日本標準商品分類番号 874291

抗悪性腫瘍剤　ヒト化抗CD20モノクローナル抗体

生物由来製品、劇薬、処方箋医薬品*

ガザイバ®点滴静注1000mg

GAZYVA®

obinutuzumab

オビヌツズマブ（遺伝子組換え）注

*注意－医師等の処方箋により使用すること

®F.ホフマン・ラ・ロシュ社（スイス）登録商標

Product Overview of GAZYVA® Intravenous Infusion 1000 mg

Naoko Oya
GAZYVA® Lifecycle Leader
Chugai Pharmaceutical Co., Ltd.

Forward-Looking Statements

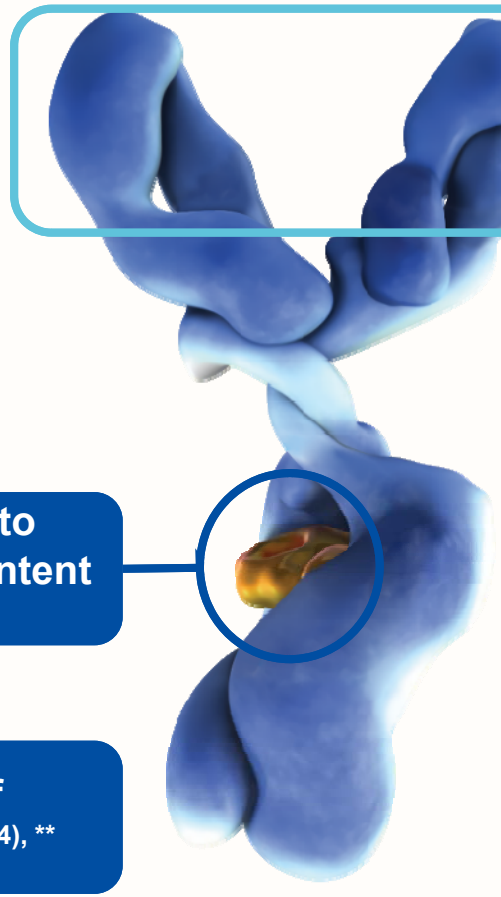
This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends. Actual results may differ from expectations based on risks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

Characteristics of Obinutuzumab: Mode of Action

- A glycoengineered type II antibody using a novel antibody engineering technology -

Image



Type II anti-CD20 monoclonal antibody[1)]

High direct cell death induction activity[2)]

Glycoengineering to reduce the fucose content in the Fc region[3)]

High activities of ADCC* and ADCP[3, 4), **]

- **Humanized anti-CD20 monoclonal antibody (IgG1)**
- **Identifying CD20 molecule epitopes expressing specifically on B cells**
- **Glycoengineering to reduce the fucose content in the Fc region and having unique characteristics as a type II antibody**

* ADCC: antibody-dependent cell-mediated cytotoxicity
** ADCP: antibody-dependent cell-mediated phagocytosis

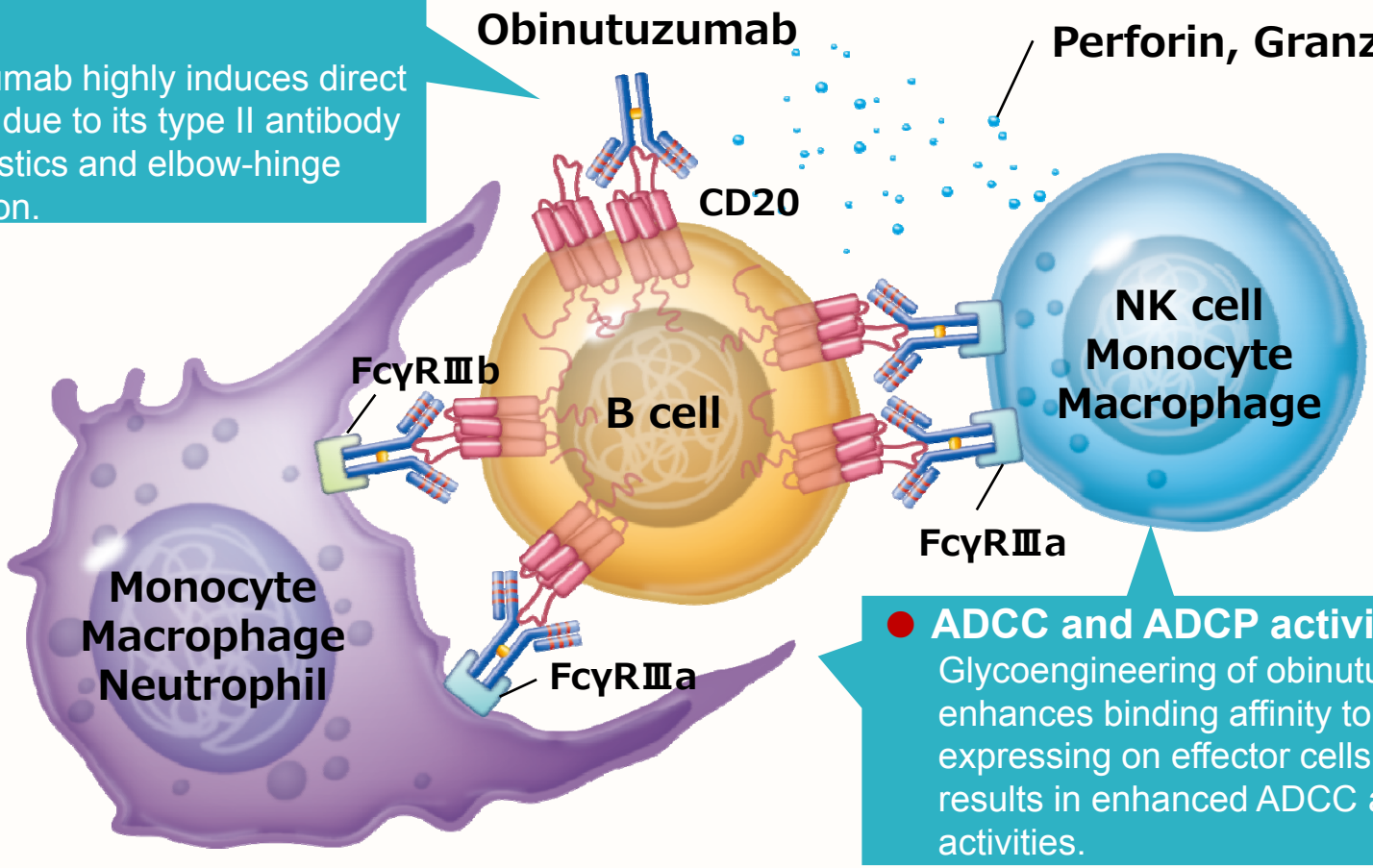
1）Niederfellner G, et al.: Blood 118（2）: 358–367（2011）、2）Alduaij W, et al.: Blood 117（17）: 4519–4529（2011）
3）Mössner E, et al.: 115（22）: 4393–4402（2010）、4）Herter S, et al.: Mol Cancer Ther 12（10）: 2031–2042（2013）

Mode of Action of Obinutuzumab

Image

● **Direct cell death induction activity**

Obinutuzumab highly induces direct cell death due to its type II antibody characteristics and elbow-hinge modification.



● **ADCC and ADCP activity**

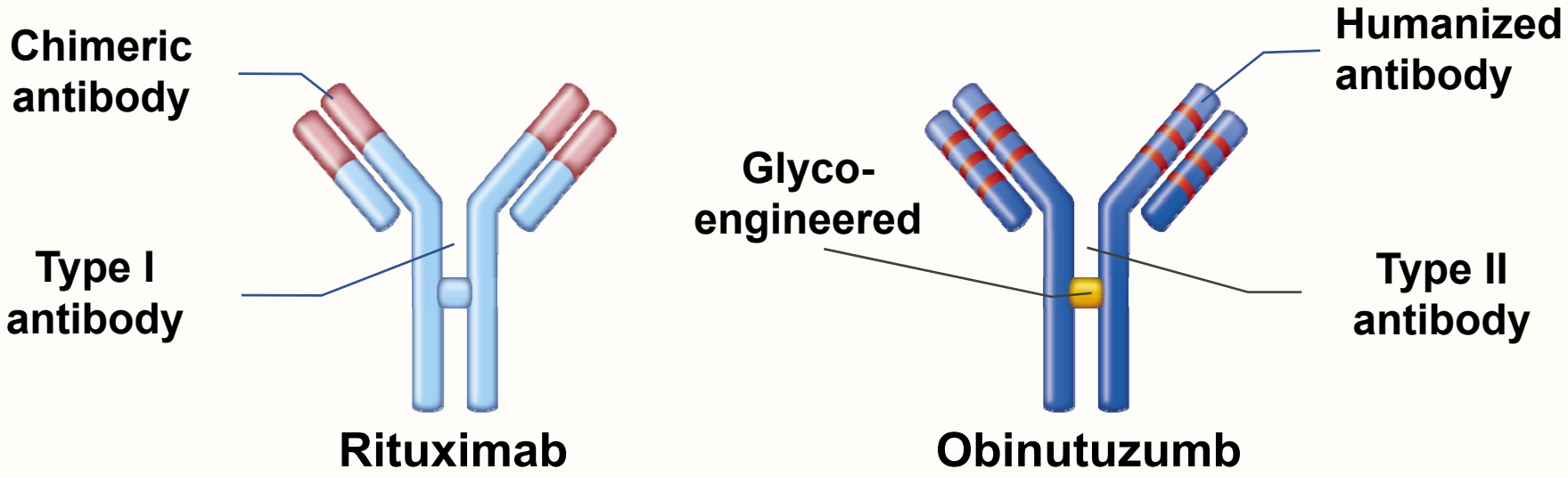
Glycoengineering of obinutuzumab enhances binding affinity to FcγRIII expressing on effector cells, which results in enhanced ADCC and ADCP activities.

Maloney DG. N Engl J Med. 366（21）: 2008-2016（2012）
Tobinai K, et al.: Adv Ther 34（2）: 324（2017）) with modifications

The Difference of Rituximab and Obinutuzumab

Image

	Difference due to antibody types (type I and type II)		Difference due to glycoengineering
	Direct cell death induction activity* Proportion of cell death (%)	CDC activity* EC_{50} (μg/mL)	ADCC activity* EC_{50} (ng/mL)
Rituximab	6.5 - 36.5	0.027 - 0.062	4.32 - 26.18
Obinutuzumab	19.1 - 73.5	2.7 - 12	0.459 - 2.471



* The activities of obinutuzumab and rituximab on various B-NHL-derived cell lines

Indications

CD20-positive follicular lymphoma

<Precautions related to Indications>

GAZYVA should be used in patients who test positive for CD20 antigen using flow cytometry or another method.

Dosage and administration

The usual adult dose is 1000 mg obinutuzumab (recombinant) administered by intravenous infusion. In induction treatment, using the cycle durations and number of cycles shown as follows, GAZYVA is administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycle 2 and beyond. In maintenance treatment, GAZYVA is administered as monotherapy once every 2 months, continuing treatment for up to 2 years.

