Information Meeting on Polivy

Agenda

Moderator: Toshiya Sasai, Head of Corporate Communcations Dept.,
Chugai Pharmaceutical Co., Ltd.

1. **Product Overview of Polivy**

   Dr. Takaki Koga, Polivy Lifecycle Leader, Chugai Pharmaceutical Co., Ltd.

2. **Treatment Options for Relapsed/Refractory Diffuse Large B-cell Lymphoma (DLBCL)**

   Koji Izutsu, M.D., Ph.D., Department of Hematology, National Cancer Center Hospital

3. **Q&A Session**

POLIVY®
polatuzumab vedotin

Product Overview

Polivy® Intravenous Infusion 30 mg/140 mg

June 3, 2021

Dr. Takaki Koga
Polivy Lifecycle Leader
Chugai Pharmaceutical Co., Ltd.

Product Outline

[Brand name]

Polivy® Intravenous Infusion 30 mg

Polivy® Intravenous Infusion 140 mg

[Generic name]

polatuzumab vedotin

(genetical recombination)

[Indications]

Relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL)

PO For the strength of **polatuzumab vedotin**

LIV For the promise of **life***

Y For the **antibody-drug conjugate**

*As per GO29365 efficacy data.

POLIVY® polatuzumab vedotin

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

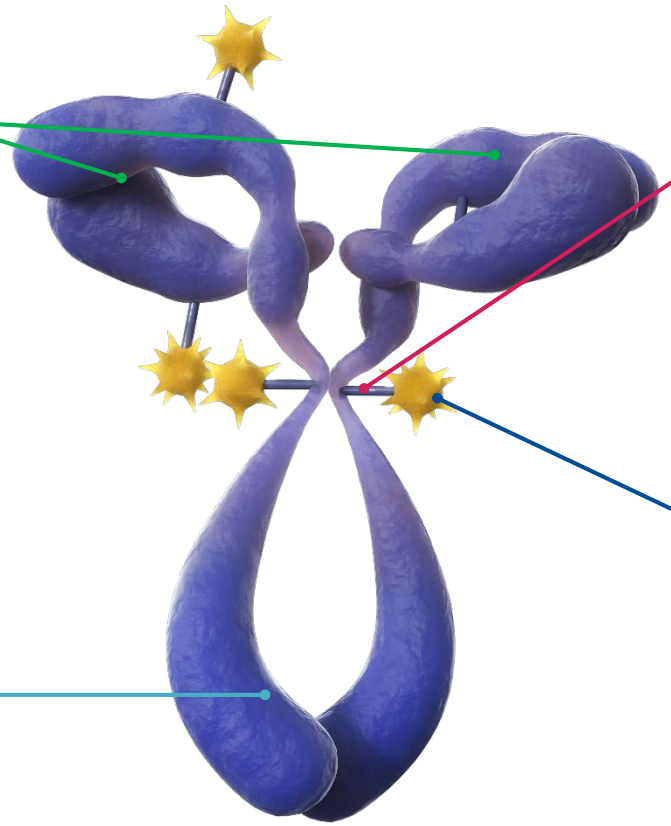
FL: Follicular lymphoma
DLBCL: Diffuse large B-cell lymphoma
PRIME: Priority Medicines

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

Structure of Polivy (conceptual image)

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

Binding site for CD79b[2)]



Linkers cleavable by lysosomal protease[3)] (Stable in circulating blood)

MMAE (monomethyl auristatin E): Mitotic inhibitor that inhibits microtubule polymerization[4)]

Fc domain (inactive)

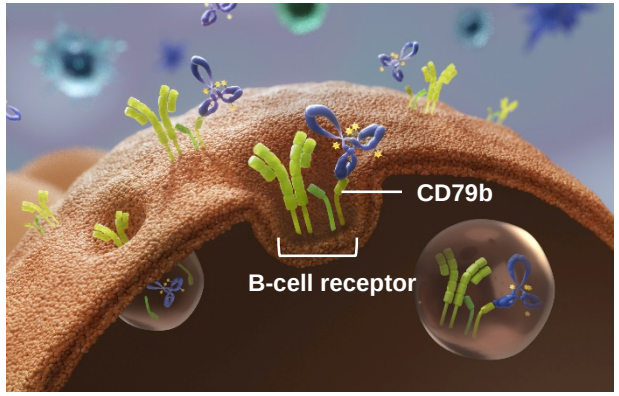
1)Li D, et al. Br J Pharmacol. 2019; 176(19): 3805-3818.
2)Polson AG, et al. Expert Opin Investig Drugs. 2011; 20(1): 75-85.
3)Dornan D, et al. Blood. 2009; 114(13): 2721-2729.
4)Doronina SO, et al. Nat Biotechnol. 2003; 21(7): 778-784.

[COI: The literature 1, 2) includes the employees of Genentech.
The literature 3) includes the employees of Genentech and the authors funded by Genentech.]

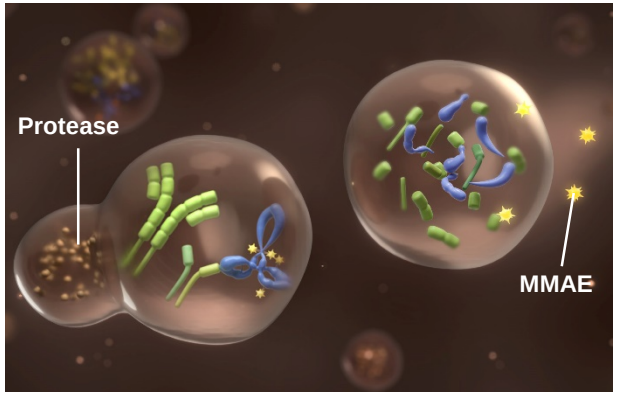
POLIVY® polatuzumab vedotin

Mode of Action (conceptual image)

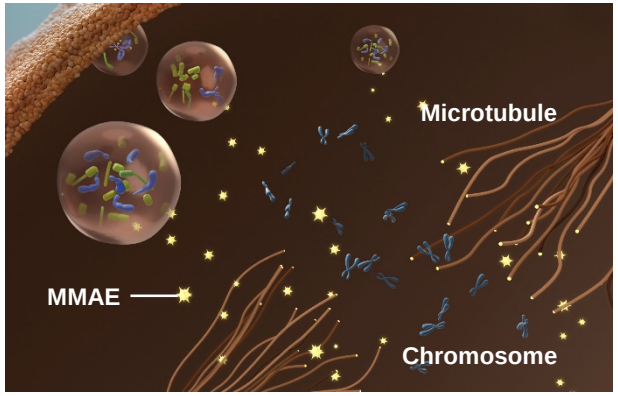
1 **Binding of Polivy and CD79b, intracellular transfer**



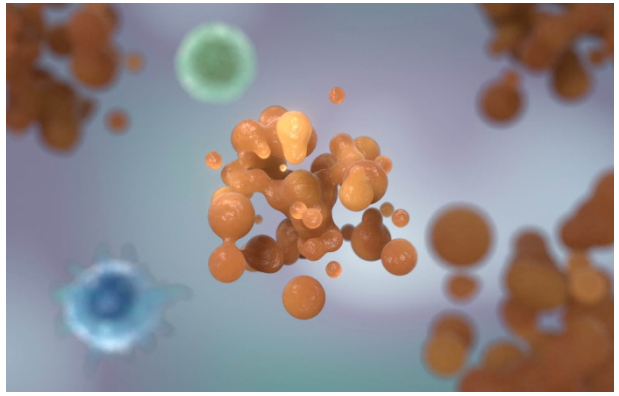
2 **Degraded by lysosomal proteases, releasing MMAE**



3 **Inhibiting microtubule polymerization**



4 **Inhibiting cell proliferation, inducing apoptosis**



- 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].

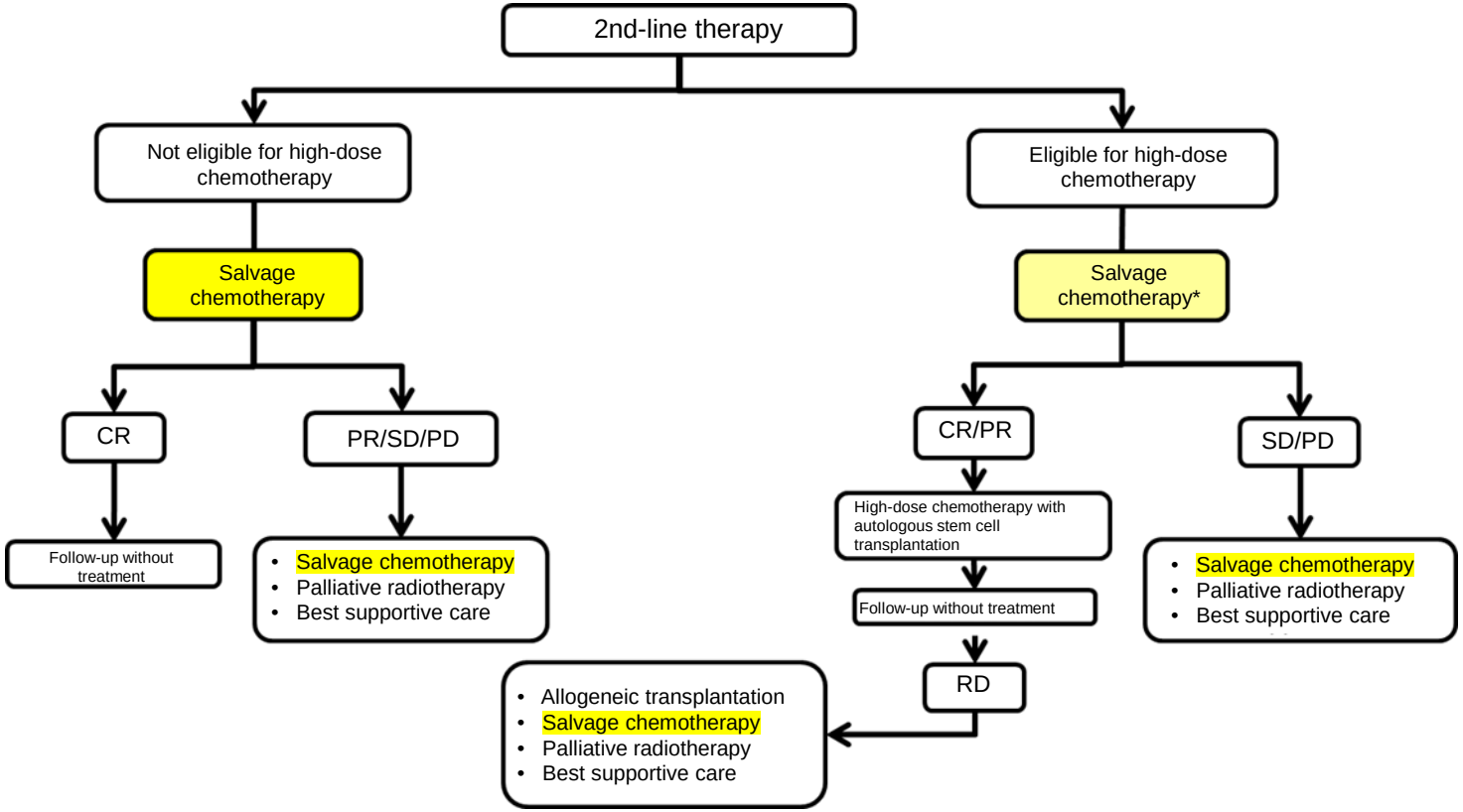
MMAE: Monomethyl auristatin E

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.]

