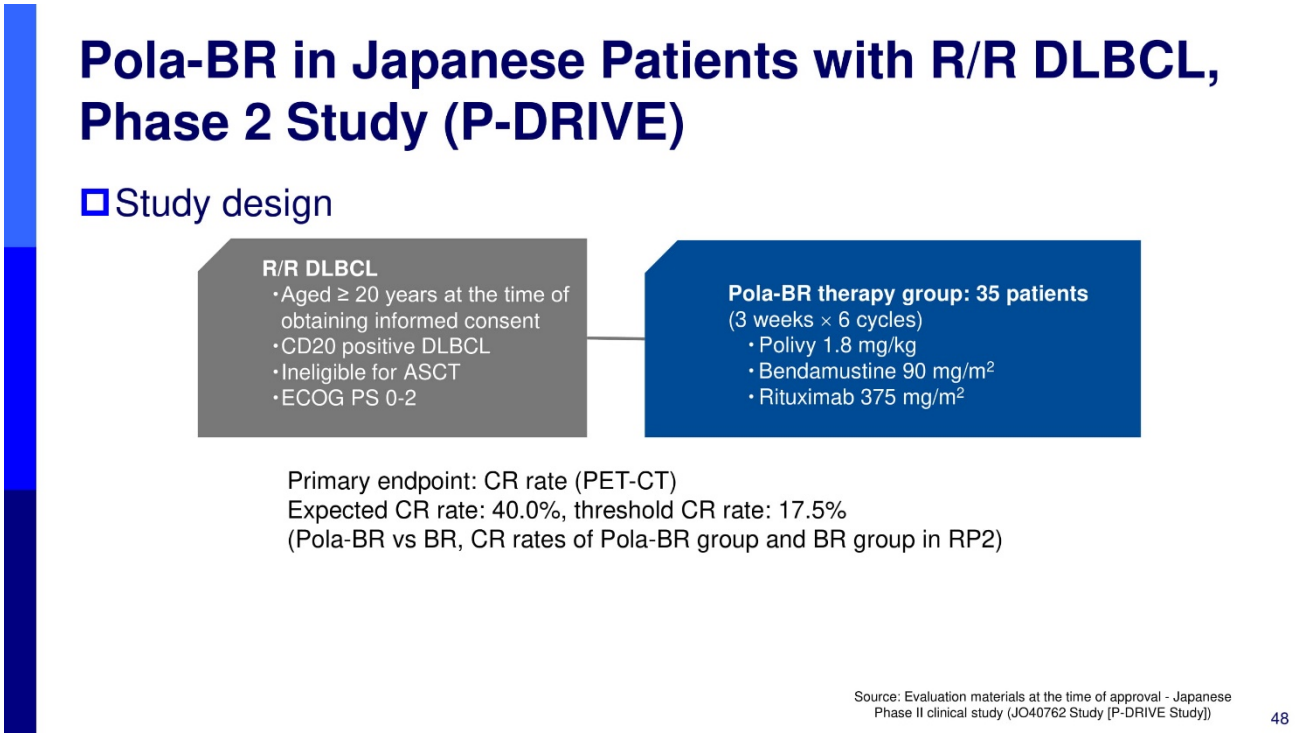
This slide covers the number of courses necessary for treatment.

The median is a maximum of 6 cycles, but the median for Pola-BR was 5 cycles.

In the group that did not include Polivy, many people were unable to complete 6 cycles, stopping at a median of 3 cycles, mainly due to disease progression during the course of the study.

In the Pola-BR group, 46% of patients could complete 6 cycles.

Although there was a certain amount of dose reduction and delay in administration due to various reasons such as peripheral neuropathy and hematological toxicity, the adverse events were generally considered manageable.



Up to this point, randomized Phase II trials were conducted overseas, not including Japan, but a Phase II trial called P-DRIVE was conducted in Japan to confirm the safety and efficacy of the drug in Japanese patients.

This trial, like the randomized Phase II trial mentioned earlier, was also for patients with relapsed or refractory DLBCL who were ineligible for autologous transplantation.