- If administering with cyclophosphamide hydrate, doxorubicin hydrochloride, vincristine sulfate, and prednisolone or methylprednisolone

  Eight 3-week cycles

- If administering with cyclophosphamide hydrate, vincristine sulfate, and prednisolone or methylprednisolone

  Eight 3-week cycles

- If administering with bendamustine hydrochloride

  Six 4-week cycles

Pathology of Follicular Lymphoma and Clinical Trial Results of Obinutuzumab

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Deputy Director,

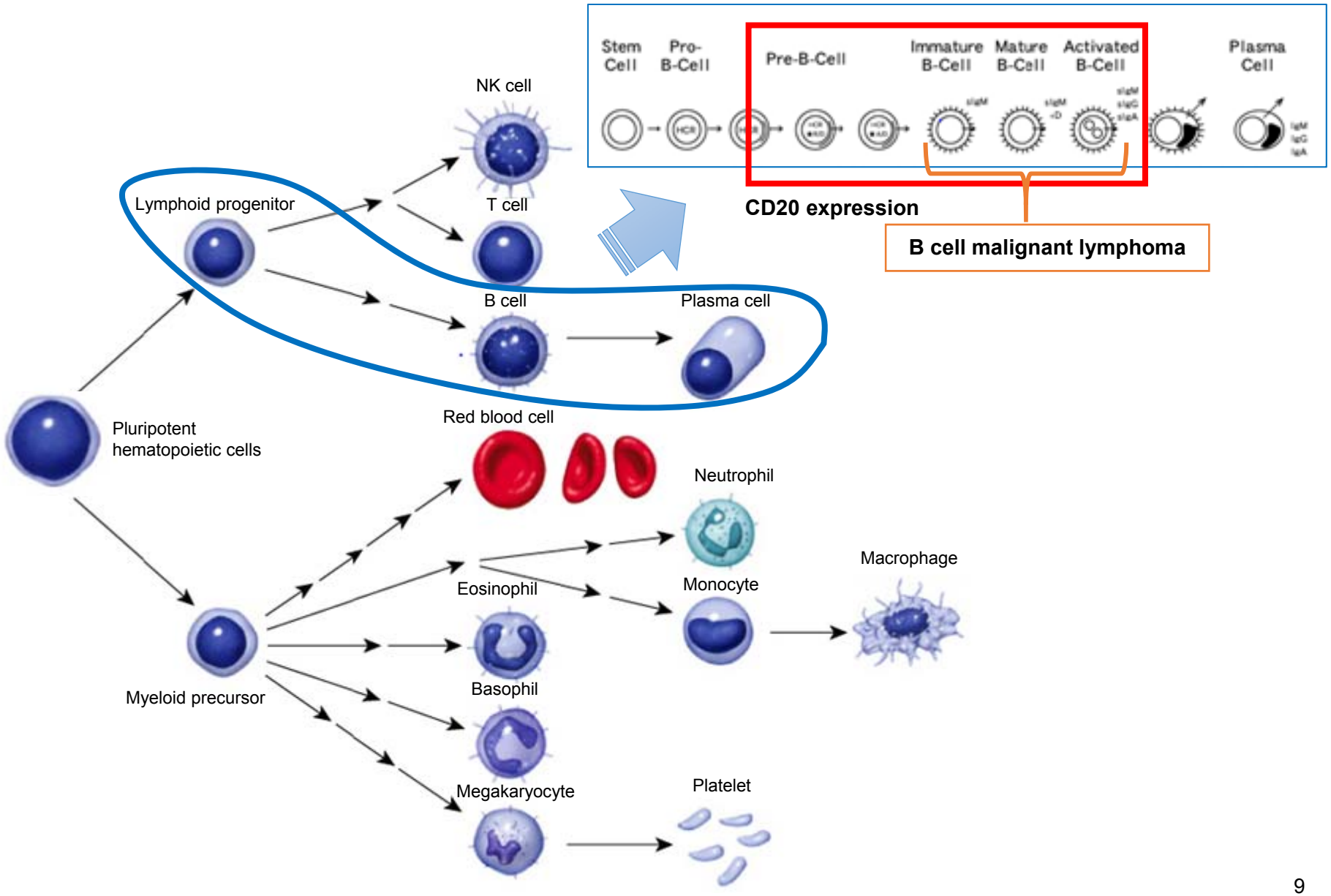
Head of the Malignant Tumor and Hematologic Tumor Center at the International University of Health and Welfare, Mita Hospital

Conflict of interest disclosure

Name of lead presenter	Kiyohiko Hatake	Institution or company/position	Head of the Malignant Tumor and Hematologic Tumor Center at the International University of Health and Welfare, Mita Hospital

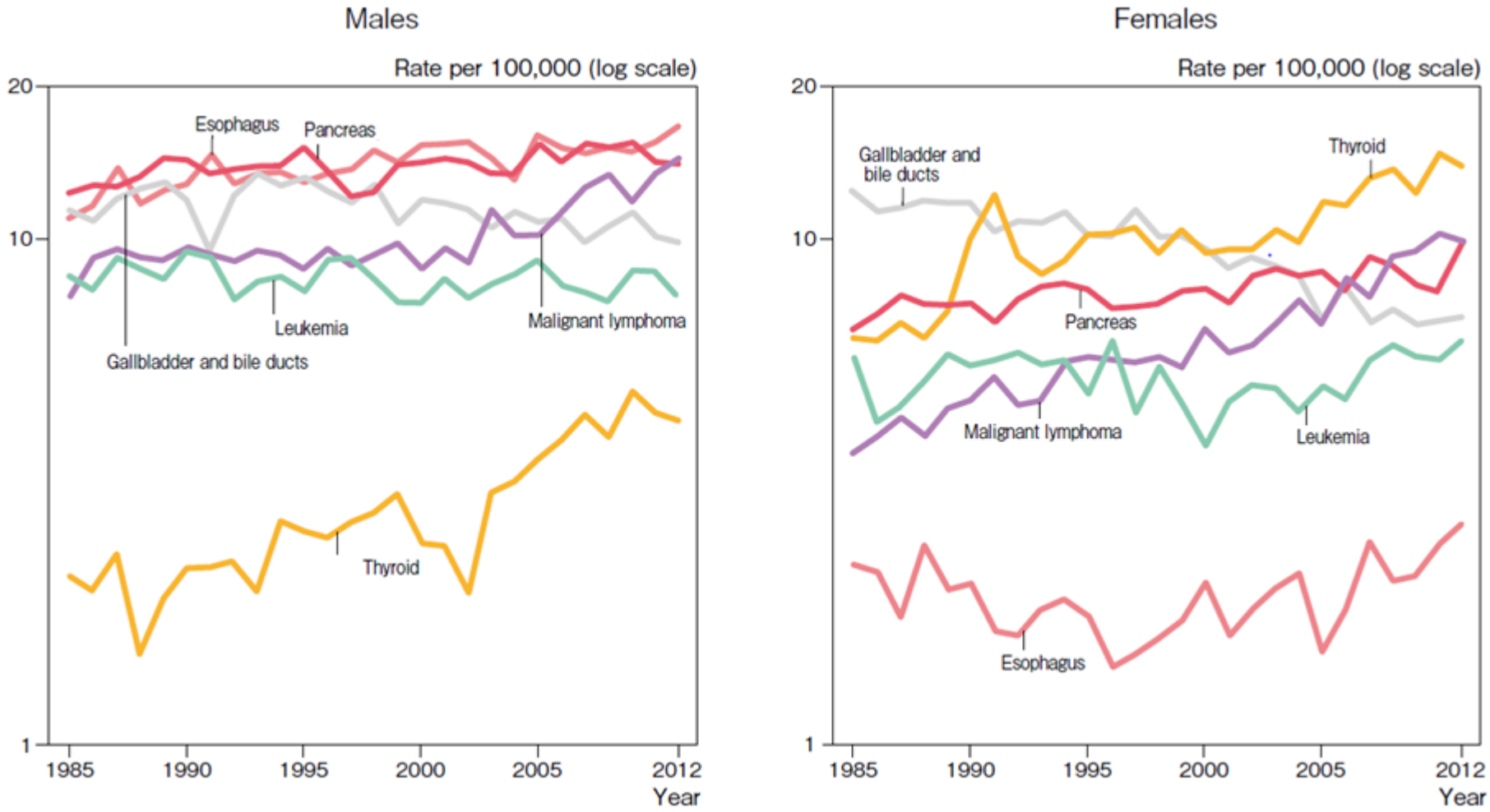
	No	If yes, please specify the name of company and/or organization, your status.
employee of company and/or profit-making organization	☑	no
adviser of company and/or profit-making organization	☑	no
profit of stock	☑	none
lecturer fees		Chugai, Eisai, Kyowa Hakko Kirin, Otsuka, Takeda, Celgene
manuscript fees	☑	
research expenses	☑	
contributions	☑	
fees of testimony, judgment, comment, etc.	☑	
representative of organization for clinical study receiving research expenses from company	☑	
presents or any payment	☑	

Classification of hematopoietic tumors



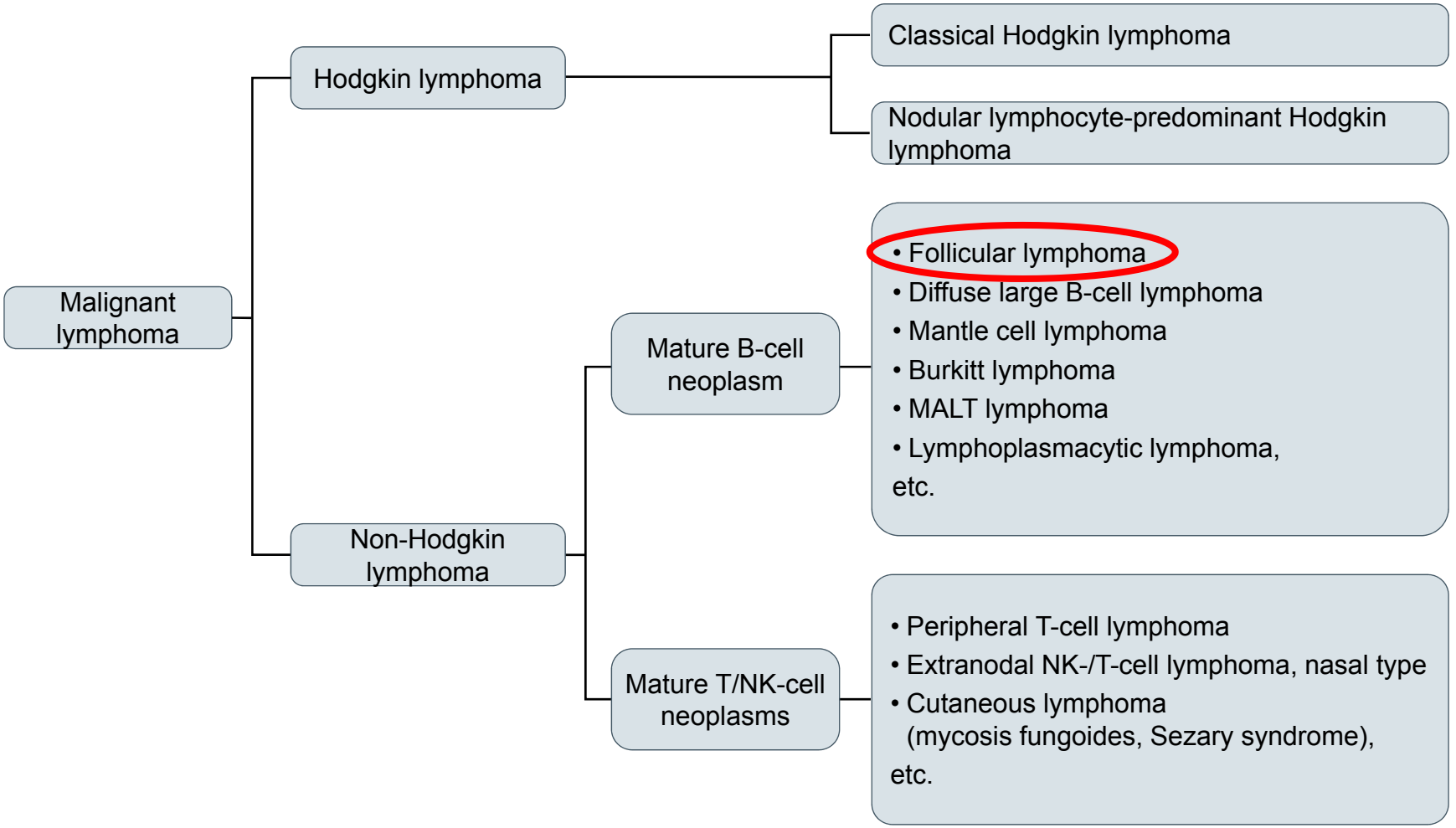
Incidence of malignant lymphoma

By site Annual time course of age-adjusted cancer incidence (1985 to 2012)