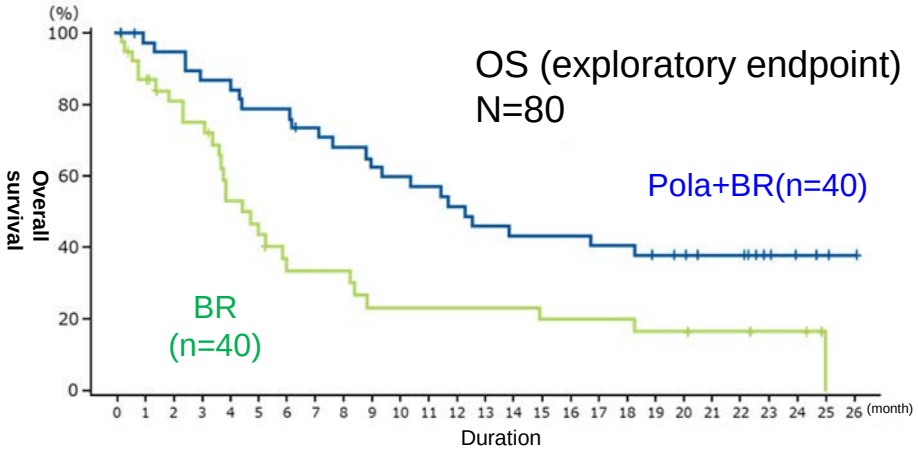
Contribution to Treatment of Patients with R/R DLBCL

Treatment algorithm (modified from the literature[1])



There is no evidence of comparative studies for salvage chemotherapy described in the current guidelines[1].

Pola + BR demonstrated efficacy in a comparative study.



Global phase Ib/II clinical study (GO29365 Study) (phase II randomized part)[2]

Pola+BR is expected to be a treatment option that may improve survival, compared to existing chemotherapy, in R/R DLBCL for which no standard therapy is available other than stem cell transplantation

POLIVY® polatuzumab vedotin

Pola: Polivy
BR: bendamustine + rituximab

1) Practical Guidelines for Hematological Malignancies, Revised version in 2018
2) Pola + BR vs BR, 40 patients per arm, randomized controlled study, 6 cycles of each regimen every 3 weeks in patients for whom high-dose chemotherapy is not indicated: Sehn LH, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. Journal of Clinical Oncology 2020; 38:155-165
*: Efficacy and safety have not been established because there is no evidence in patients for whom high-dose chemotherapy.

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	

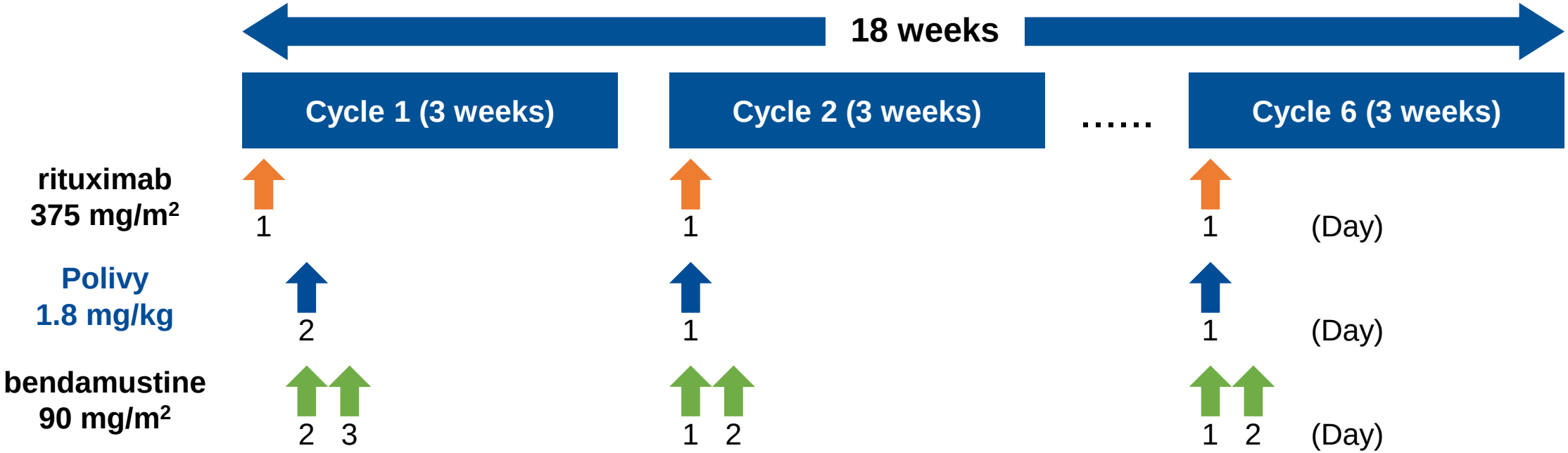
Note 1) Upon reconstitution with water for injection (for IV Infusion 30 mg: 1.8 mL; 140 mg: 7.2 mL)
Note 2) Ratio to physiological saline

POLIVY®
polatuzumab vedotin

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

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)

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.

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

Treatment Options for Relapsed/Refractory DLBCL

Koji Izutsu, M.D., Ph.D.

kizutsu@ncc.go.jp

Department of Hematology

National Cancer Center Hospital

COI disclosure

Presenter: Koji Izutsu

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

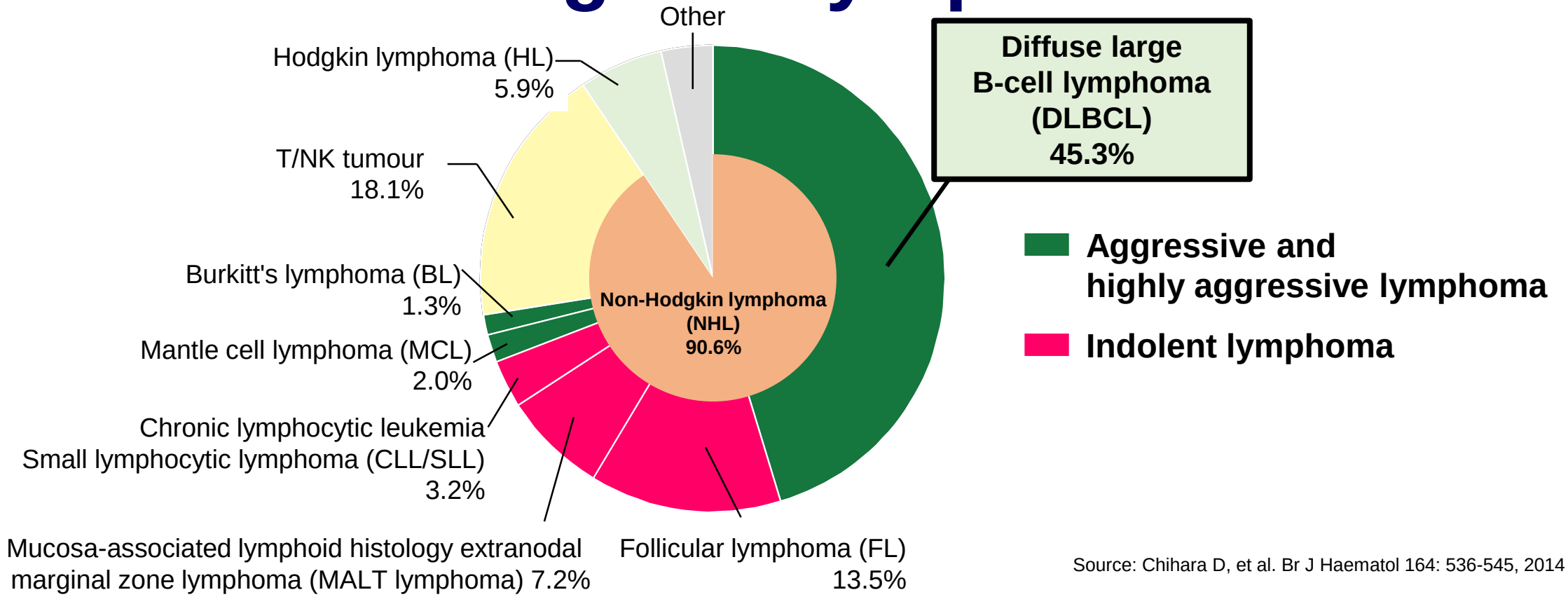
(1) Advisor, etc.:	**None**
(2) Stock ownership / profit:	**None**
(3) Patent royalty:	**None**
(4) Lecture fee:	**Janssen Pharmaceutical, Ono Pharmaceutical**
(5) Manuscript fee:	**None**
(6) Contract/joint research expenses:	**AbbVie, Insight, Celgene, Novartis, Chugai Pharmaceutical, Janssen Pharmaceutical, 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**

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

DLBCL Percentage in Lymphoma



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

[Research method]
Used population-based cancer registry data from Japan and the US. The period covered in this analysis is 1993–2008.
Japanese data: N=125,148, US population data: N=172,925
[Analytical method] Rates of sex-specific disease incidence and 95% confidence intervals (CI) were estimated and standardized by age-adjustment according to the world standard population. Incidence rates for Japan were additionally age-adjusted to the 1985 Japanese population, and those for the US were age-adjusted to the 2000 US population. Incidence rate ratios (IRR; US/Japan with 95% CI) was calculated for 2008 to compare incidence rates in the latest year between Japan and the US. Also, the annual percent change was calculated using Joinpoint regression analysis and estimated the annual percent change (APC), as well as the significance of the trend as described in detail elsewhere. Standard error of the age-standardized rates was estimated for each year.
All computations were performed with stata version 11 (STATA Corporation, College Station, TX, USA), except for the Joinpoint regression analysis for which we used the Joinpoint Regression Program version 3.3 (US National Cancer Institute, Bethesda, MD, USA). For Joinpoint regression analysis, two-sided P values <0·05 were considered statistically significant.