This was a single-arm study, with the same dosage and administration as the Pola-BR arm in the randomized Phase II study mentioned earlier, and the primary endpoint was similar: PET-CR rate at the end of treatment.

The study was conducted with the statistical hypothesis of 40% expected CR rate and 17.5% threshold CR rate.

Pola-BR in Japanese Patients with R/R DLBCL, Phase 2 Study (P-DRIVE)

Baseline characteristics

	Pola-BR (n=35)	Pola-BR (overseas) (n=40)	BR (overseas) (n=40)
Median age	71 (46-86)	67 (33-86)	71 (30-84)
ECOG PS 2	8.6%	15%	20%
ABC-DLBCL	40.6%	47.5%	47.5%
GCB-DLBCL	43.8%	37.5%	42.5%
Primary reason for transplantation ineligibility			
age	65.7%	32.5%	47.5%
comorbidities	-	2.5%	2.5%
insufficient response to salvage therapy	17.1%	30.0%	22.5%
failed prior transplantation	8.6%	25.0%	15.0%
Bulky disease (>7.5 cm)		25.0%	37.5%
DOR of last treatment ≤ 12 mo	74.3%	80%	82.5%
Lines of prior therapy (median)	3L+ 42.9%	2 (1-7)	2 (1-5)
Prior bendamustine	?	2.5%	0%

Source: Evaluation materials at the time of approval - Japanese Phase II clinical study (JO40762 Study [P-DRIVE Study])

49

This slide shows the baseline patient background.

The median age was 71 years.

Patients who were ineligible or unsuitable for autologous transplantation were eligible for the study, so it was the same, and 42% of the patients had 3 or more lines of previous treatment, so the main target was patients with a long history of treatment, as in the overseas study.

Pola-BR in Japanese Patients with R/R DLBCL, Phase 2 Study (P-DRIVE)

P-DRIVE Study: Efficacy

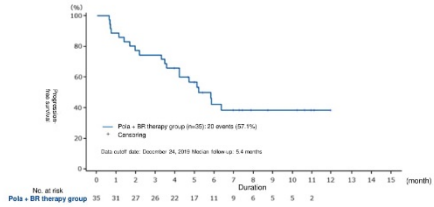
- CR rate (INV): 34.3% (95% CI: 19.1-52.2%)
- ORR (INV): 42.9%
- ORR (best response): 71.4%
- Median DOR: 6.6 mo
- Median PFS: 5.2 mo

P-DRIVE Study: Safety

- Grade ≥ 3 adverse events: ≥ 5%

P-DRIVE Study: Exposure

- Polivy: 5 cycle (median)
- Bendamustine: 5 cycle (median)
- Rituximab: 5 cycle (median)



	Pola-BR therapy group (n=35)
Number of cases	31 (88.6%)
Anemia	13 (37.1%)
Neutropenia	11 (31.4%)
White blood cell count decreased	8 (22.9%)
Thrombocytopenia	7 (20.0%)
Platelet count decreased	7 (20.0%)
Neutrophil count decreased	7 (20.0%)
Febrile neutropenia	4 (11.4%)
Hypokalemia	2 (5.7%)

G-CSF prophylactic administration 97.1%

Source: Evaluation materials at the time of approval - Japanese Phase II clinical study (JO40762 Study [P-DRIVE Study])