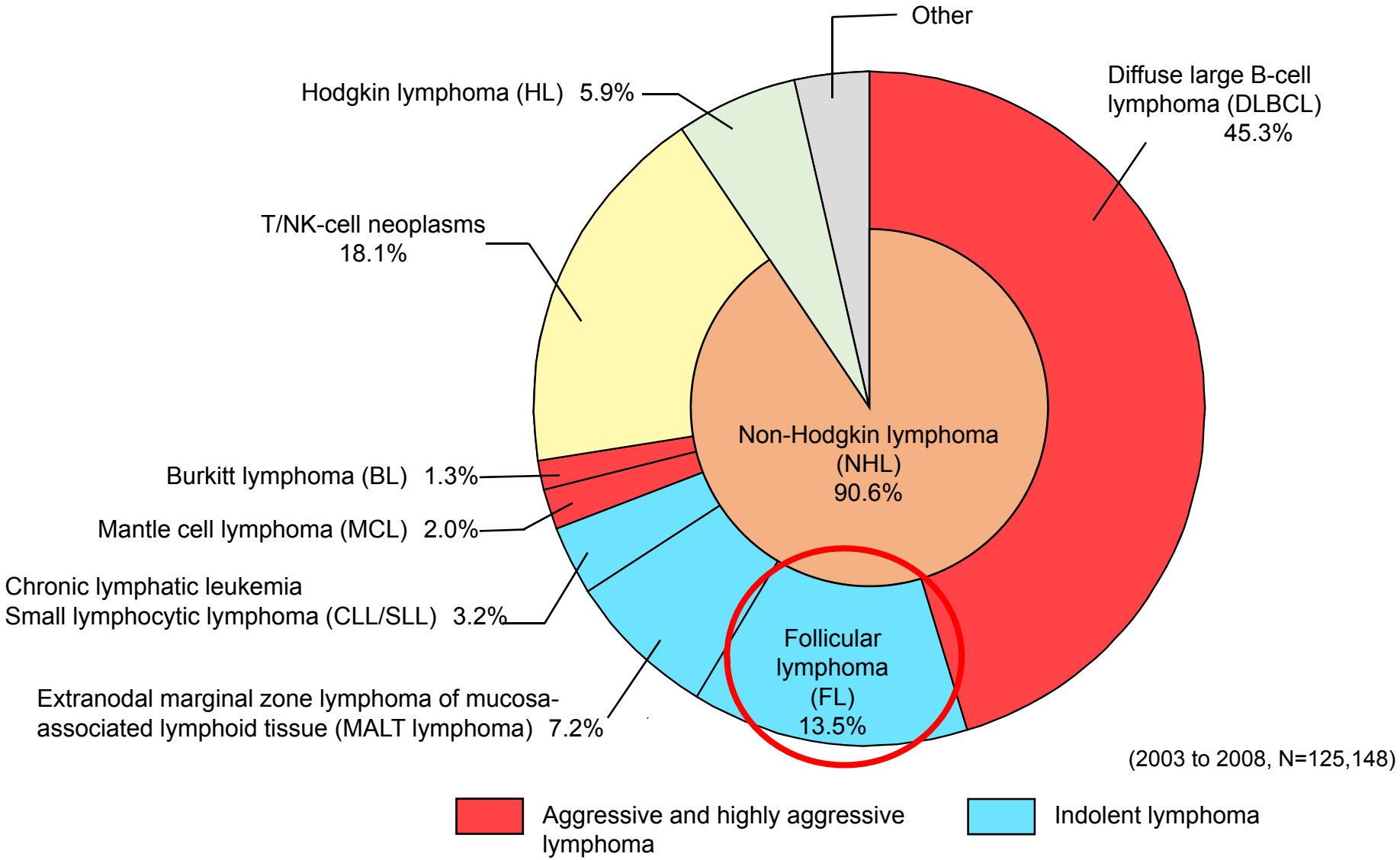
Cancer Information Service, National Cancer Center, "Cancer Registry and Statistics," Cancer Statistics in Japan – 2017, p49
Available from: https://ganjoho.jp (October 12, 2018)

Classification of malignant lymphoma (overview)



Prepared using the 2018 Clinical Practice Guidelines of Hematopoietic Tumor, Kanehara & Co., LTD., p167-170 as a reference

Proportion of new patients by type of malignant lymphoma (Japan)



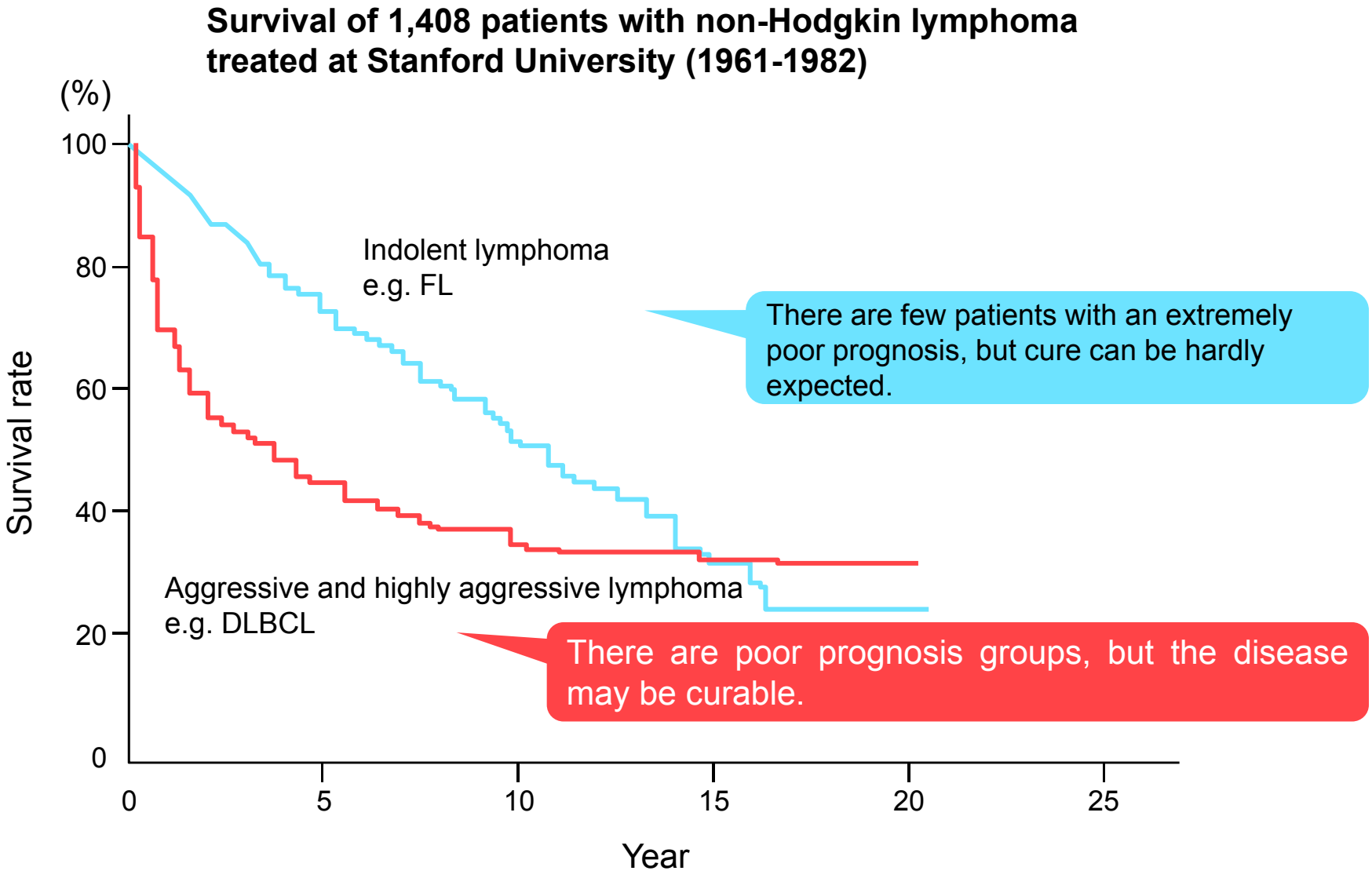
Chihara D, et al. Br J Haematol 164: 536-545, 2014

Classification of non-Hodgkin lymphoma by aggressiveness

Aggressiveness	Progression rate	Representative disease type	Remarks
Indolent lymphoma	Year	• MALT lymphoma • Follicular lymphoma, etc. (GAZYVA is a drug for the treatment of follicular lymphoma.)	Observation can be appropriate in patients with low tumor burden.
Aggressive lymphoma	Week to month	• Mantle cell lymphoma • Diffuse large B-cell lymphoma, etc.	Treatment is required upon diagnosis.
Highly aggressive lymphoma	Day to week	• Lymphoblastic lymphoma • Burkitt lymphoma, etc.	Intensive inpatient treatment is required.

Prepared using the National Cancer Center Anti-Cancer Information Center: Malignant lymphoma in March 2017 as a reference.

Prognosis of malignant lymphoma



Rosenberg SA. J Clin Oncol 3(3):199, 1985

Clinical features of follicular lymphoma

	Characteristics
Clinical classification	The clinical course often gradually progresses on a “yearly basis.” A representative disease type of indolent B cell lymphoma
Incidence	FL accounts for approximately 14% of malignant lymphoma, with a growing incidence in recent years.
Age of onset	Most frequently affecting people in their mid-50’s and 60’s
Symptoms	Apart from the swelling of lymph nodes in the neck, chest, abdomen, etc., there is few subjective symptoms, and FL is often asymptomatic even if it has progressed.
Lesion	Mainly in lymph nodes, and often accompanied by abdominal bulky tumor
Stage at diagnosis (Ann Arbor Staging)	Advanced stage: Stage III or higher (approximately 80%) Nearly half of these are Stage IV with bone-marrow invasion
Subclassification	Grades 1, 2, 3A and 3B (Grade 3B is often managed as aggressive B-cell lymphoma.)
Prognosis (Median survival)	Before the emergence of rituximab, 7 to 10 years After the emergence of rituximab, 15 years or more

Lymphoma Seminar for Improving Knowledge, Nankodo, p123-124, 2014
The 2018 Clinical Practice Guidelines of Hematopoietic Tumor, Kanehara & Co., LTD., p179, 2018

Four treatment options

Chemotherapy

Target

Majority of malignant lymphoma

Characteristics

- Combination therapy is conducted.
- The remission rate has been improving due to standard of care represented by CHOP therapy.

Radiotherapy

Target

Limited stage follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), etc.

Characteristics

- It is performed for localized lymphoma.
- It is carried out alone or in combination with chemotherapy.
- Palliative radiation may be given to patient with recurrent or relapsed lymphoma.

Hematopoietic cell transplantation

Target

Disease types without standard of care and disease types of which cure cannot be expected with normal-dose chemotherapy

Characteristics

- Aim to recover hematopoietic function lost by chemotherapy and radiotherapy.
- More potent chemotherapy and radiotherapy may be administered on the premise of transplantation.