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)

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

DLBCL Treatment Options

Drug therapy

Applicable to
Most DLBCL

Characteristic
- It is the mainstay of DLBCL treatment. Patients are usually treated with combination chemotherapy.
- With the advent of antibody drugs, remission rates have improved

Radiotherapy

Applicable to
Localized DLBCL (after chemotherapy)
Generalized DLBCL (achieving PR after chemotherapy)

Characteristic
- High local control efficacy

Hematopoietic cell transplantation

Applicable to
R/R DLBCL
(Young patients and patients without organ damage)

Characteristic
- Autologous transplantation (auto) as supportive therapy for intensive chemotherapy
- Allogeneic transplantation (allo) for allogeneic immune response

CAR-T

Applicable to
DLBCL after 3rd-line therapy

Characteristic
- Administer CAR-expressing T cells (CAR-T cells), manufactured by introducing genes encoding a chimeric antigen receptor (CAR) into the patient‘s T cells

Source: Manuals for the treatment of lymphoma, 2020, P119-124, P174-182, Nankodo

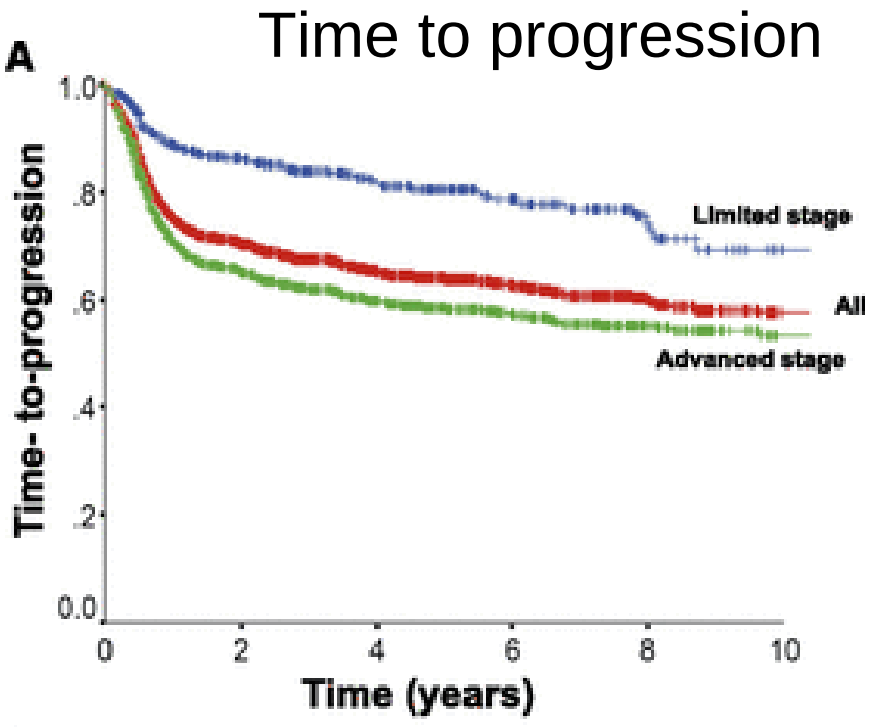
R-CHOP Regimen

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

R-CHOP in Previously Untreated DLBCL Patients

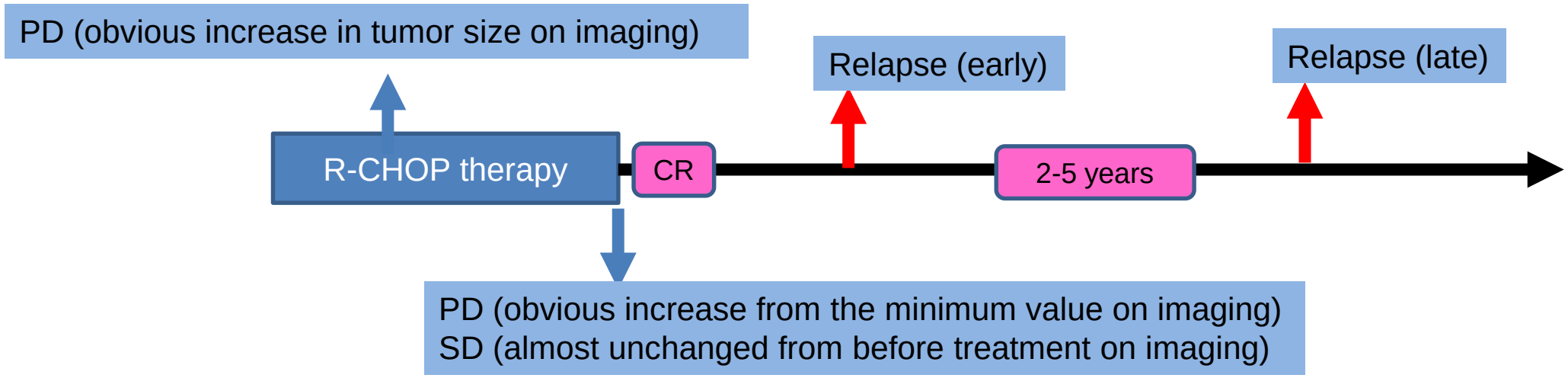
- British Colombia, Canada
  - N=1,660, diagnosed between 2001-2013
  - Localized stage n=433, advanced stage n=1,227



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

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,

2nd-line Treatment for R/R DLBCL

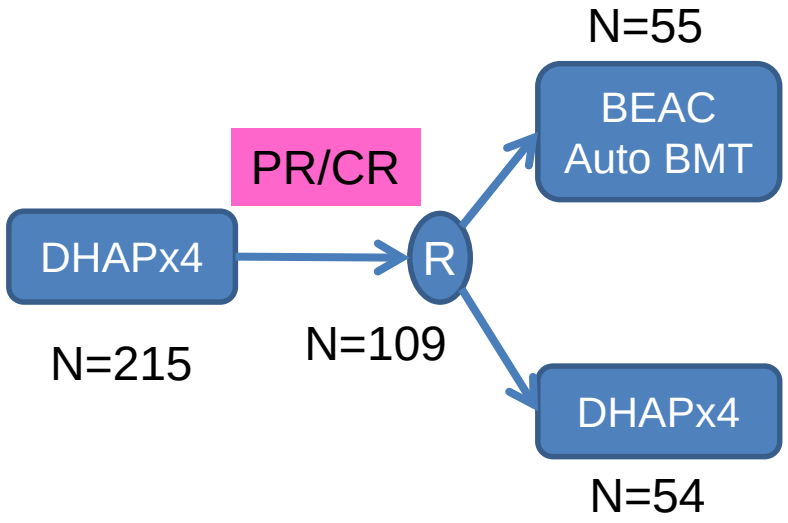
- Eligible for autologous transplantation (age/organ disorder)
  - Combination chemotherapy (mainly anthracycline and non-cross-resistant drug)
    - Total dose of anthracycline (R-CHOPx6 →DXR 300 mg/m^2)
    - Anthracycline refractory
  - Chemosensitivity → Autologous transplantation as consolidation therapy

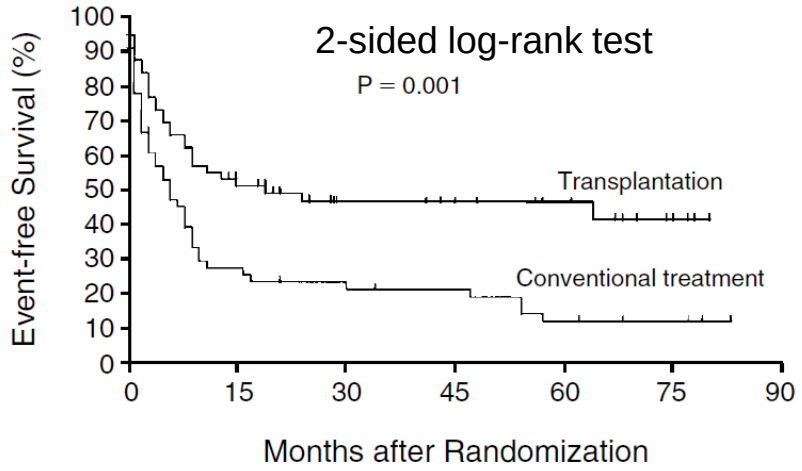
- Ineligible for autologous transplantation
  - Dose-reduced combination chemotherapy
  - Single-agent chemotherapy
  - Radiotherapy
  - BSC (Best supportive care)

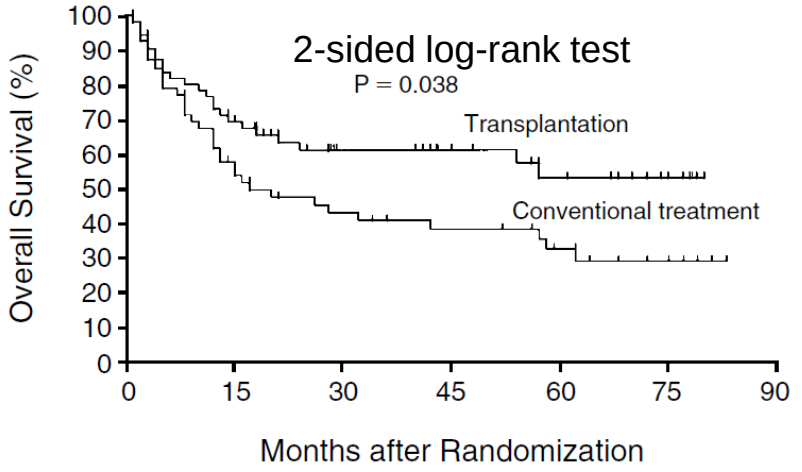
DXR: Doxorubicin
Source: Japanese Society of Hematology. Practical Guidelines for Hematological Malignancies, 2018,

High-dose Chemotherapy with Autologous Transplantation for Relapsed Aggressive Lymphoma

- Parma Study
  - Intermediate/High-grade lymphoma
  - Relapse







DHAP: dexamethasone + cisplatin + cytarabine
BEAC: carmustine + etoposide + cytarabine + cyclophosphamide
Auto BMT: autologous bone marrow transplant
Source: Philip T et al. N Engl J Med 1995; 333:1540

Note: Carmustine included in BEAC regimen is not approved for the treatment of lymphoma in Japan.