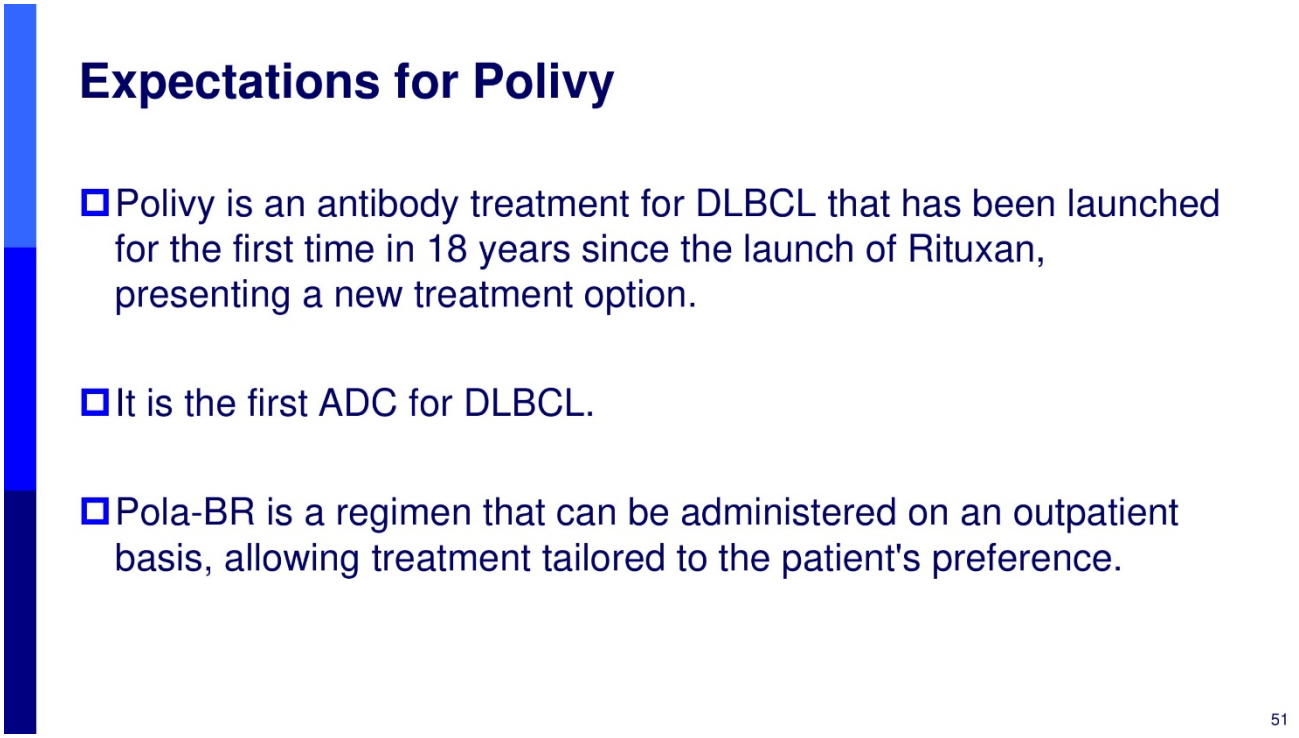
50

As for efficacy, the CR rate for the primary endpoint was 34.3%, so the primary endpoint was met.

Although the observation period is still not very long, the duration of response and progression-free survival have been reported in this way.

In terms of safety, hematological toxicity was found to be equivalent, and peripheral neuropathy was also found to be equivalent. In this study, the prophylactic administration of G-CSF was mandatory.

In the Japanese study, it was possible to administer a median 5 cycles of Pola-BR, with data similar to those overseas.



Based on the results of overseas and Japanese Phase II trials, polatuzumab vedotin, or Polivy, has been approved for the treatment of relapsed or refractory DLBCL, and can now be used in clinical practice. I have the following expectations for this drug.