Watchful waiting

Target

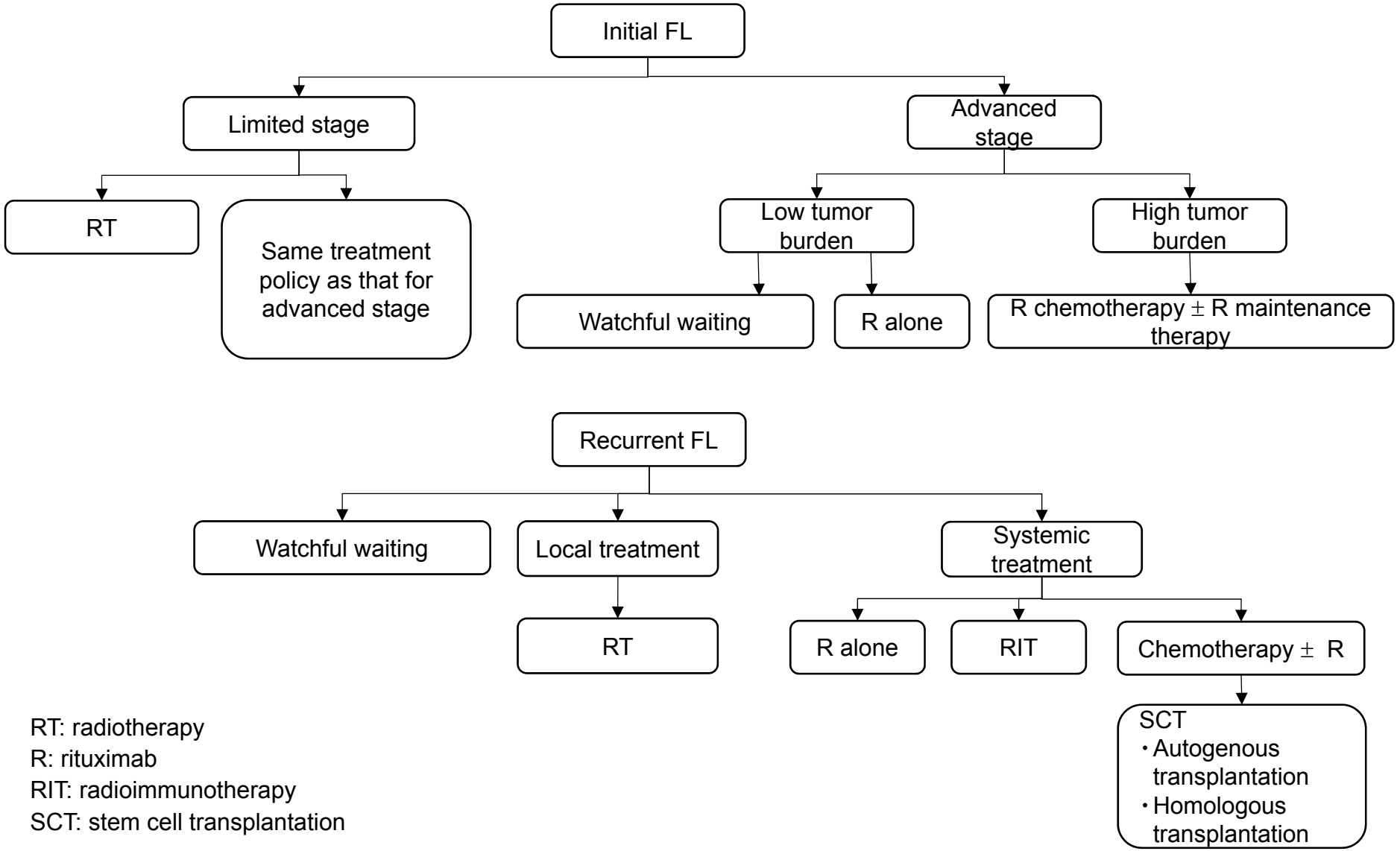
Asymptomatic indolent lymphoma, etc.

Characteristics

- It is implemented when the usefulness of early treatment is not obvious.
- Acute and late-onset adverse events can be avoided, but a close discussion with patients is needed.

FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma

Treatment algorithm of follicular lymphoma



RT: radiotherapy
R: rituximab
RIT: radioimmunotherapy
SCT: stem cell transplantation

The 2018 Clinical Practice Guidelines of Hematopoietic Tumor, Kanehara & Co., LTD., p181

Representative regimens used for the treatment of follicular lymphoma

Representative regimens used for the treatment of initial, advanced, high-tumor-burden FL

- R-CVP therapy (R, CPA, VCR and PSL)
- R-CHOP therapy (R, CPA, DXR, VCR and PSL)
- BR therapy (bendamustine and R)

Treatment for the first relapse of FL

- Watchful waiting
- R monotherapy
- Bendamustine alone or R + bendamustine
- Fludarabine (FLU) alone or combination therapy containing FLU
- R-CHOP therapy (when the previous treatment is a regimen not containing anthracycline)
- Multidrug chemotherapy
- RI-labelled antibody therapy (ibritumomab tiuxetan)

Molecular target drugs used for malignant lymphoma

Disease	Product name	Nonproprietary name	Manufacturer	Launching	Target (category)
CD20-positive B-cell non-Hodgkin lymphoma	Rituxan	Rituximab	Chugai Pharmaceutical/ Zenyaku Kogyo	2001	CD20
CD20-positive relapsed or refractory indolent lymphoma or mantle cell lymphoma	Zevalin	Yttrium (90Y) ibritumomab tiuxetan	Mundipharma	2008	CD20 (radiolabelled)
Mantle cell lymphoma	Velcade	Bortezomib	Janssen Pharma /Takeda Pharmaceutical	2015 (Additional indication)	Proteasome
Relapsed or refractory mantle cell lymphoma	Imbruvica	Ibrutinib	Janssen Pharma	2016	BTK
CCR4-positive adult T-cell leukemia-lymphoma Relapsed or refractory CCR4-positive peripheral T-cell lymphoma Relapsed or refractory cutaneous T-cell lymphoma	Poteligeo	Mogamulizumab	Kyowa Hakko Kirin	2012	CCR4
Untreated CD30-positive Hodgkin lymphoma Relapsed or refractory CD30-positive Hodgkin lymphoma and anaplastic large cell lymphoma	Adcetris	Brentuximab vedotin	Takeda Pharmaceutical	2014	CD30 (ADC)
Relapsed or refractory classical Hodgkin lymphoma	Opdivo	Nivolumab	Ono Pharmaceutical/ Bristol-Myers Squibb	2016 (Additional indication)	PD-1
Relapsed or refractory CD20-positive chronic lymphatic leukemia	Arzerra	Ofatumumab	Novartis Pharma	2013	CD20
Relapsed or refractory chronic lymphatic leukemia	MabCampath	Alemtuzumab	Sanofi	2015	CD52

Prepared using Therapeutic Manual of Malignant Lymphoma Revised Version 4, Nankodo, p95-113, 2015 and package inserts of each product

GAZYVA obtained approval on July 2, 2018

Indications

CD20-positive follicular lymphoma

<Precautions related to Indications>

GAZYVA should be used in patients who test positive for CD20 antigen using flow cytometry or another method.

Dosage and administration

The usual adult dose is 1000 mg obinutuzumab (recombinant) administered by intravenous infusion. In induction treatment, using the cycle durations and number of cycles shown as follows, GAZYVA is administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycle 2 and beyond. In maintenance treatment, GAZYVA is administered as monotherapy once every 2 months, continuing treatment for up to 2 years.

- If administering with cyclophosphamide hydrate, doxorubicin hydrochloride, vincristine sulfate, and prednisolone or methylprednisolone

  Eight 3-week cycles

- If administering with cyclophosphamide hydrate, vincristine sulfate, and prednisolone or methylprednisolone

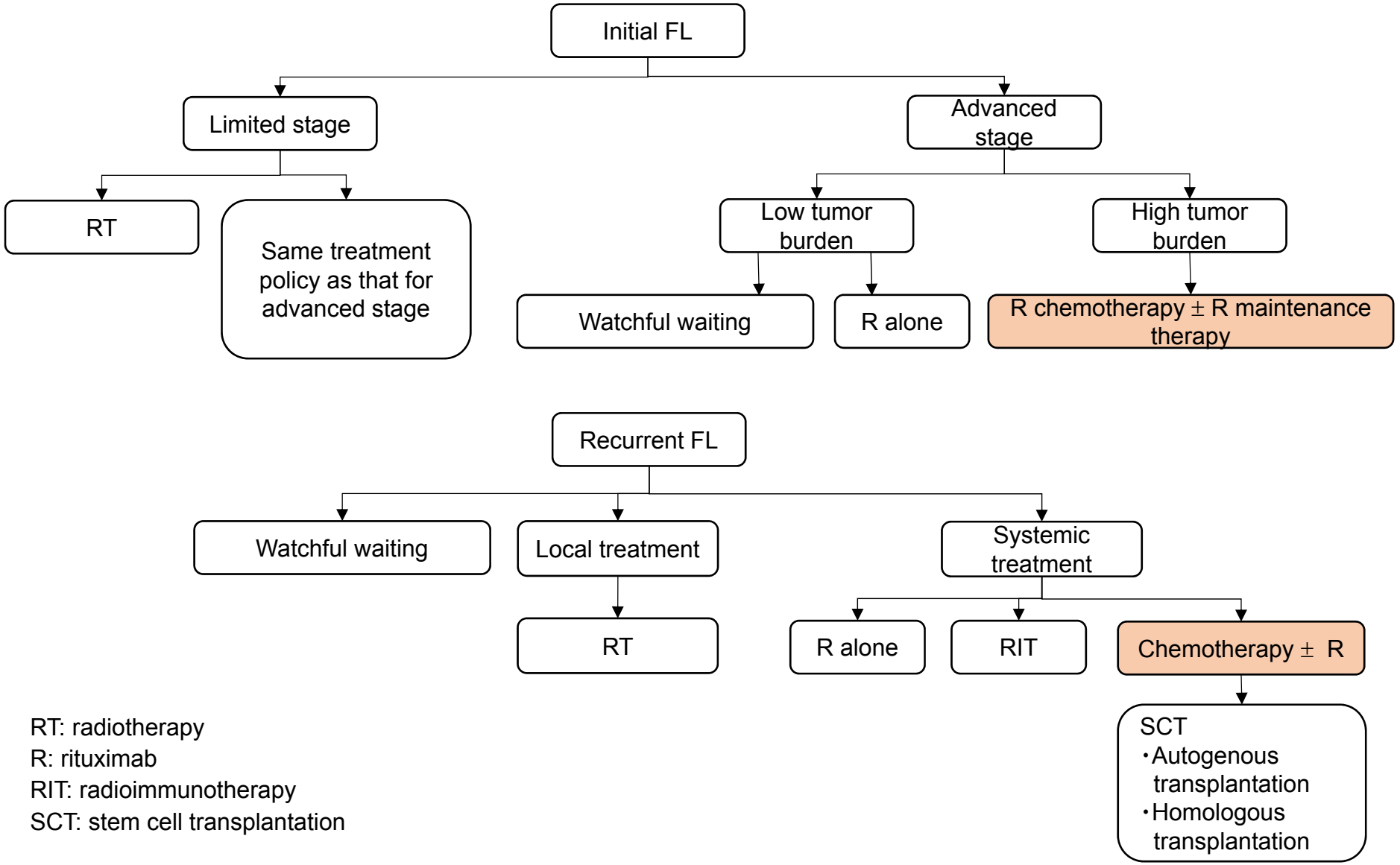
  Eight 3-week cycles

- If administering with bendamustine hydrochloride

  Six 4-week cycles

GAZYVA package insert (ver 3)

Treatment algorithm of follicular lymphoma



RT: radiotherapy
R: rituximab
RIT: radioimmunotherapy
SCT: stem cell transplantation

The 2018 Clinical Practice Guidelines of Hematopoietic Tumor, Kanehara & Co., LTD., p181

Global phase III study
(BO21223 [The GALLIUM study])
Overseas data including those from Japanese patients[1, 2)]

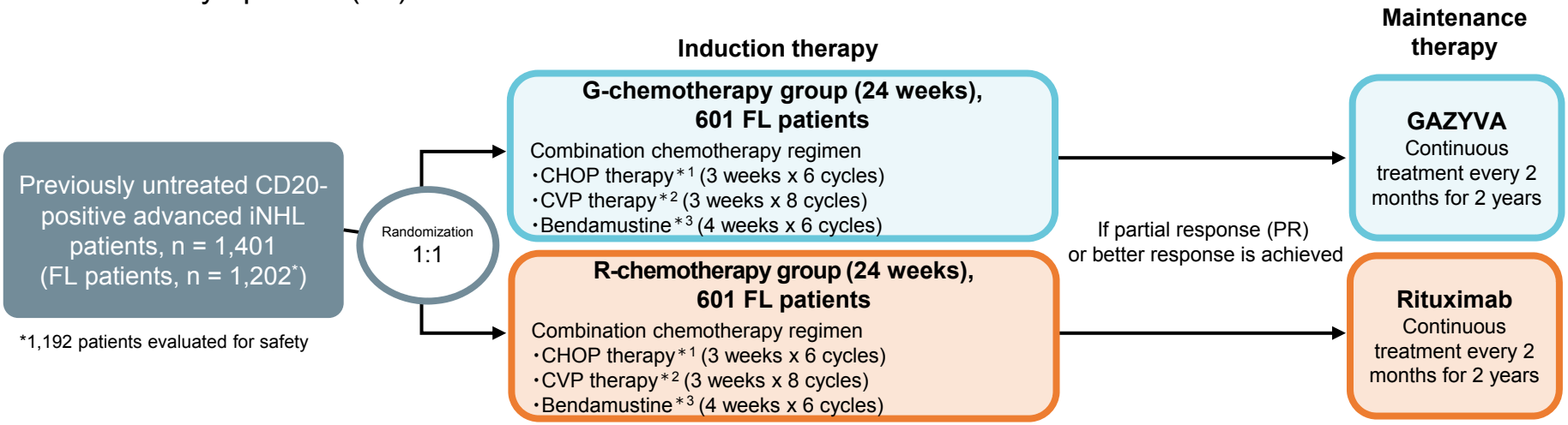
- Multicenter, randomized, open-label study

1) Evaluation dossier for GAZYVA approval: Global phase III study (BO21223)
2) Marcus R, et al.: N Engl J Med 377: 1331 (2017) (Evaluation dossier for GAZYVA approval)

GAZYVA has been approved based on clinical results from Japanese Phase I and II studies as well as overseas Phase III studies and global Phase III studies including Japanese subjects. They therefore contain some results that are different from those approved in Japan.