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

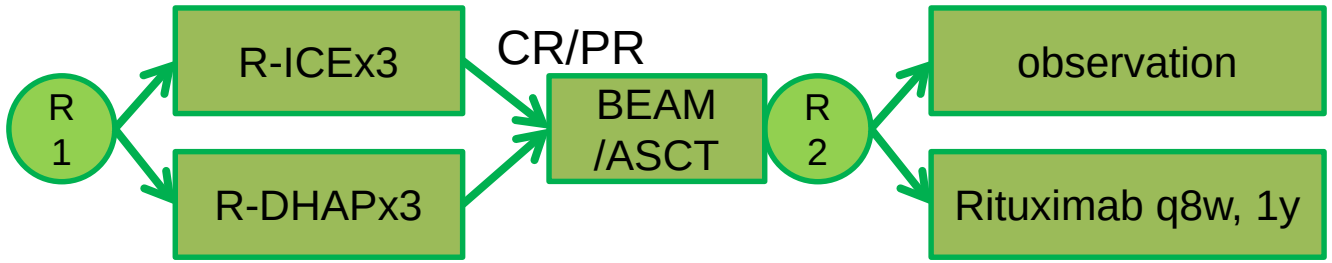
Table: Prepared by the presenter

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

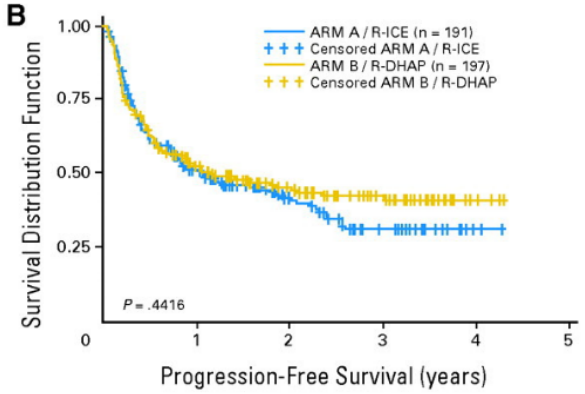
R-ESHAP: methylprednisolone, etoposide, cytarabine, cisplatin + rituximab
CHASER: cyclophosphamide, cytarabine, dexamethasone, etoposide + rituximab
R-ICE: ifosfamide, carboplatin, etoposide + rituximab
R-DeVIC: dexamethasone, etoposide, ifosfamide, carboplatin + rituximab
R-GDP: gemcitabine, dexamethasone, 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

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

- CORAL Study N=396
  - R/R DLBCL



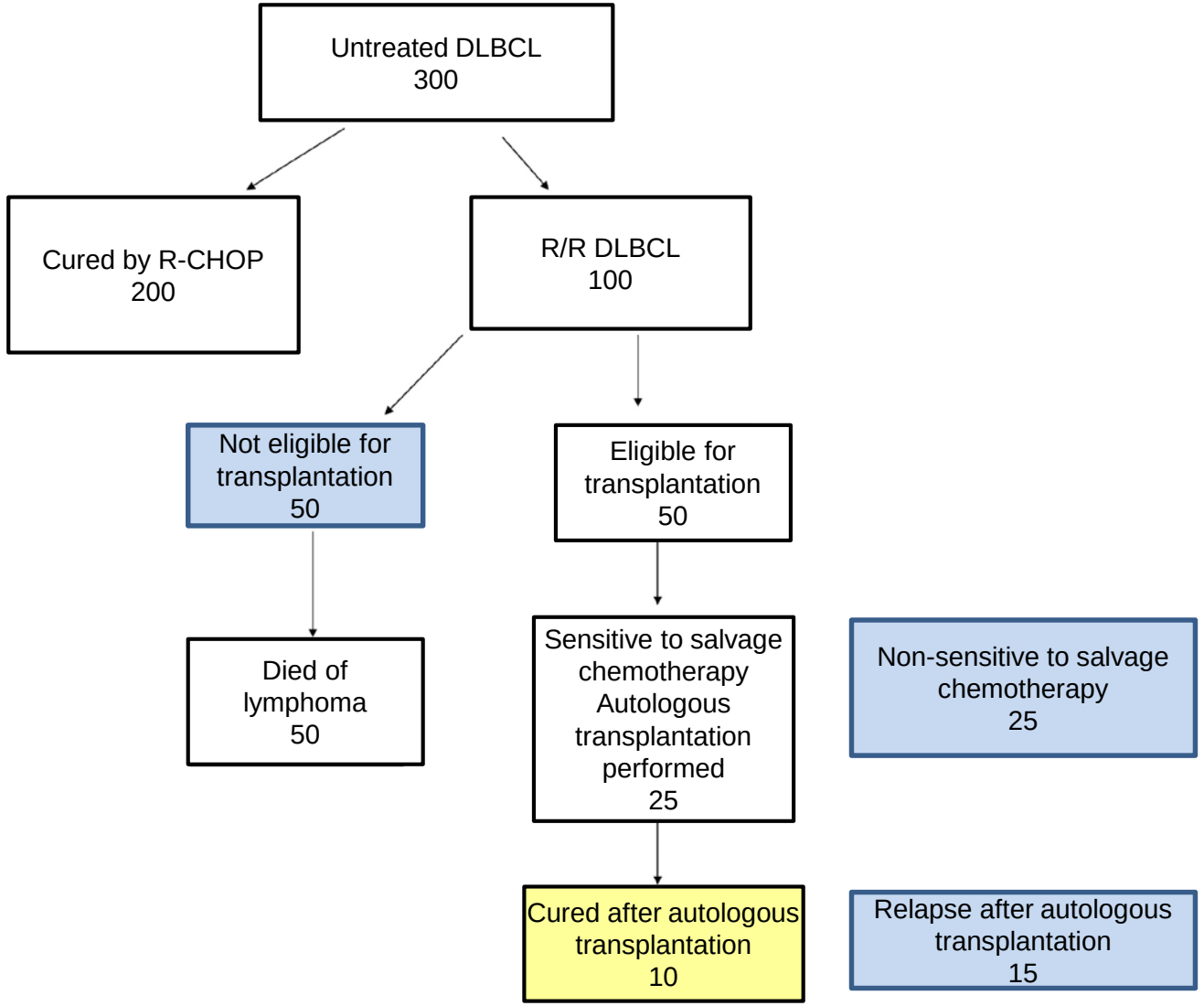
- Response rate: R-ICE 63.5% vs R-DHAP 62.8%
- Mobilization-adjusted response rate: R-ICE 52.3% vs R-DHAP 54.5%
- Autologous transplantation rate: R-ICE 51% vs R-DHAP 55%



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

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

Challenging Situations for the Treatment of R/R DLBCL

- Secondary treatment unresponsive (refractory to 2nd-line salvage chemo)
- Post-autotransplant relapse (ASCT failure)

- Elderly patients who are ineligible for autotransplantation

Challenging Situations for the Treatment of R/R DLBCL

- Secondary treatment unresponsive (refractory to 2nd-line salvage chemo)
- Post-autotransplant relapse (ASCT failure)

- Elderly patients who are ineligible for autotransplantation

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

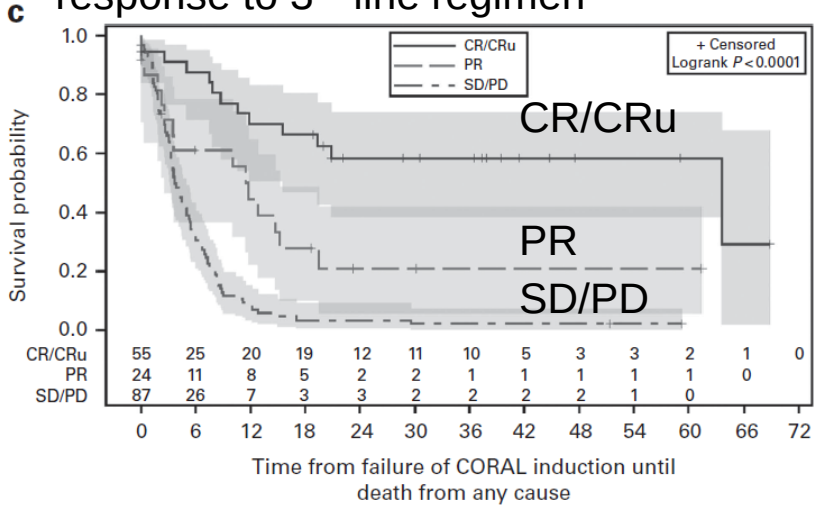
2nd line (CORAL)	3rd line	ORR to 3rd line
R-DHAP (n=94)	ICE-like (n=23)	45.3%
R-ICE (n=109)	DHAP (n=26)	42.3%