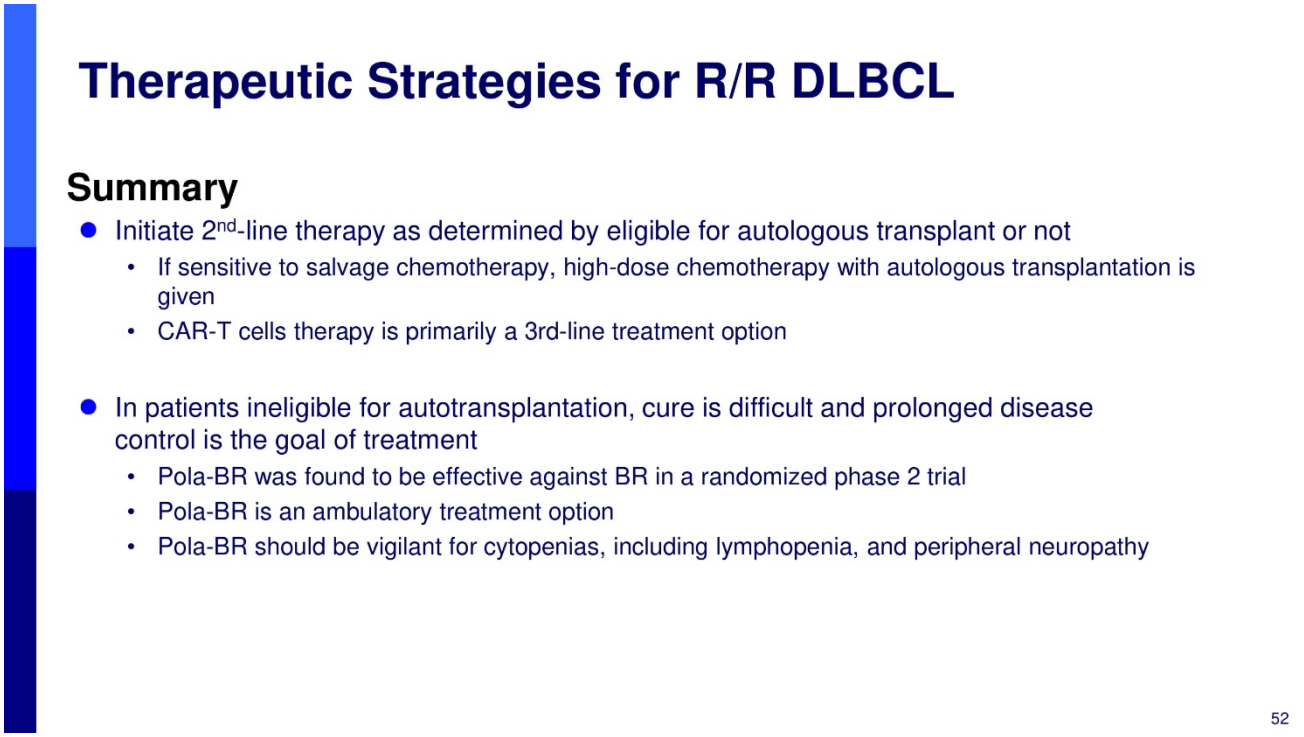
First of all, although various antibody drugs have long been developed for the treatment of relapsed and refractory DLBCL, this is the first time in 18 years, since Rituxan, that a drug has actually been available for clinical use.

Antibody drugs have an advantage in terms of toxicity, especially hematotoxicity, compared to pure cytotoxic drugs. The other advantage of this treatment is that it can be used as soon as it is needed.

As I mentioned earlier, an antibody-drug conjugate called brentuximab vedotin is already approved and used for lymphoma, but Polivy is the first antibody-drug conjugate approved for DLBCL.

Unfortunately, for patients with DLBCL who are not eligible for autologous transplantation, it is difficult to provide curative treatment, so a treatment strategy that allows them to live longer while maintaining their QOL is very useful.

Unfortunately, there are many problems with the current treatments, such as the need for hospitalization and the extremely strong adverse event profile, but I think that the ability to manage the disease on an outpatient basis is a great advantage.



These are the main treatment options for relapsed and refractory DLBCL.

Secondary treatment can be considered for relapsed and refractory DLBCL, depending on whether autologous transplantation is eligible or not.

For patients who are eligible for autologous transplantation, the treatment options are still rescue chemotherapy, strong multi-drug chemotherapy, and then proceeding to autologous transplantation. For such young patients, CAR-T cell therapy has recently emerged as an option.

However, unfortunately, there is still a limit to the number of cases of CAR-T cell therapy that can be conducted, so this is still a problem at the moment.