Study design (1)

[Objective] To evaluate the efficacy of GAZYVA + chemotherapy (G-chemotherapy) followed by GAZYVA maintenance therapy as compared with rituximab + chemotherapy (R-chemotherapy) followed by rituximab maintenance therapy in patients with previously untreated advanced follicular lymphoma (FL).



- G-chemotherapy group: GAZYVA 1,000 mg was administered on Day 1 of each cycle and Days 8 and 15 only for Cycle 1 every 3 weeks when administered in combination with CHOP or CVP therapy and every 4 weeks when administered in combination with bendamustine. During the induction therapy period, the number of cycles was 8 when administered every 3 weeks and 6 when administered every 4 weeks.
- R-chemotherapy group: Rituximab 375 mg/m^2 mg was administered on Day 1 of each cycle every 3 weeks when administered in combination with CHOP or CVP therapy and every 4 weeks when administered in combination with bendamustine. During the induction therapy period, the number of cycles was 8 when administered every 3 weeks and 6 when administered every 4 weeks.

* 1 Cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 and vincristine 1.4 mg/m^2 (2 mg at a maximum) were administered on Day 1 of each cycle, and prednisone (not approved in Japan)/prednisolone 100 mg or methylprednisolone 80 mg was administered on Days 1 to 5 of each cycle.
* 2 Cyclophosphamide 750 mg/m^2 and vincristine 1.4 mg/m^2 (2 mg at a maximum) were administered on Day 1 of each cycle, and prednisone (not approved in Japan)/prednisolone 100 mg or methylprednisolone 80 mg was administered on Days 1 to 5 of each cycle.
* 3 Bendamustine 90 mg/m^2 was administered on Days 1 and 2 of each cycle.

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Study design (2)

[Endpoints]

Primary endpoint: Progression-free survival (PFS) in FL patients (investigator-assessed)

Secondary endpoints: PFS (independent review committee-[IRC] assessed), overall survival (OS) in FL patients, complete response (CR) rate and overall response rate (ORR) (investigator-assessed and IRC-assessed) at end of induction (EOI) in FL patients, safety, etc.

For their evaluations, the patients were followed up after the end of treatment whether or not maintenance therapy was administered, and image assessments were carried out.

[Analysis plan]

<Statistical analysis of the primary endpoint>

- For PFS (investigator-assessed), the superiority of the G-chemotherapy group to the R-chemotherapy group was to be demonstrated using the stratified log-rank test with combination chemotherapy regimens (CHOP therapy, CVP therapy and bendamustine) and risk groups based on the FLIPI* (low, intermediate and high risks) as stratification factors (significance level in the 3rd interim analysis = 0.012).
- PFS rate and period in the two groups were estimated using the Kaplan-Meier method, and treatment response was estimated using stratified hazard ratios calculated in a stratified Cox proportional hazard analysis (including 95% confidence interval [CI]).

<Subgroup analyses>

- The analyses of the primary endpoint (PFS in Japanese FL patients [investigator-assessed]) and secondary endpoints in 123 Japanese FL patients who received at least one dose of the investigational drug were planned beforehand.
- Post hoc analyses of PFS were performed by background characteristic of the FL patients and by stratification factor.

* FLIPI: follicular lymphoma international prognostic index

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Baseline characteristics (patients with follicular lymphoma) (1)

		GAZ + Chemo (n=601)	RIT + Chemo (n=601)
Median age, years (range)		60.0 (26-88)	58.0 (23-85)
Sex	Male	283 (47.1%)	280 (46.6%)
ECOG PS	0-1	585 (97.5%)	576 (96.2%)
	2	15 (2.5%)	23 (3.8%)
Stage (Ann Arbor Staging)	I	10 (1.7%)	8 (1.3%)
	II	41 (6.9%)	44 (7.4%)
	III	208 (34.8%)	209 (35.0%)
	IV	339 (56.7%)	336 (56.3%)
FLIPI	Low (0, 1)	128 (21.3%)	125 (20.8%)
	Intermediate (2)	224 (37.3%)	223 (37.1%)
	High (≥ 3)	249 (41.4%)	253 (42.1%)
FLIPI 2	Low (0)	51 (8.8%)	55 (9.4%)
	Intermediate (1-2)	296 (51.1%)	290 (49.5%)
	High (≥ 3)	232 (40.1%)	241 (41.1%)

Stratification factors: combination chemotherapy regimens, FLIPI risk groups or IPI risk groups of patients with non-follicular lymphoma, and regions

FLIPI: Follicular Lymphoma International Prognostic Index

Patients with unknown data were excluded from the tabulation of each item.

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Baseline characteristics (patients with follicular lymphoma) (2)

		GAZ + Chemo (n=601)	RIT + Chemo (n=601)
Bone-marrow invasion	Yes	318 (53.7%)	295 (49.3%)
Extranodal involvement	Yes	392 (65.2%)	396 (65.9%)
Bulky disease (> 7 cm)	Yes	255 (42.5%)	271 (45.2%)
B symptoms	Yes	201 (33.4%)	206 (34.3%)
Combination chemotherapy regimen	CHOP	195 (32.4%)	203 (33.8%)
	CVP	61 (10.1%)	57 (9.5%)
	Bendamustine	345 (57.4%)	341 (56.7%)

Stratification factors: combination chemotherapy regimens, FLIPI risk groups or IPI risk groups of patients with non-follicular lymphoma, and regions

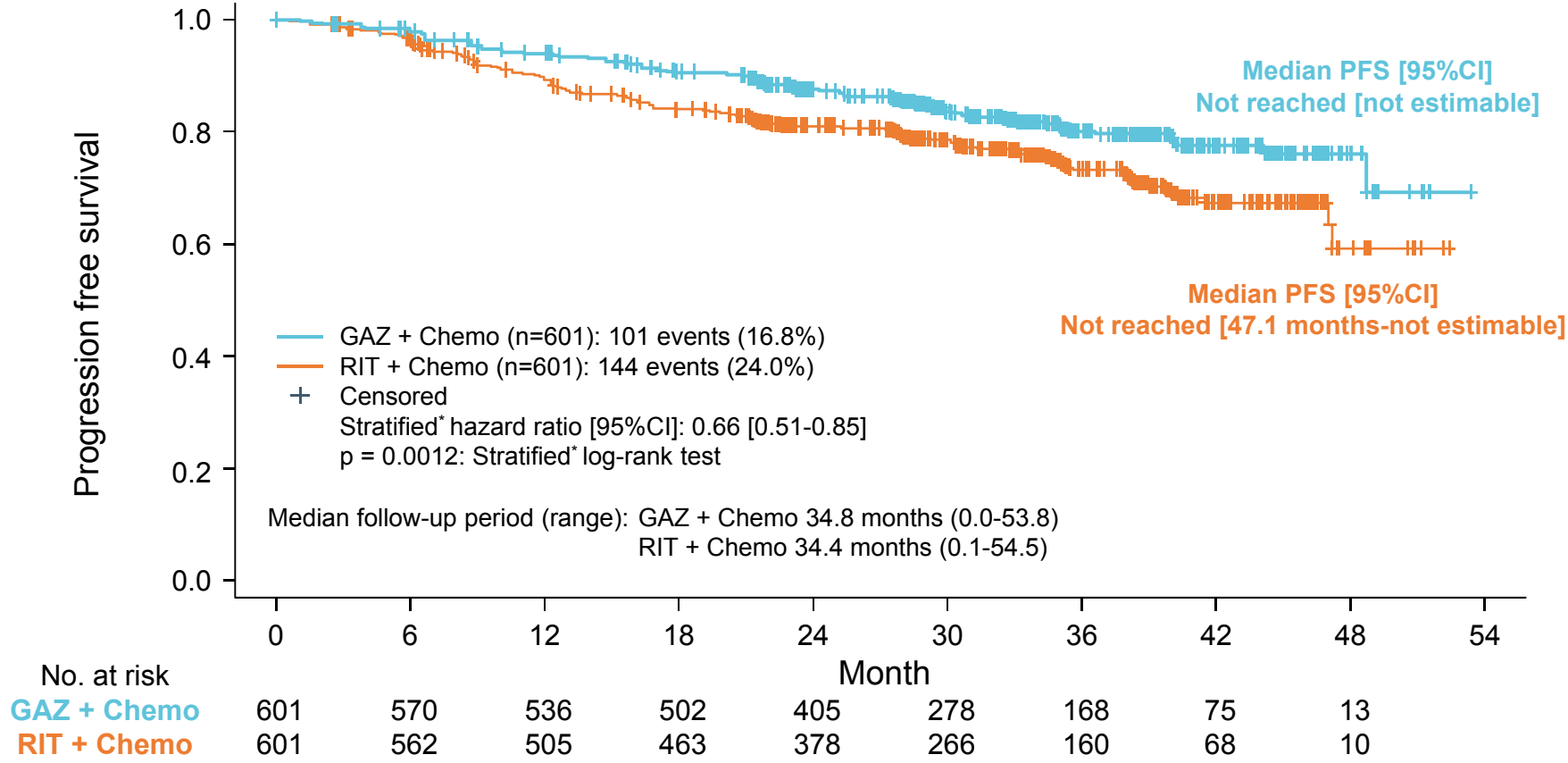
Patients with unknown data were excluded from the tabulation of each item.

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

GALLIUM

Primary endpoint

Progression free survival in patients with follicular lymphoma (assessed by investigator)



* Stratification factors: combination chemotherapy regimens (CHOP, CVP and bendamustine), and FLIPI risk groups (low risk, intermediate risk and high risk)