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

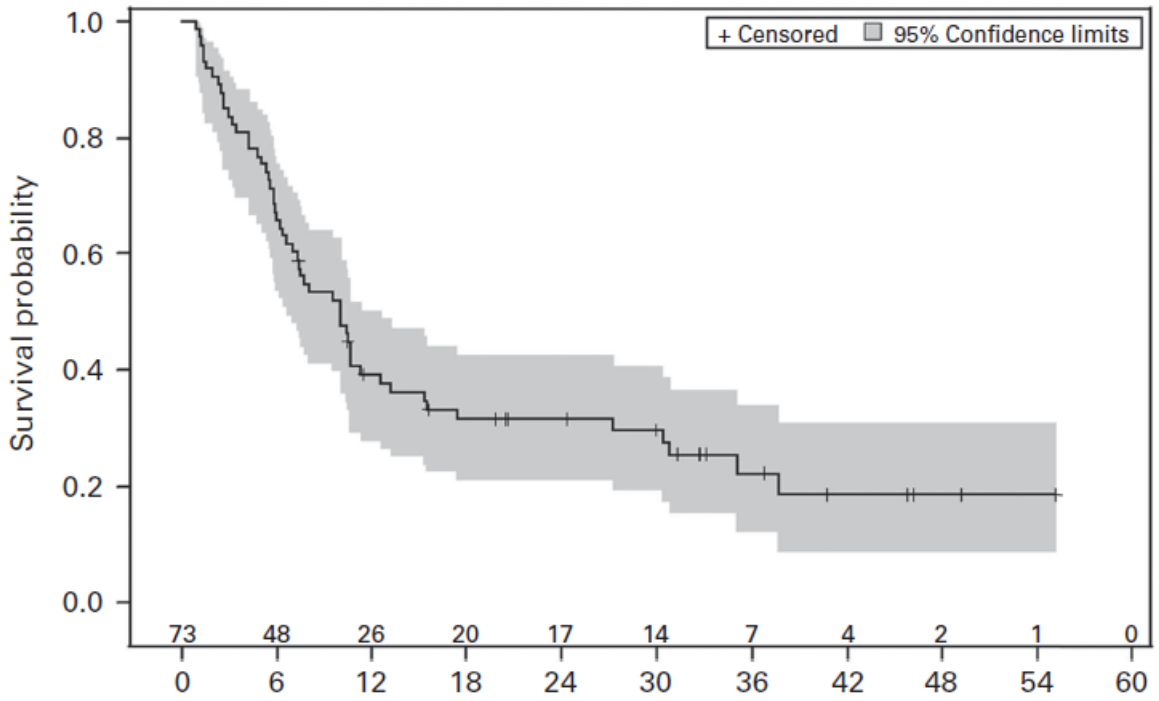
2nd-line: SD/PD
→ 3rd-line CR/PR 32% (43/135)

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



Relapse after ASCT

- CORAL study

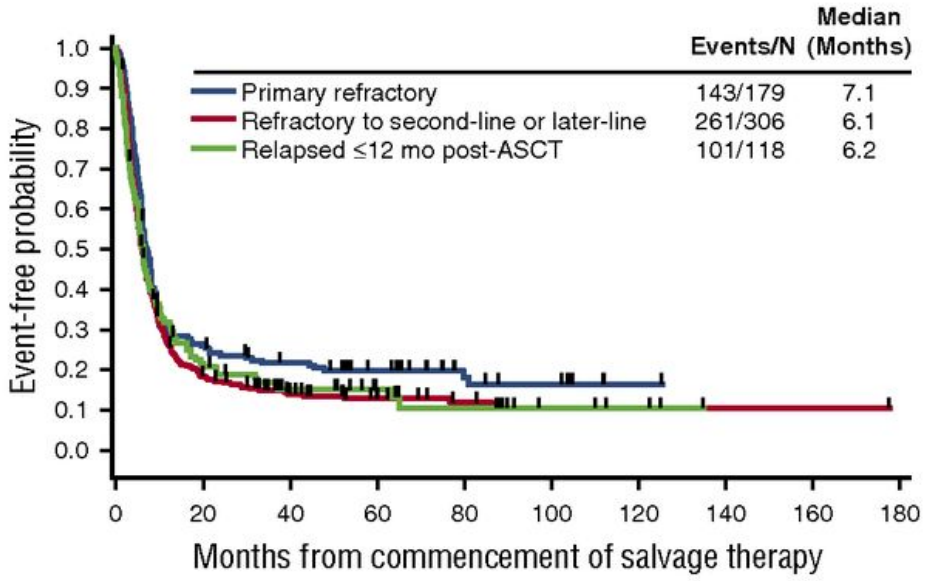


N=73
Median time ASCT-PD: 7.1 mo
ORR to 3rd-line chemo 44%
Median OS 10.0 mo
13 allo SCT

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

Prognosis of Refractory DLBCL

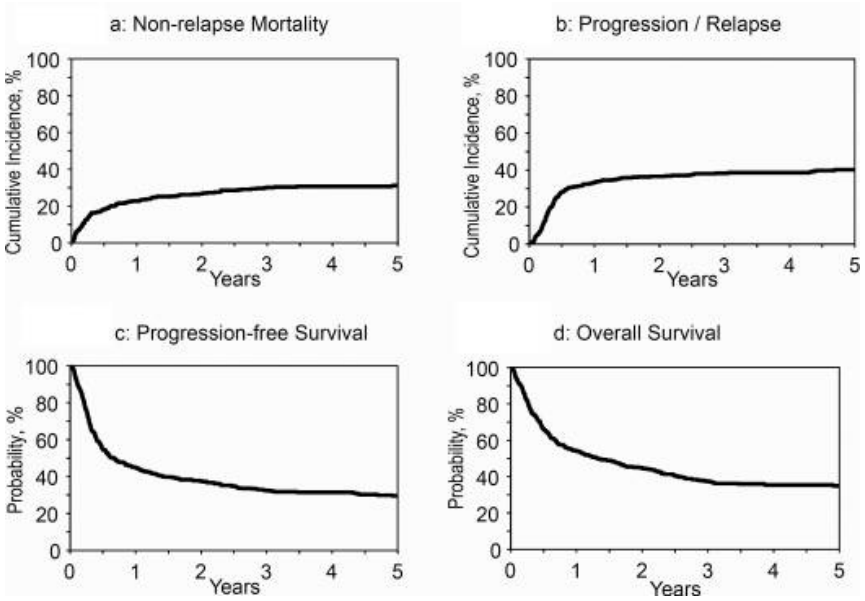
- SCHOLAR-1 Study (retrospective study)
  - "Refractory" DLBCL
    - 1st-line therapy R-CHOP x 4→ SD/PD
    - After 2nd-line therapy →SD/PD
    - Relapse within 12 months after autologous transplantation
  - Response to the next-line therapy: Overall response rate 26%, CR rate 7%



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

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%

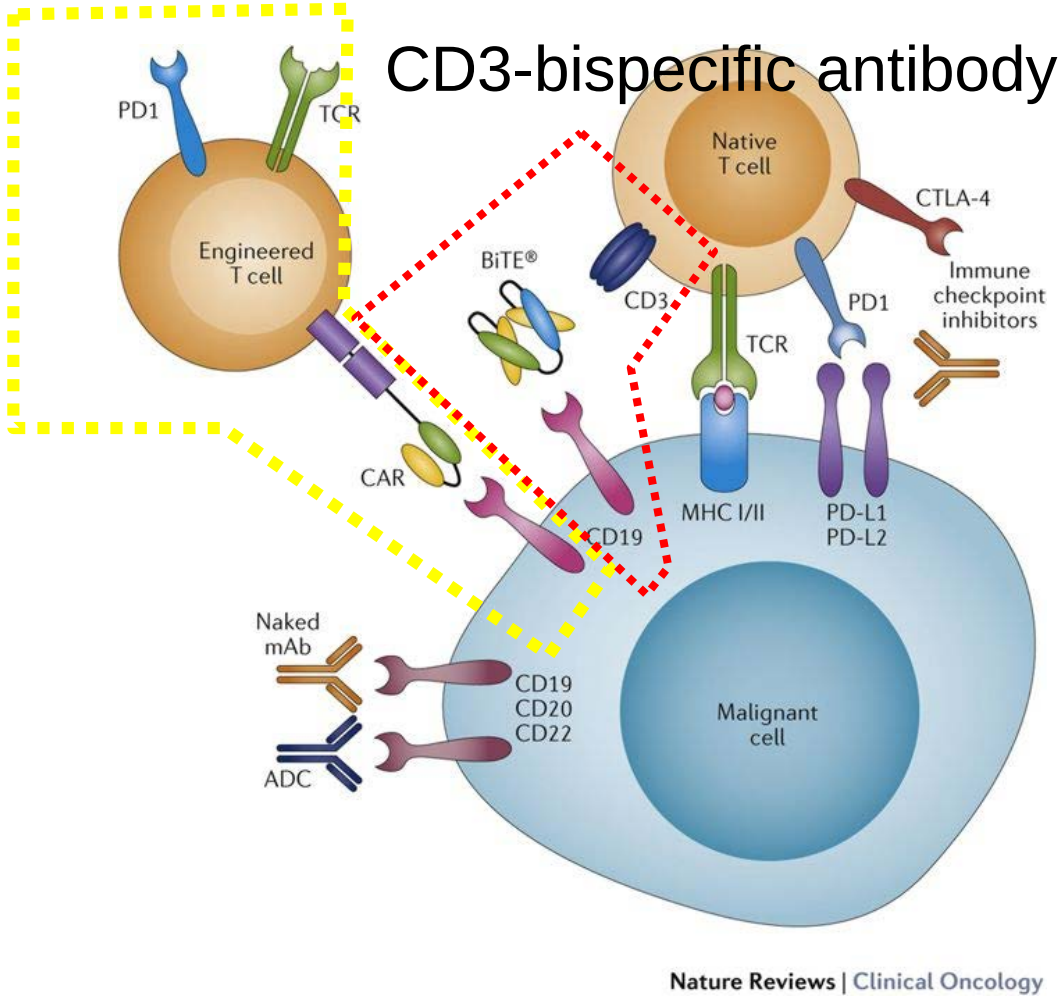


BM: bone marrow
PB: peripheral blood
Source: Fenske TS et al. Br J Haematol 2016; 174:235

Immunotherapy Targeting CD19

CAR-T

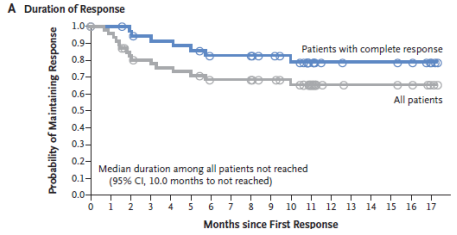
CD3-bispecific antibody

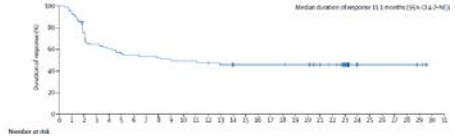


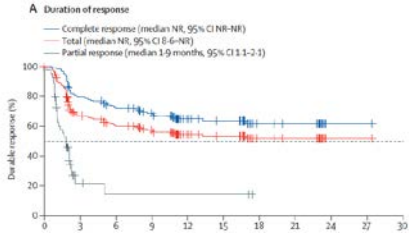
source：Batlevi CL et al. Nat Rev Clin Oncol 2016; 13:25-40

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

	Tisagenlecluce (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

Challenging Situations in the Treatment of R/R DLBCL

- Secondary treatment unresponsive (refractory to 2nd-line salvage chemo)
- Post-autotransplant relapse (ASCT failure).