For patients who are not eligible for an autologous transplant, as I mentioned earlier, there have been no good treatment options, and they often have to be hospitalized.

Pola-BR is a treatment that can be administered on an outpatient basis in terms of dosage and administration regimen, although there are certain adverse events such as hematological toxicity that require careful attention.

I talked about the fact that this is a very promising treatment option as a regimen that can be managed on an outpatient basis, and the results of clinical trials are in line with this.

That's all. Thank you very much for your attention.

Sasai: Thank you very much, Dr. Izutsu.

Question & Answer

Sasai: I would now like to move on to the question-and-answer session.

The first question. Mr. Hashiguchi of Daiwa Securities, please.

Hashiguchi: This is Hashiguchi from Daiwa Securities. Thank you for your explanation.

The first question is about page 26. I would like to know how to interpret this table. Is it correct to say that the target patients for this approved indication are 90 patients, which is the sum of 50, 25, and 15, and that the first-line POLARIX trial is being conducted on the top 300 patients?

Dr. Izutsu, do you feel that if the drug is approved for first line use as well, it will be the drug of choice for many of these 300 patients without much hesitation? Or do you feel that it is still too early to tell about first-line treatment until you see the test results?

Koga: I will answer the first question, and Dr. Izutsu will answer the second one.

As you can see in the figure on page 26, first of all, POLARIX, the first-line Phase III, is currently being conducted for untreated patients, so the first 300 patients will be targeted.

Polivy is eligible for the second-line patients. Patients who are not eligible for transplant are eligible for Polivy. In the case of transplantation eligible patients, the standard of care is transplantation, so that includes patients who receive transplantation and then unfortunately relapse, or patients who are not able to receive transplantation due to the results of pre-transplant chemotherapy. If you add up those, 50, 25, and 15, you get 90 people.

That's the image in a nutshell.

Izutsu: I'd like to talk about my point of view in response to your question about the initial launch, as well as your first question.

As you pointed out, out of 100, 100 minus 10, which is the blue marker, are the patients who can potentially be treated with Pola-BR.

However, the number of patients who will proceed directly to CAR-T therapy may be deducted from this number. The number of people who are currently eligible for CAR-T cell therapy is quite limited, but even so, this is something to keep in mind.

As for first-line DLBCL treatment, the IPI is limited to 2 to 5, which is an international prognostic index, but conversely, only those with an IPI of 0 and 1 are excluded from the study, so I understand that a large portion of these 300 patients are included in the POLARIX study.

So, if the primary endpoint of the POLARIX trial is met and leads to approval, I think that most of the first-line treatment of untreated DLBCL will be treatment with POLA, or a combination of POLA-R-CHP.

Hashiguchi: Thank you very much. Secondly, I would like to know about CAR-T therapy. I think you mentioned earlier that there is a limit to the number of cases that can be treated, but I would like to know what you mean by that. If that is to be resolved, what needs to be done? Given its efficacy and safety, do you feel that CAR-T

therapy has the potential to be used in a wide range of patients, including earlier stage patients, if the issue is resolved?

Izutsu: That's a difficult question. First of all, I said "frame," but that may have been a bit of a misnomer.

CAR-T cell therapy involves the collection of lymphocytes, which are the raw material for CAR-T cells, from the patient, and the production of CAR-T cells at a manufacturing facility for at least 2 weeks, although the process varies depending on the type of CAR-T cells.

The first issue is whether the lymphocytes that will be used as raw materials can be harvested, and the second issue is whether the patient can control the current disease for several weeks after the raw materials are harvested until the lymphocytes are returned as the product of CAR-T cells.

In the past, it has been difficult for patients with refractory disease to receive CAR-T cell therapy, and there were often patients who were considered for CAR-T cell therapy but did not go through with it. That's one big bottleneck.

Also, in fact, CAR-T cell therapy, such as leukocyte apheresis or cell administration, has only been approved in a limited number of facilities. Diffuse large B-cell lymphoma is a disease with a large number of patients, so it is treated in many facilities, and second and third line therapies are being carried out.