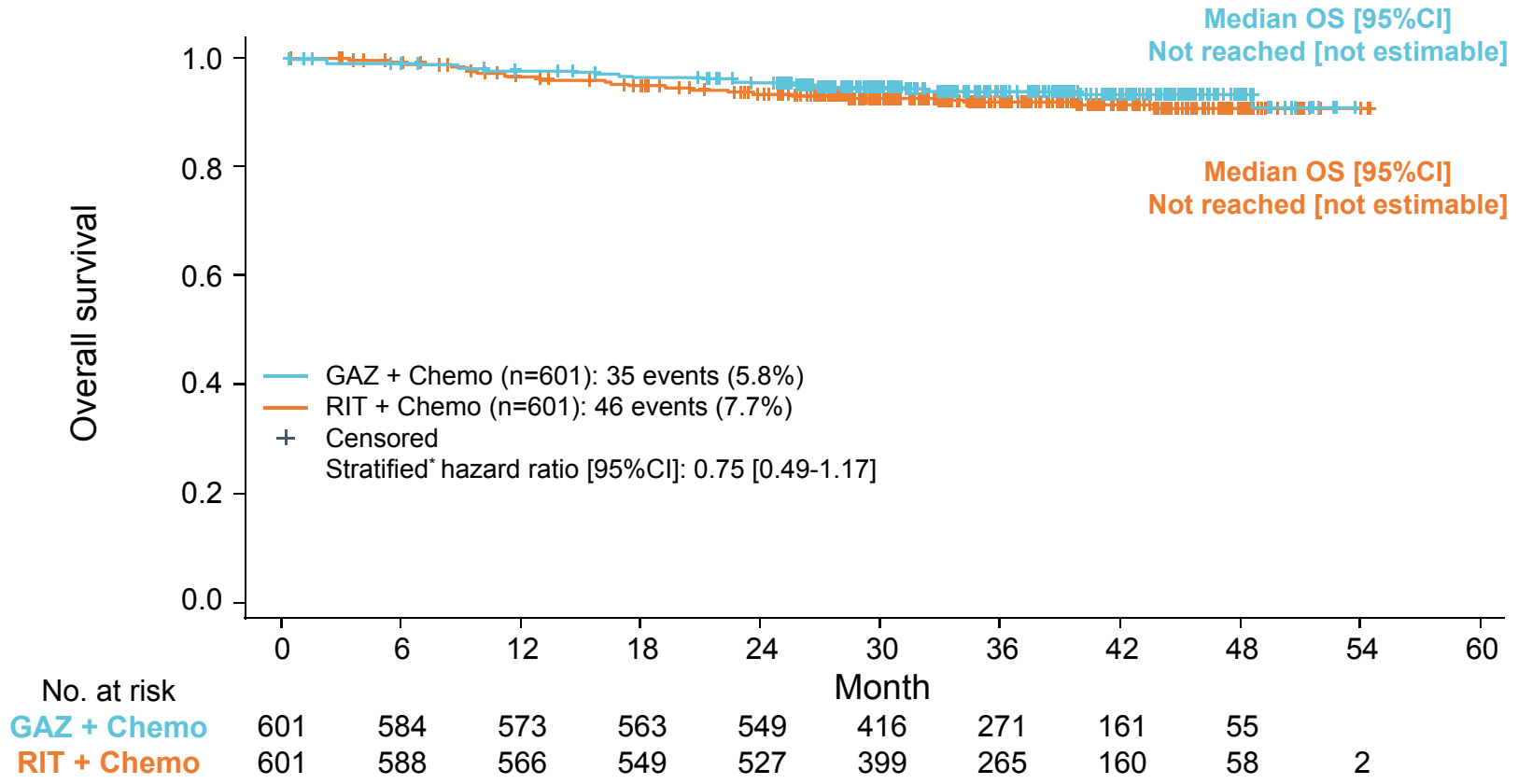
Data cut off: January 31, 2016

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

GALLIUM

Secondary endpoint

Overall survival in patients with follicular lymphoma

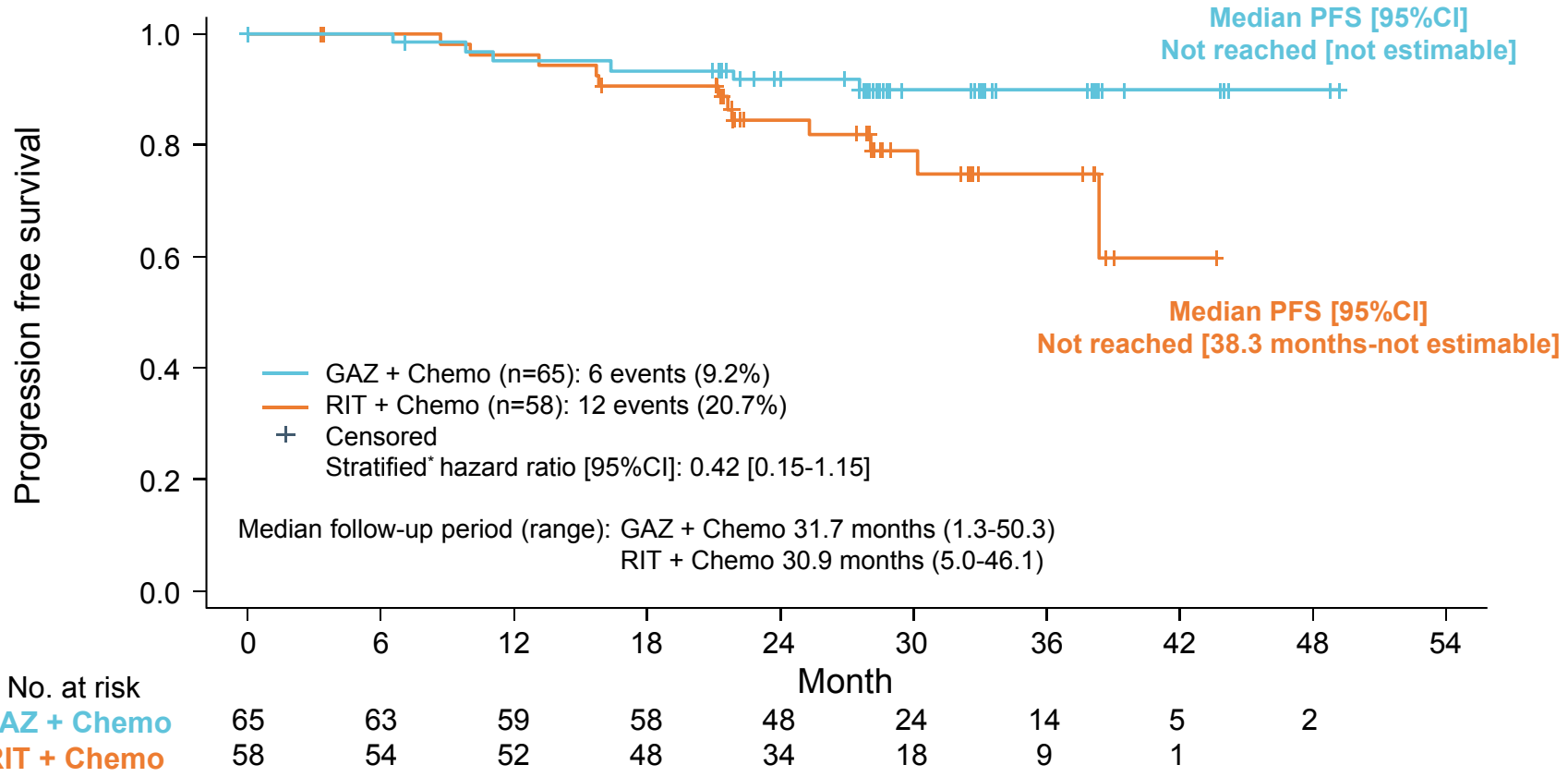


* Stratification factors: combination chemotherapy regimens (CHOP, CVP and bendamustine), and FLIPI risk groups (low risk, intermediate risk and high risk)

Data cut off: January 31, 2016

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Progression free survival in Japanese patients with follicular lymphoma (assessed by investigator)



* Stratification factors, combination chemotherapy regimens (CHOP, CVP and bendamustine) and FLIPI risk groups (low risk, intermediate risk and high risk)

Data cut off: January 31, 2016

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Safety (patients with follicular lymphoma) (1)

- **Summary of safety profiles**

	GAZ + Chemo (n=595)	R + Chemo (n=597)
Number of patients	592 (99.5%)	587 (98.3%)
Grade ≥3 AEs*1	444 (74.6%)	405 (67.8%)
Serious AEs*2	274 (46.1%)	238 (39.9%)
AEs leading to discontinuation of any investigational drug*3	97 (16.3%)	85 (14.2%)
AEs leading to death	24 (4.0%)	20 (3.4%)

*1 The grade was according to the NCI-CTCAE v4.0.

*2 Serious adverse events were defined as an event that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect in newborns or infants born from mothers exposed to the investigational drug, and is determined by a primary physician to be a medically important event.

*3 Gazyva, rituximab or any chemotherapy

Data cut off: January 31, 2016

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Safety (patients with follicular lymphoma) (2)

- **Summary of safety profiles (More than 20% in either arm)**

	GAZ + Chemo (n=595)	R + Chemo (n=597)
Number of patients	592 (99.5%)	587 (98.3%)
Infusion reaction	351 (59.0%)	292 (48.9%)
Neutropenia	289 (48.6%)	260 (43.6%)
Nausea	279 (46.9%)	278 (46.6%)
Fatigue	214 (36.0%)	218 (36.5%)
Constipation	210 (35.3%)	188 (31.5%)
Fever	164 (27.6%)	127 (21.3%)
Diarrhea	160 (26.9%)	131 (21.9%)
Cough	152 (25.5%)	144 (24.1%)
Vomiting	139 (23.4%)	122 (20.4%)
Headache	122 (20.5%)	101 (16.9%)

The terms used in the aggregation were according to the MedDRA v18.1.

Data cut off: January 31, 2016

The approved indication effect of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Global phase III study
(GAO4753g [The GADOLIN study])
Overseas Clinical Study Results[1, 2)]

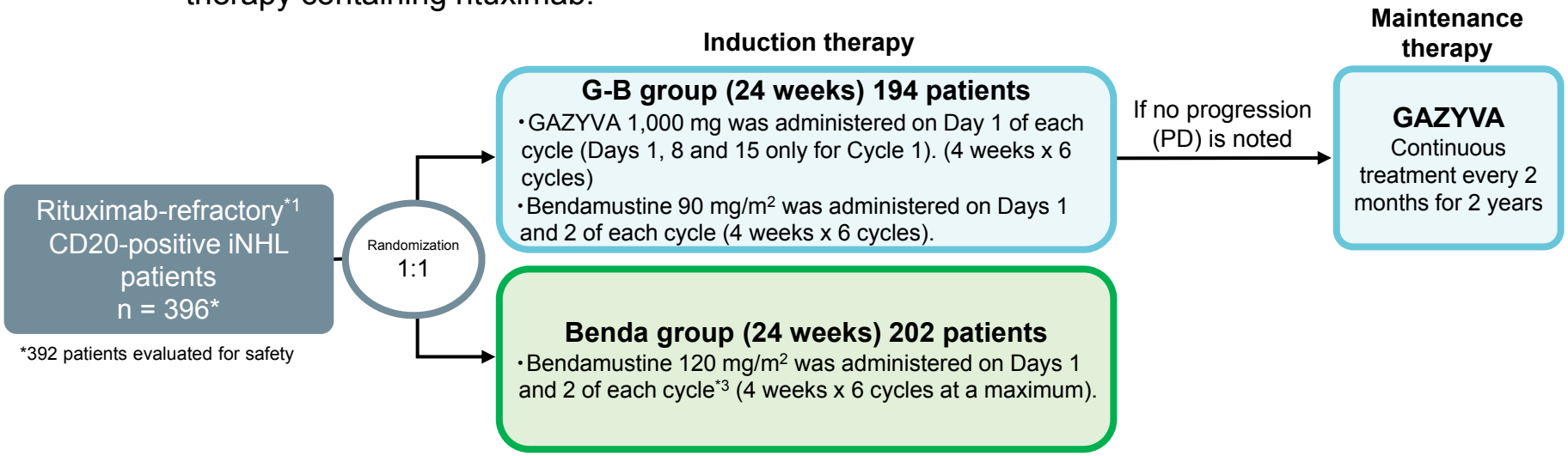
- Multicenter, randomized, open-label study

1) Evaluation dossier for GAZYVA approval: Global phase III study (GAO4753g)
2) Sehn LH, et al.: Lancet Oncol 17: 1081 (2016) (Evaluation dossier for GAZYVA approval)

GAZYVA has been approved based on clinical results from Japanese Phase I and II studies as well as overseas Phase III studies and global Phase III studies including Japanese subjects. They therefore contain some results that are different from those approved in Japan.

Study design (1)

[Objective] To compare the clinical usefulness of GAZYVA in combination with bendamustine vs. bendamustine alone in patients with indolent non-Hodgkin lymphoma (iNHL) resistant to previous therapy containing rituximab.



*1 In this study, rituximab-refractory was defined as not responding to recent treatment containing rituximab or progression within 6 months after the completion of treatment and meeting any of the following 3 criteria.
If not only the most recent previous treatment but also any previous treatment in the past met the criteria, it was to be handled as rituximab-refractory:
- PD was determined during treatment after administration of at least 1 cycle of rituximab monotherapy or rituximab + chemotherapy or during rituximab maintenance therapy (after administration of at least one dose or a total dose of 375 mg/m^2).
- Clinical response (partial response [PR] or better) was not achieved after at least 4 doses of rituximab alone once weekly or at least 4 cycles of rituximab + chemotherapy.
- The disease relapsed within 6 months after at least 4 doses of rituximab alone once weekly or at least 4 cycles of rituximab + chemotherapy.