- Elderly patients who are ineligible for autotransplantation

R/R DLBCL in Elderly Patients

- Multidrug salvage chemotherapy (+/-dose reduction)
  - ICE-like, Gem-containing > HDAC+CDDP

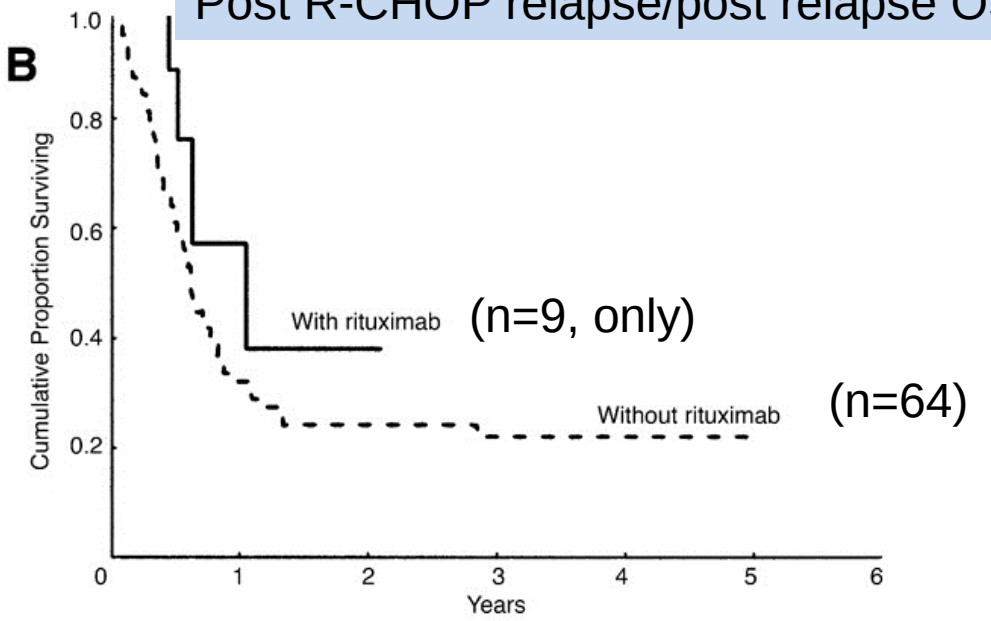
    - No prospective studies have been conducted. Treatment has been selected based on empirical clinical experiences.
    - Cure is difficult.
    - High toxicity: myelosuppression, nephropathy etc.
    - Need hospitailzation: continuous infusion on daily basis, severe myelosuppression

- Single agent
  - Gem
  - Oral agent
- Radiotherapy
- Best supportive care

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

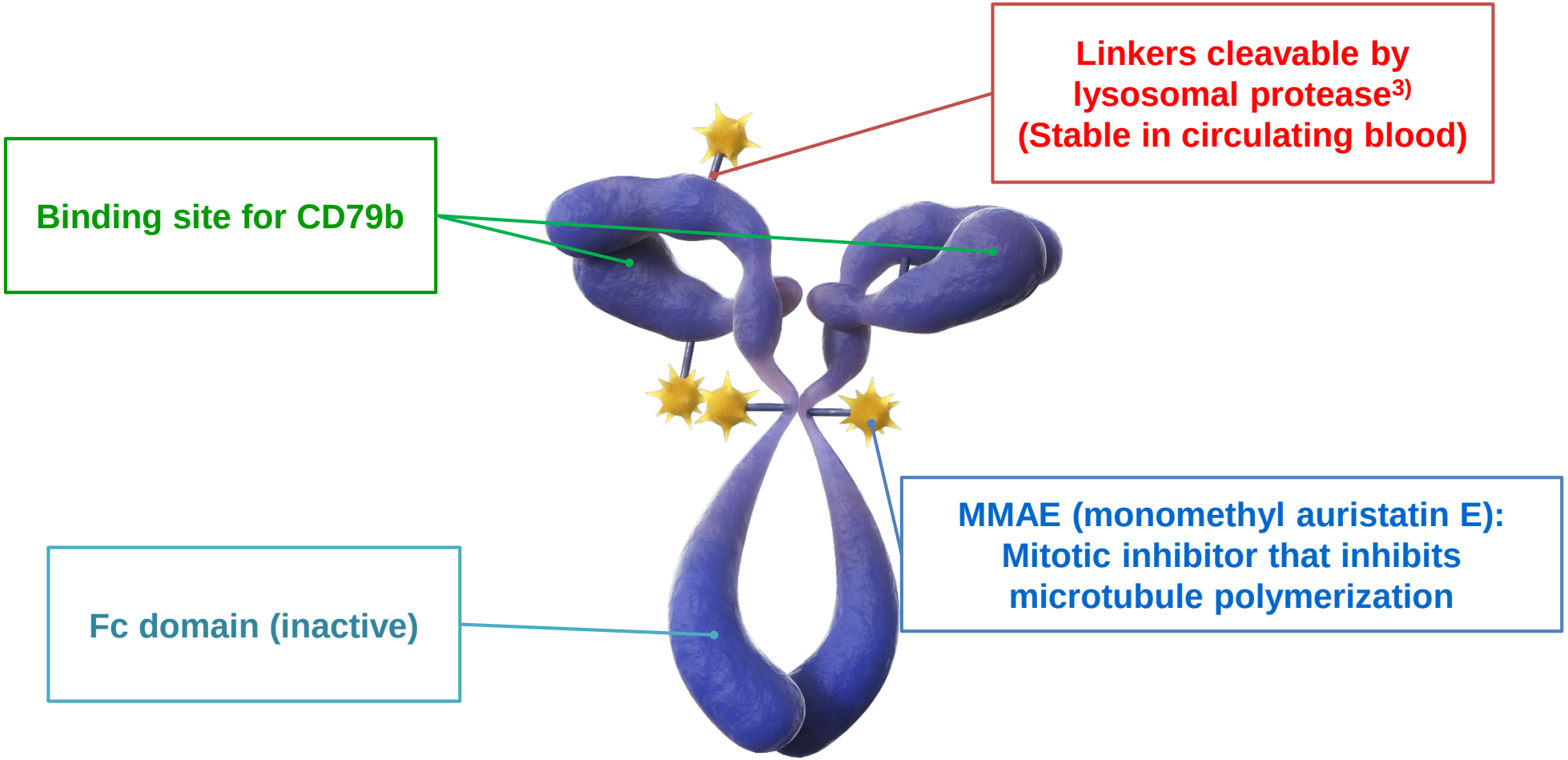
- GELA LNH98-5 study (R-CHOP vs CHOP)
  - DLBCL, 60-80 years old
  - Progression after R-CHOP 77
  - Salvage chemo: DHAP, ESHAP, ICE (+ASCT, n=1)

Post R-CHOP relapse/post relapse OS



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

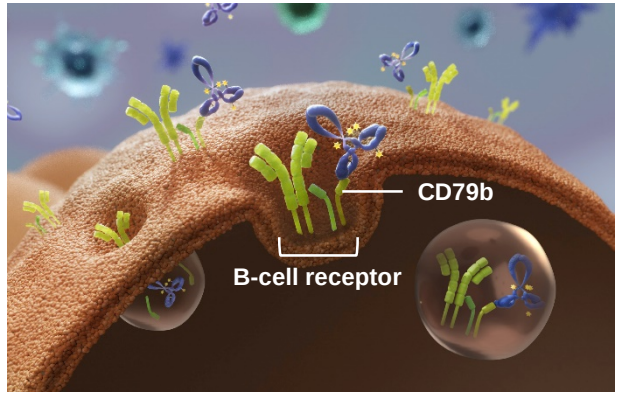
Polatuzumab vedotin (PV, Pola) anti-CD79b ADC



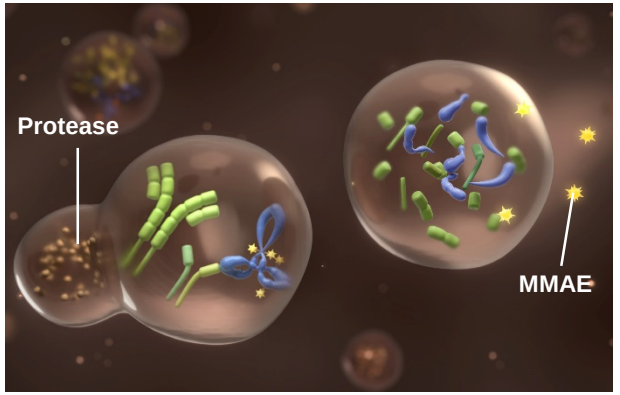
Source：Burke JM et al. Exp Rev Clin Pharmacol 2020; 13:1073-83
Shingeleton JR et al. J Clin oncol 2020;38:166-168

Mode of Action

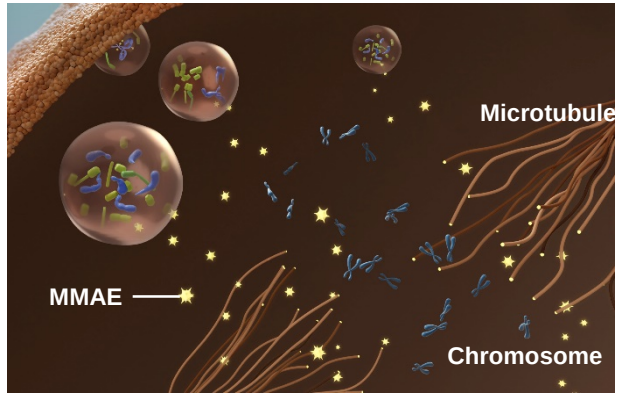
1 **Binding of Polivy and CD79b, intracellular transfer**



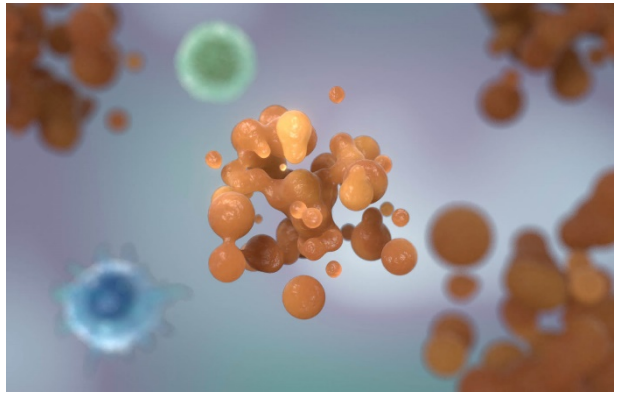
2 **Degraded by lysosomal proteases, releasing MMAE**