Right now, only a small percentage of facilities that provide secondary and tertiary treatment are providing CAR-T cell therapy, and I think that due to the nature of the treatment, it cannot be a treatment that can be provided at every medical institution. I think that the situation where only a small number of patients with relapsed or refractory disease are eligible for CAR-T cell therapy will remain unchanged, both in terms of the momentum of the disease and also in terms of the nature of the treatment.

Hashiguchi: Thank you very much. That's all.

Sasai: Thank you very much. Now I would like to move on to the next question. Mr. Muraoka of Morgan Stanley MUFG Securities, please go ahead.

Muraoka: Hello, my name is Muraoka from Morgan Stanley. I would like to ask Dr. Izutsu to tell me about this, but I think a CD19 ADC was also recently approved for DLBCL in the US, but I think it was third line.

How should we think about the positioning of this drug and Polivy when this drug is used in Japan in the future? If I were to say third line and second line, that might be all there is to it, but could you tell me a little bit about that?

Izutsu: I think the patient population is quite close to the one that will be used. However, the ADC for CD19 is used as a single agent, not in combination with multiple drugs, as I recall, so it may be more applicable to patients with more complications or who are older.

However, it is difficult to compare the results of clinical trials, so it is difficult to give an answer. Pola-BR is used as a multi-drug chemotherapy, and I think CD19 and ADC are positioned as regimens for the same patient population.

Muraoka: Thank you very much. Are there any promising new treatments for DLBCL that you are focusing on that are still in the early stages?

Izutsu: Thank you for your question. What you see on the screen now is an immunotherapy targeting CD19. In immunotherapy, CAR-T cell therapy involves genetic manipulation of cells, so it is a time-consuming treatment.

Similarly, as a treatment using immunity, a dual-specificity antibody, which has the ability to bind tumor cells and T cells that are in charge of immunity, is under development. Several dual specificity antibodies targeting CD20 have been developed for malignant lymphoma.

They have the advantage of being off-the-shelf, ready-to-administer, usable therapies, unlike CAR-T cell therapy, so we are watching the progress of their development.

Muraoka: Thank you very much. I'm sorry, I haven't been able to keep track of this, but wasn't the CD19-CD3 dual-specificity compound recently put on clinical hold in the US due to side effects? Is that not the case?

Izutsu: I'm not aware of that. I was talking about CD20 and CD3 bispecific antibodies, and of the 3 such drugs that are being developed now, I am not aware of any such event.

Muraoka: I understand. Thank you very much. That's all.

Sasai: Thank you very much. Next, Mr. Yamaguchi from Citigroup Global Markets Japan, please go ahead.

Yamaguchi: My name is Yamaguchi from Citigroup. Thank you very much for your time today. I would like to ask you one layman's question, but I think there may be some differences in the background of the overseas and domestic studies you mentioned.

The period of time until survival rate reaches a plateau is much shorter in the domestic trials, which is different when you just look at the charts and graphs, but the CR and other factors are in the same range. Is there any background to these differences, or is it just a coincidence?

Izutsu: I don't know if this is the correct interpretation, but the P-DRIVE trial in Japan had a very short follow-up period, and the primary endpoint was met and the data cutoff occurred very early, so I think we need to be a little careful about how we look at the PFS curve.

Yamaguchi: I see. I think it depends on the setting of the observation period.

Izutsu: Yes.

Yamaguchi: Probably. Yes, I understand, thank you.

Sasai: And now, Mr. Zhou from Goldman Sachs Japan, please go ahead.

Zhou: My name is Zhou from Goldman Sachs. Thank you. I would also like to ask you about the interpretation of data from overseas and domestic clinical trials.

I also have the impression that age is an important factor in the patient population for which the drug is indicated. In this context, I think that the median age is quite different between Japan and overseas, and the PFS curve is about 10 months in overseas countries and about 5 months in Japan, which is quite a gap. How much of a factor is age in this area? Thank you.