*2 It was administered on Days 2 and 3 of Cycle 1 in the first 10 enrolled patients for performing pharmacokinetic tests.

*3 Approved dosage and administration of bendamustine monotherapy in Japan: The usual adult dosage is 120 mg/m^2 (body surface area) of bendamustine hydrochloride administered as an intravenous infusion over one hour once daily. The drug should be administered for 2 consecutive days followed by wash-out of 19 days. This is defined as one cycle, and treatment should be repeated. The dose should be reduced as necessary according to the patient's condition.

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Study design (2)

[Endpoints]

Primary endpoint: Progression-free survival (PFS) in iNHL patients (independent review committee [IRC]-assessed)

Secondary endpoints: Overall survival (OS) in iNHL patients, complete response (CR) rate and overall response rate (ORR) (IRC-assessed and investigator-assessed) at end of induction (EOI) in iNHL patients, safety, etc.

For their evaluations, the patients were followed up after the end of treatment whether or not maintenance therapy was administered, and image assessments were carried out.

[Analysis plan]

<Statistical analysis of the primary endpoint>

- For PFS (IRC-assessed), the superiority of the G-B group to the Benda group was to be demonstrated using the stratified log-rank test with iNHL subtypes (FL and other), treatment-refractory types (rituximab monotherapy and rituximab + chemotherapy) and the number of previous treatment regimens (≤ 2 and ≥ 3) as stratification factors (significance level in the 3rd interim analysis = 0.015).
- Median PFS and 95% confidence interval (CI) were estimated using the Kaplan-Meier method.

<Subgroup analyses>

- The analyses of the primary endpoint and secondary endpoints (PFS in FL patients [IRC-assessed], OS in FL patients, and CR rate and ORR [IRC-assessed and investigator-assessed] at EOI in FL patients) in 321 FL patients who received at least one dose of the investigational drug were planned beforehand.

* IRC: independent review committee

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Baseline characteristics (patients with indolent non-Hodgkin lymphoma)

		G-B group (n=194)	Benda group (n=202)
Median age, years (range)		63.0 (34-87)	63.0 (21-87)
Gender	Male	110 (56.7%)	118 (58.4%)
Disease type	MALT lymphoma	13 (6.7%)	13 (6.4%)
	Follicular lymphoma	155 (79.9%)	166 (82.2%)
	Nodal marginal zone lymphoma	11 (5.7%)	5 (2.5%)
	Small lymphocytic lymphoma	12 (6.2%)	16 (7.9%)
	Splenic marginal zone lymphoma	3 (1.5%)	1 (0.5%)
	Other	0	1 (0.5%)
ECOG PS	0-1	185 (95.4%)	190 (95.5%)
	2	9 (4.6%)	9 (4.5%)
Stage (Ann Arbor Staging)	I	10 (5.2%)	12 (6.0%)
	II	16 (8.2%)	19 (9.5%)
	III	38 (19.6%)	53 (26.4%)
	IV	117 (60.3%)	106 (52.7%)
	Unknown	13 (6.7%)	11 (5.5%)
IPI	Low	11 (28.9%)	9 (25.0%)
	Low-Intermediate	6 (15.8%)	6 (16.7%)
	High-Intermediate	9 (23.7%)	6 (16.7%)
	High	1 (2.6%)	1 (2.8%)
	Unknown	11 (28.9%)	14 (38.9%)

		G-B group (n=194)	Benda group (n=202)
Bone-marrow invasion	Yes	60 (32.1%)	69 (36.7%)
Extranodal involvement	Yes	107 (55.2%)	98 (48.8%)
Bulky disease (> 6 cm)	Yes	66 (34.0%)	70 (35.2%)
Serum LDH level	Normal	128 (67.0%)	137 (68.8%)
	High	63 (33.0%)	62 (31.2%)
No. of previous treatment regimens	1	92 (47.4%)	84 (41.6%)
	2	62 (32.0%)	74 (36.6%)
	>3	40 (20.6%)	44 (21.8%)
	Median (range)	2 (1-10)	2 (1-7)
Treatment-refractory type	Rituximab monotherapy	38 (19.6%)	45 (22.3%)
	Rituximab + chemotherapy	156 (80.4%)	157 (77.7%)

Stratification factors: iNHL subtypes, treatment-refractory types, No. of previous treatment regimens, and regions

IPI:International Prognostic Index

Patients with unknown data were excluded from the tabulation of each item.

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Baseline characteristics (Patients with follicular lymphoma)

		G-B group (n=155)	Benda group (n=166)
Median age, years (range)		63.0 (34-87)	63.5 (35-87)
Gender	Male	85 (54.8%)	95 (57.2%)
ECOG PS	0-1	147 (94.8%)	157 (95.7%)
	2	8 (5.2%)	7 (4.3%)
Stage (Ann Arbor Staging)	I	9 (5.8%)	9 (5.5%)
	II	15 (9.7%)	19 (11.5%)
	III	31 (20.0%)	45 (27.3%)
	IV	90 (58.1%)	82 (49.7%)
	Unknown	10 (6.5%)	10 (6.1%)
FLIPI	Low (0, 1)	42 (27.1%)	34 (20.6%)
	Intermediate (2)	47 (30.3%)	58 (35.2%)
	High (≥ 3)	60 (38.7%)	67 (40.6%)
	Unknown	6 (3.9%)	6 (3.6%)
FLIPI 2	Low (0)	8 (5.2%)	10 (6.1%)
	Intermediate (1-2)	81 (52.3%)	82 (49.7%)
	High (≥ 3)	60 (38.7%)	67 (40.6%)
	Unknown	6 (3.9%)	6 (3.6%)

		G-B group (n=155)	Benda group (n=166)
Bone-marrow invasion	Yes	42 (28.0%)	50 (32.3%)
Extranodal involvement	Yes	82 (52.9%)	76 (46.1%)
Bulky disease (> 6 cm)	Yes	49 (31.6%)	58 (35.4%)
Serum LDH level	Normal	101 (65.6%)	108 (65.9%)
	High	53 (34.4%)	56 (34.1%)
No. of previous treatment regimens	1	76 (49.0%)	72 (43.4%)
	2	49 (31.6%)	58 (34.9%)
	>3	30 (19.4%)	36 (21.7%)
	Median (range)	2 (1-10)	2 (1-7)
Treatment-refractory type	Rituximab monotherapy	25 (16.1%)	39 (23.5%)
	Rituximab + chemotherapy	130 (83.9%)	127 (76.5%)

Stratification factors: iNHL subtypes, treatment-refractory types, No. of previous treatment regimens, and regions

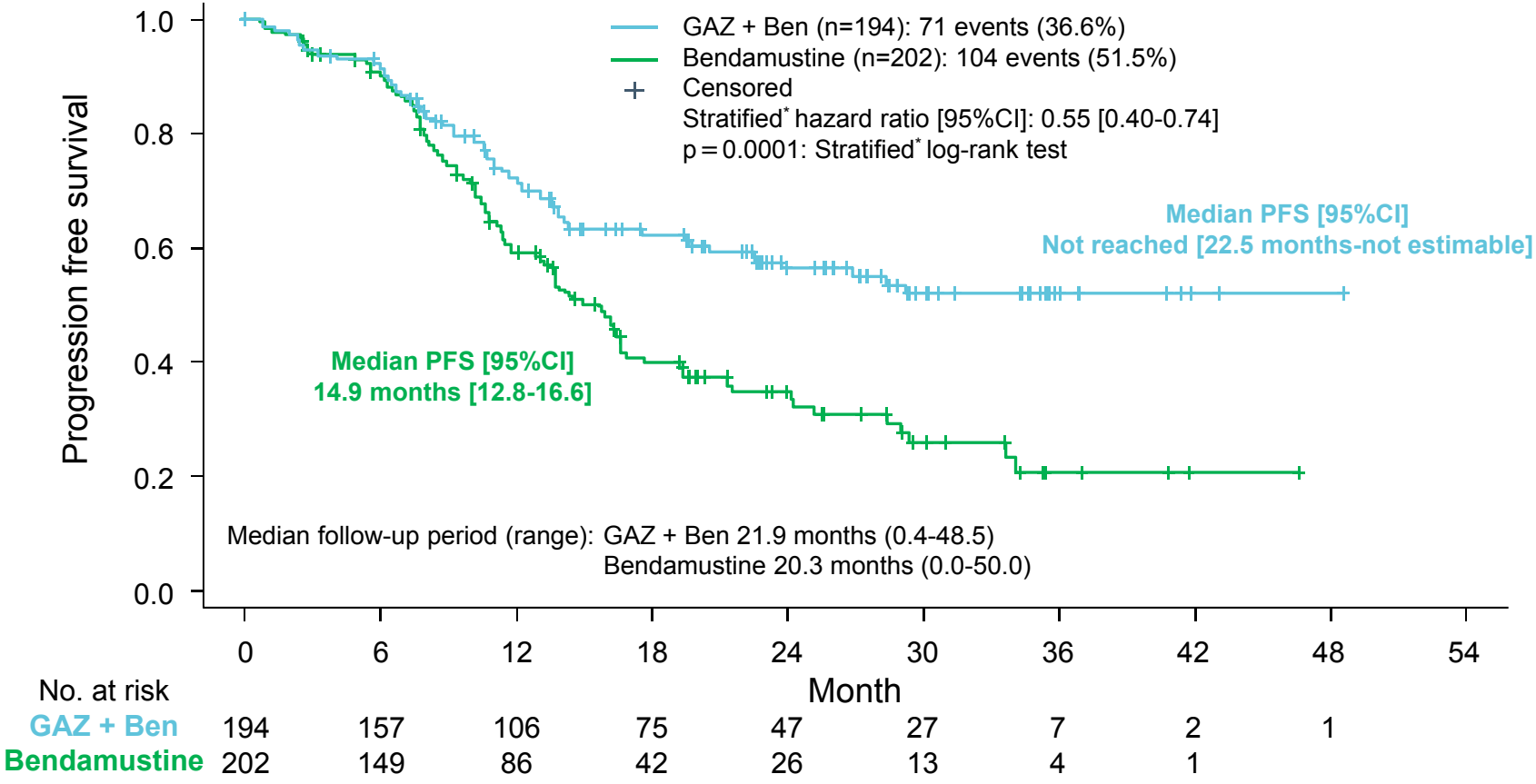
FLIPI: Follicular Lymphoma International Prognostic Index

Patients with unknown data were excluded from the tabulation of each item.