3 **Inhibiting microtubule polymerization**



4 **Inhibiting cell proliferation, inducing apoptosis**

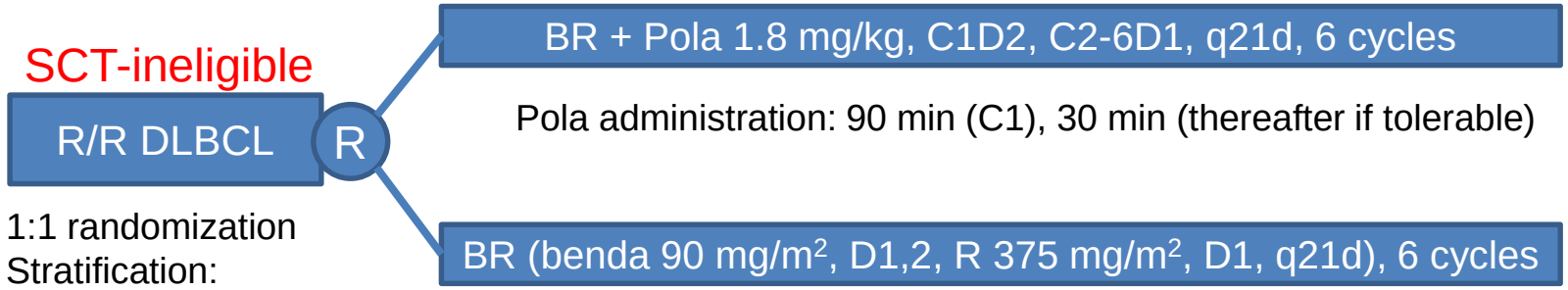


Source：Burke JM et al. Exp Rev Clin Pharmacol 2020; 13:1073-83
Shingeleton JR et al. J Clin oncol 2020;38:166-168

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

Study Design

Phase Ib safety run-in: BR+Pola 1.8 mg/kg, n=6
Phase 2: open-label randomized phase 2, n=80



1:1 randomization
Stratification:
DOR ≤12mo vs >12 mo

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

Pola-BR vs BR in R/R DLBCL

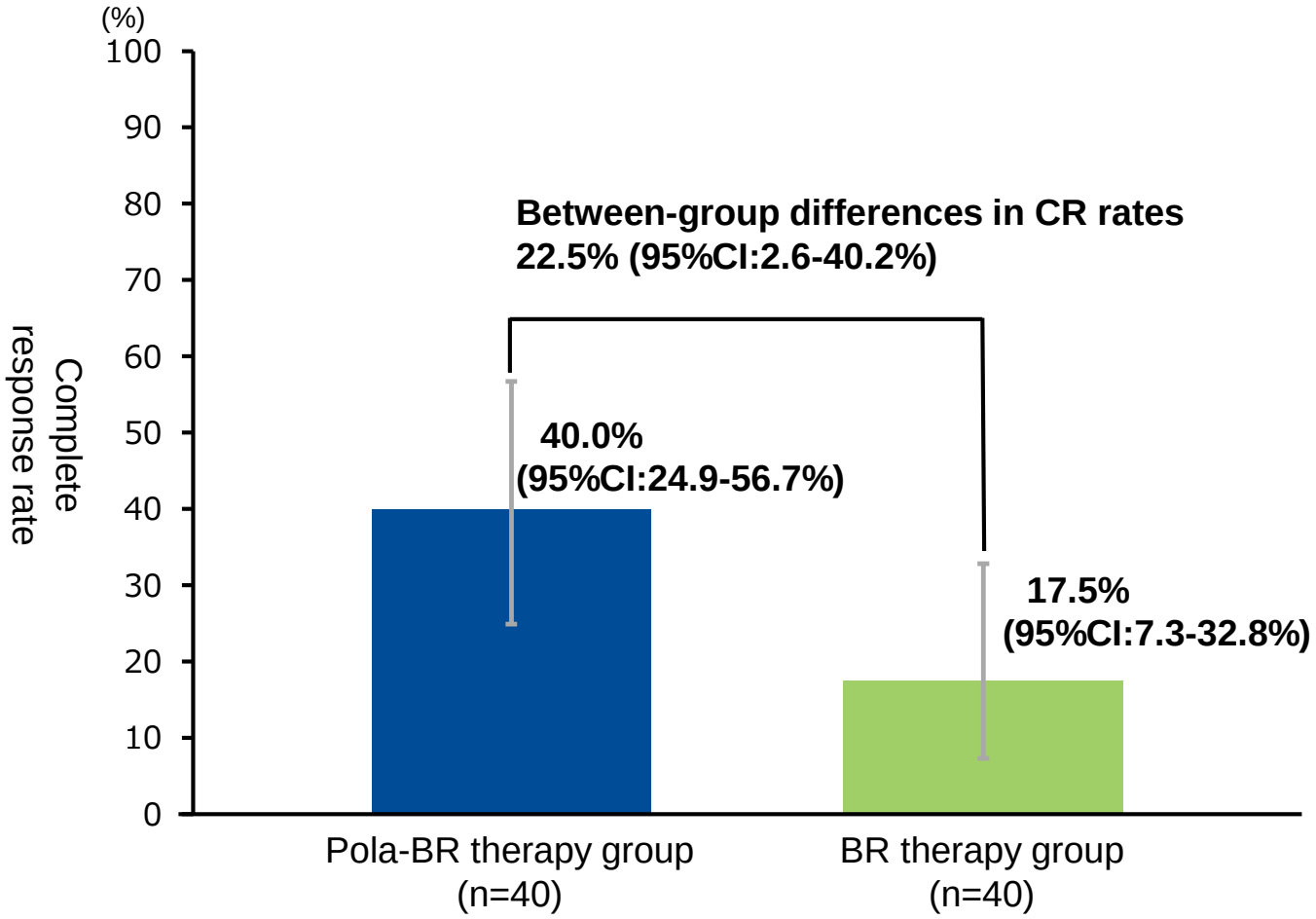
Baseline Characteristics

	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

Pola-BR vs BR in R/R DLBCL

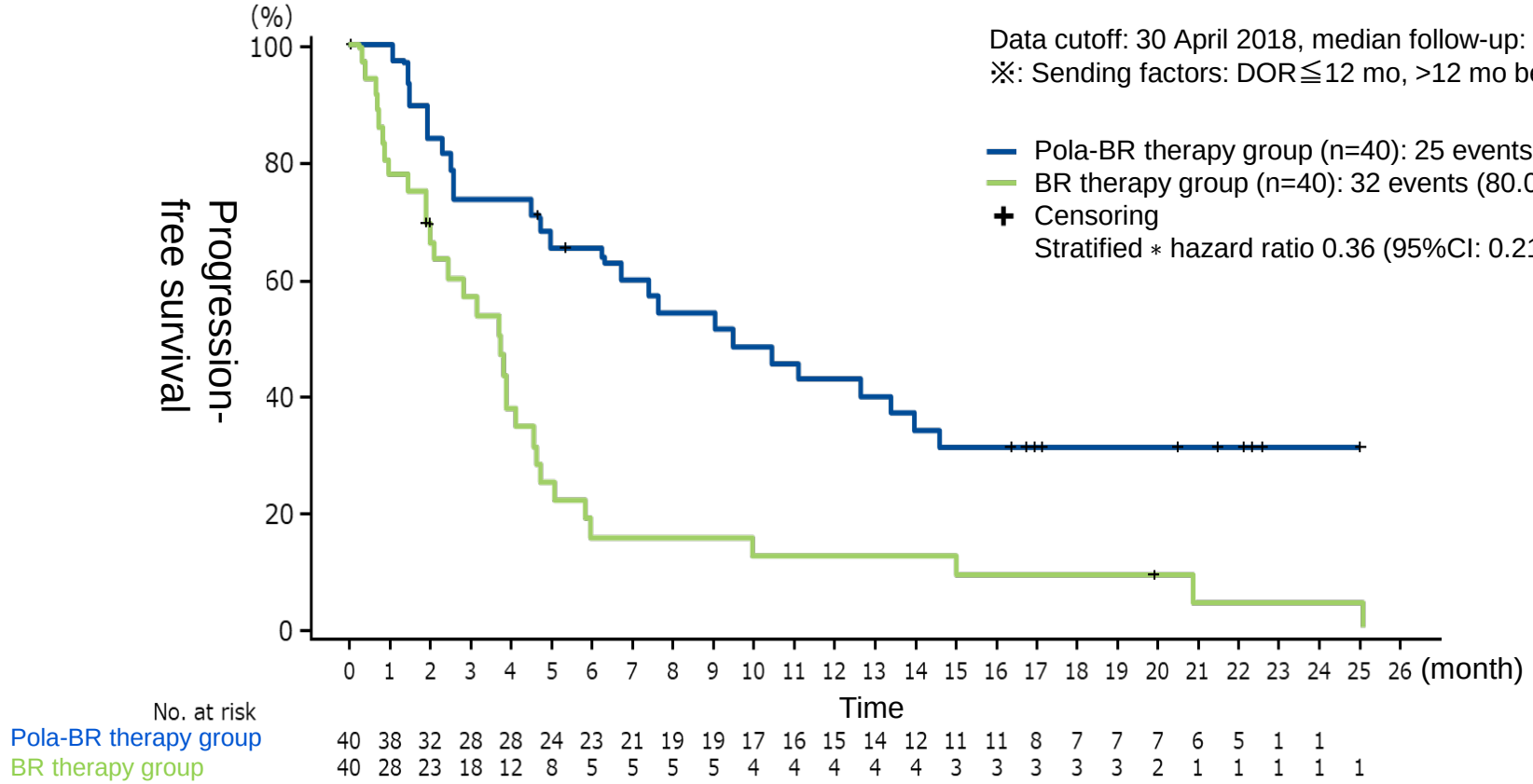
- Efficacy (CR rate: Primary endpoint)