Izutsu: First of all, the median age is 71 years in the domestic study, and 67 years in the Pola-BR group in the overseas study, which is a difference of 4 years. I suspect that the median age will not be too different from the target group, since the overseas BR therapy group is 71 years old.

The main reason for transplant incompatibility was age, which was the reason for 65% of patients in Japan. The percentage of patients with post-transplant recurrence was low in Japan, which I think is a difference between the data of overseas trials and Japanese trials in terms of the reason for transplant incompatibility, but I am not sure I can explain that well.

Overseas, there is a tendency to avoid citing age as a reason for transplant incompatibility, while in Japan, for example, people over 65 or 70 are often judged unsuitable for transplantation.

Zhou: Okay, thank you very much.

Sasai: Thank you very much. A follow-up question. Mr. Sakai of Credit Suisse Securities Japan, please.

Sakai: My name is Sakai from Credit Suisse. Thank you very much for your time today. I also understood the factors of age and post-transplantation status as you explained in the table on page 49, in terms of domestic and overseas.

One of the reasons, Doctor, is that the prognosis of the patients who are facing this disease is also poor. I guess you could call it a willingness to come into the second or third line of treatment.

First of all, I would like to ask whether the needs of patients who want to receive treatment more and more actively are very high or not?

Izutsu: Thank you for your question. When a hematopoietic tumor is relapsed and refractory, should we continue positive treatment with second and third line therapy or proceed to best supportive care? The question is, which is the smoothest road?

As for hematopoietic tumors, rather than going for best supportive care or palliative care, we tend to treat them more aggressively than solid tumors, using some kind of chemotherapy until their condition worsens considerably or until they stop responding at all.

That's because, for one thing, chemotherapy can lead rather directly to temporary relief of the patient's symptoms, and that is something patients are of course keen on. From the perspective of the doctors who are in charge of the treatment, they often continue chemotherapy in the hope that it will temporarily improve the patient's symptoms.

Sakai: I understand. Thank you. Another question is about bendamustine. I feel that it has been attracting a lot of attention in the domestic stock market.

Is there any reason that prior bendamustine in the domestic study is presented as question mark on page 49.

Will bendamustine still be used as a base, and in the future, for example, could it be reduced in dose? On the other hand, would increasing the dose be at all possible? What do you think about this point?

Izutsu: Thank you for your question. First of all, when this study, Pola-BR, was conducted in Japan, there was no indication for bendamustine in DLBCL, so I think that was a reason of presenting as a question mark. Also, bendamustine is approved for the treatment of DLBCL, and BR therapy without Polivy is one of the treatment options.

In the case of BR therapy without Polivy, the dose of bendamustine is 120 milligrams. A Phase II study and a single-arm Phase III study are being conducted in Japan, and the latter has already been presented at an academic conference and is the basis for approval.

Bendamustine 120 milligrams every 3 weeks exhibits relatively strong hematological toxicity, and at least in patients who entered the clinical trial for development, the median number of cycles that could be administered was 4, which is one cycle less than this Pola-BR study.

Considering Polivy, I think it is a little difficult to say whether it is possible to increase the dose of bendamustine further, instead of 90, when used in combination with Pola-BR, because of the hematological toxicity.

Sakai: I understand. Thank you very much.

Izutsu: To add to what was said, polatuzumab vedotin is difficult to choose for patients who have developed severe peripheral neuropathy in response to previous treatment, because it may aggravate it. In such cases, I think BR therapy using 120 would be a good option.

Sakai: In any case, the fact that it can be treated as an outpatient means that it can be done both with and without Polivy.

Izutsu: I think it is possible to do this while being careful about blood toxicity.

Sakai: Thank you very much.

Sasai: Thank you very much. Since there are no additional questions, this concludes the Chugai Pharmaceutical Polivy Information Session.

If you have any additional questions, please contact the Corporate Communications Department at the phone number or email listed at the end of the presentation.

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

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Document Notes

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2. *Portions of the document where the audio is obscured by technical difficulty are marked with [TD].*
3. *This document has been translated by SCRIPTS Asia.*

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