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

Pola-BR vs BR in R/R DLBCL

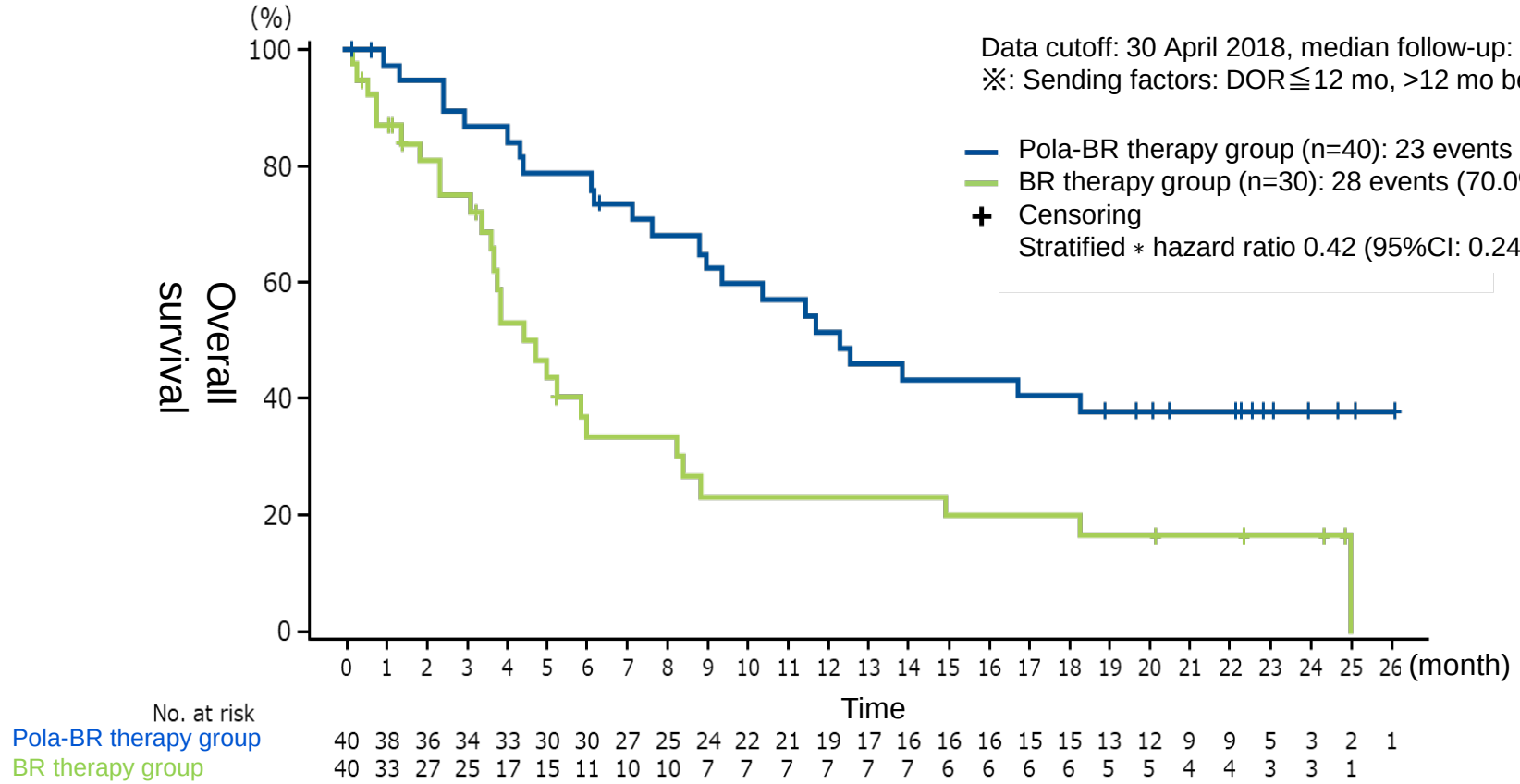
Efficacy (PFS: Secondary endpoint)



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

Pola-BR vs BR in R/R DLBCL

Efficacy (OS: Exploratory outcome)



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

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

Pola-BR vs BR in R/R DLBCL

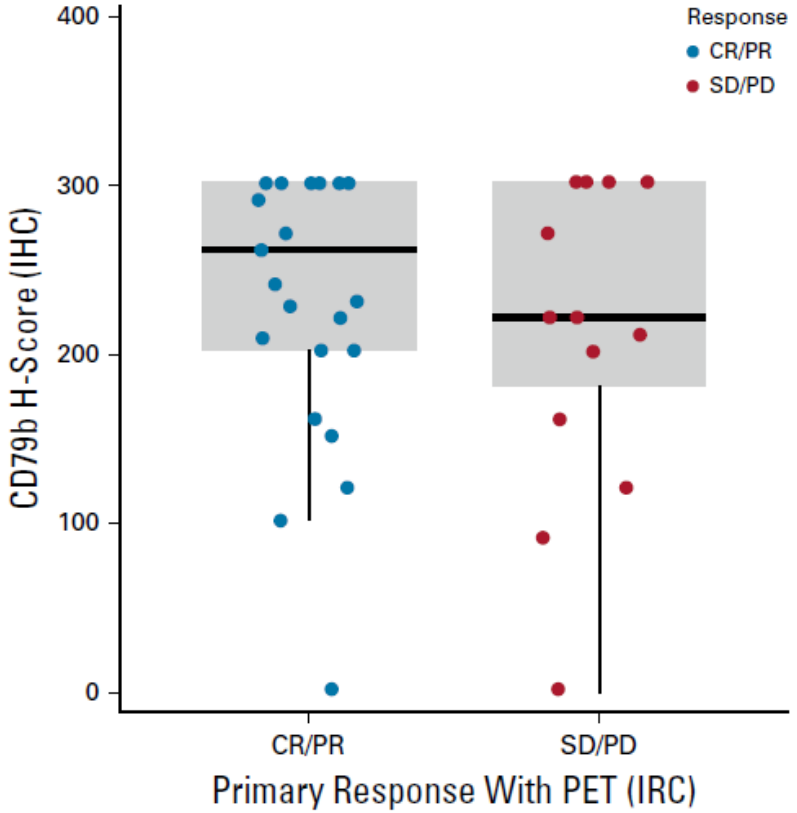
Safety

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.

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

Pola-BR vs BR in R/R DLBCL

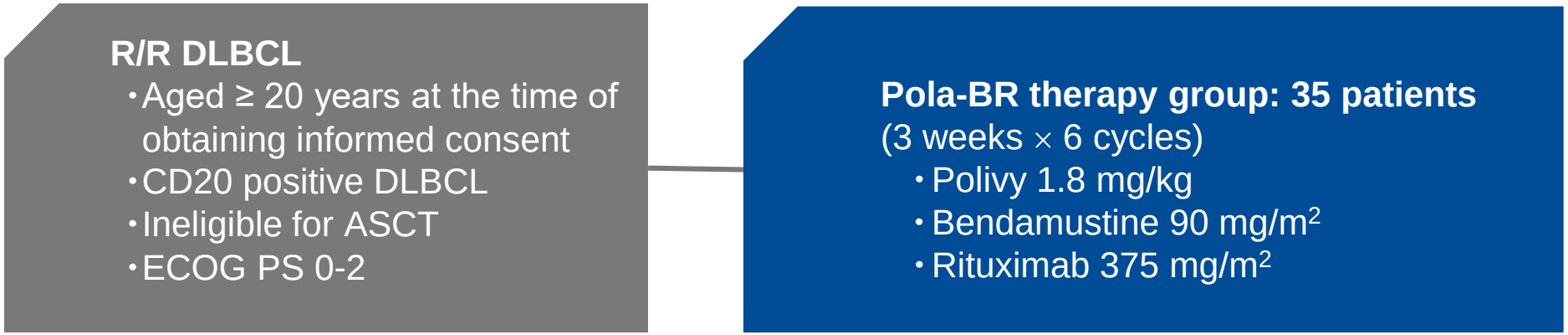
Treatment exposure

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

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

Study design



Primary endpoint: CR rate (PET-CT)
Expected CR rate: 40.0%, threshold CR rate: 17.5%
(Pola-BR vs BR, CR rates of Pola-BR group and BR group in RP2)

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

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

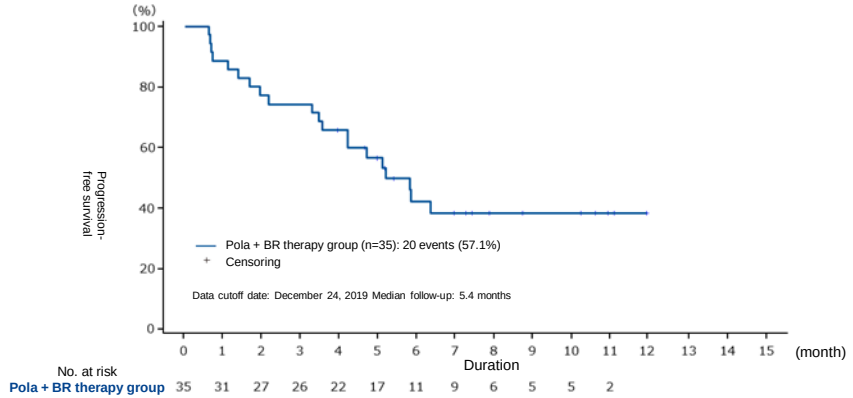
Baseline characteristics

	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])

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])

Expectations for Polivy

- Polivy is an antibody treatment for DLBCL that has been launched for the first time in 18 years since the launch of Rituxan, presenting a new treatment option.
- It is the first ADC for DLBCL.
- Pola-BR is a regimen that can be administered on an outpatient basis, allowing treatment tailored to the patient's preference.

Therapeutic Strategies for R/R DLBCL

Summary

- Initiate 2nd-line therapy as determined by eligible for autologous transplant or not
  - If sensitive to salvage chemotherapy, high-dose chemotherapy with autologous transplantation is given
  - CAR-T cells therapy is primarily a 3rd-line treatment option

- In patients ineligible for autotransplantation, cure is difficult and prolonged disease control is the goal of treatment
  - Pola-BR was found to be effective against BR in a randomized phase 2 trial
  - Pola-BR is an ambulatory treatment option
  - Pola-BR should be vigilant for cytopenias, including lymphopenia, and peripheral neuropathy

Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends.
Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.

Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.

Contacts

Corporate Communications Dept.

For Media: Media Relations Group	
Tel :	+81 (0)3-3273-0881
E-mail :	pr@chugai-pharm.co.jp
Person in charge :	Tomoko Shimizu, Chisato Miyoshi, Shumpei Yokoyama, Kaho Izumi, Mari Otsuka

For Investors: Investor Relations Group	
Tel :	+81 (0)3-3273-0554
E-mail :	ir@chugai-pharm.co.jp
Person in charge :	Takayuki Sakurai, Tomoyuki Shimamura, Sachiyo Yoshimura, Yayoi Yamada

INNOVATION BEYOND IMAGINATION