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Primary endpoint

Progression free survival in patients with indolent non-Hodgkin lymphoma (assessed by independent review committee)

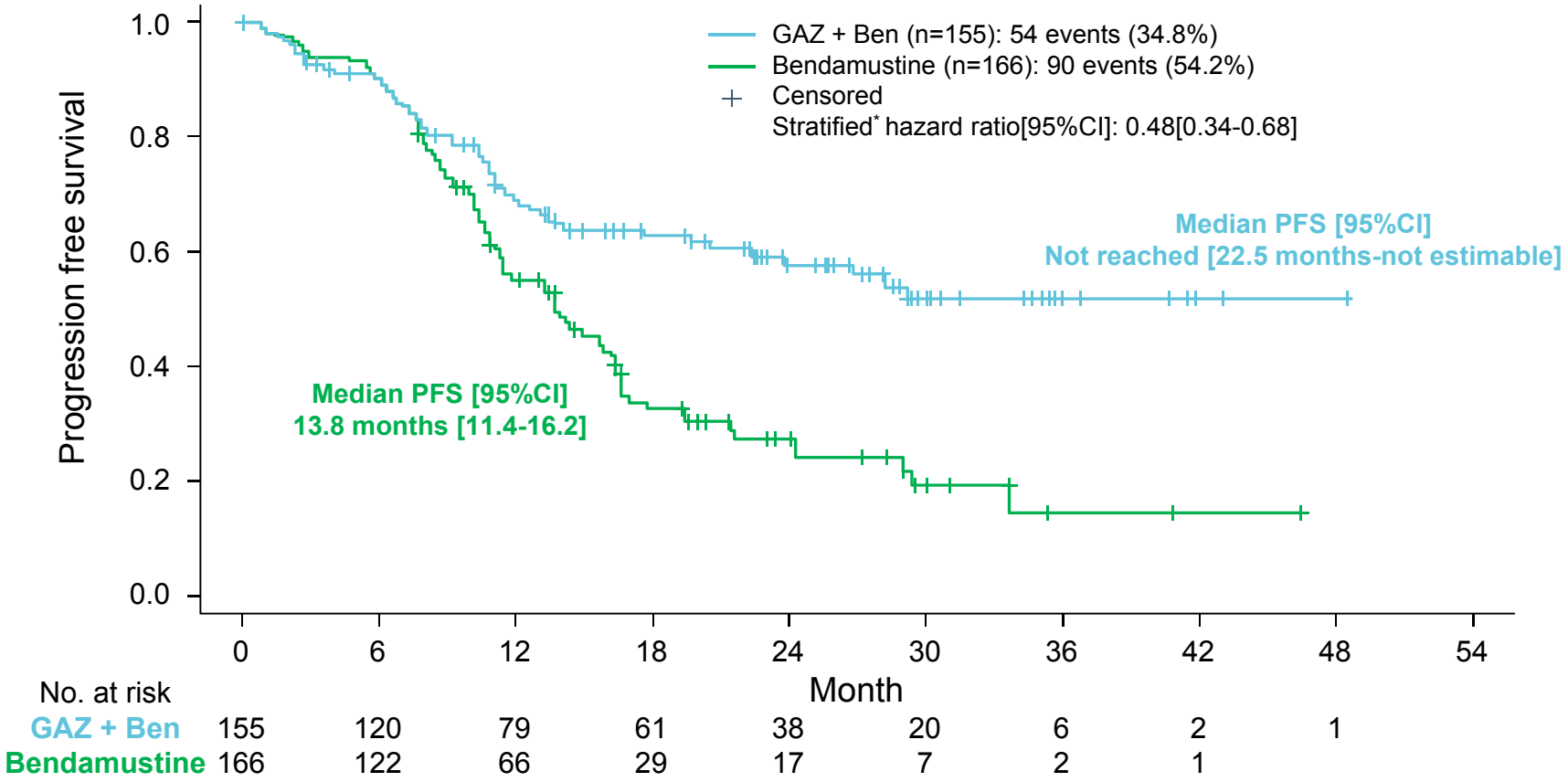


*Stratification factors: iNHL subtypes (FL and other), treatment-refractory types (rituximab monotherapy and rituximab + chemotherapy), and No. of previous treatment regimens (≤ 2 and ≥ 3)

Data cut off: September 1, 2014

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Progression free survival in patients with follicular lymphoma (assessed by independent review committee)



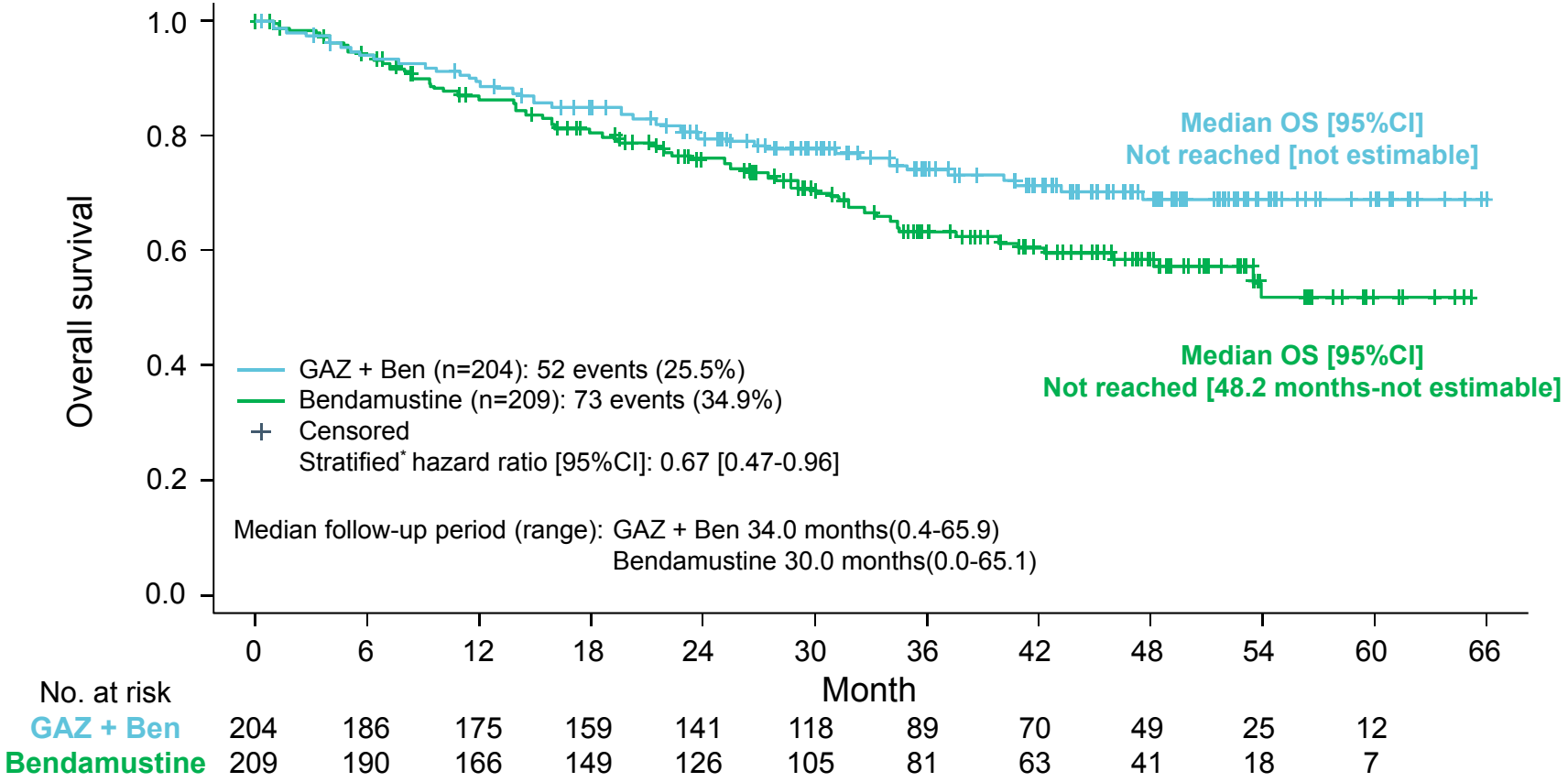
* Stratification factors: treatment-refractory types (rituximab monotherapy and rituximab + chemotherapy), and No. of previous treatment regimens (≤ 2 and ≥ 3)

Data cut off: September 1, 2014

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Secondary endpoint

Overall survival in patients with indolent non-Hodgkin lymphoma

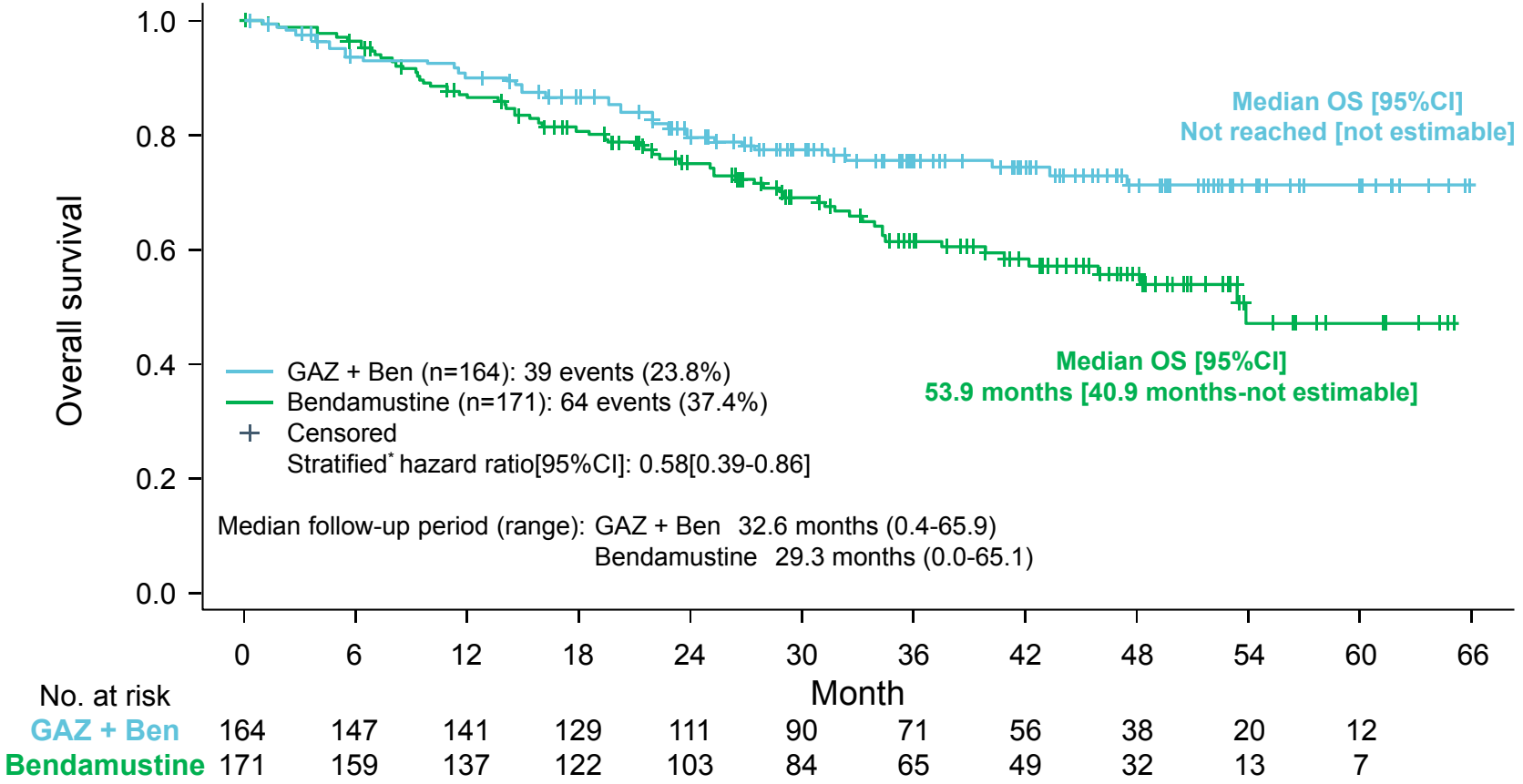


* Stratification factors: iNHL subtypes (FL and other), treatment-refractory types (rituximab monotherapy and rituximab + chemotherapy) , and No. of previous treatment regimens (≤ 2 and ≥ 3)

Data cut off: September 1, 2014

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Overall survival in patients with follicular lymphoma



*Stratification factors: treatment-refractory types (rituximab monotherapy and rituximab + chemotherapy), and No. of previous treatment regimens (≤ 2 and ≥ 3)

Data cut off: September 1, 2014

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Safety (1)

Summary of safety profiles

	indolent non-Hodgkin lymphoma		follicular lymphoma	
	GAZ + Ben (n=194)	Bendamustine (n=198)	GAZ + Ben (n=155)	Bendamustine (n=163)
Number of patients	191 (98.5%)	194 (98.0%)	154 (99.4%)	159 (97.5%)
Grade ≥3 AEs*1	132 (68.0%)	123 (62.1%)	102 (65.8%)	96 (58.9%)
Serious AEs*2	74 (38.1%)	65 (32.8%)	54 (34.8%)	52 (31.9%)
AEs leading to discontinuation of any investigational drug*3	35 (18.0%)	31 (15.7%)	25 (16.1%)	27 (16.6%)
AEs leading to death	12 (6.2%)	12 (6.1%)	8 (5.2%)	10 (6.1%)

*1 The grade was according to the NCI-CTCAE v4.0.

*2 Serious adverse events were defined as an event that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect in newborns or infants born from mothers exposed to the investigational drug, and is determined by a primary physician to be a medically important event.

*3 GAZYVA or bendamustine

Data cut off: September 1, 2014

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Safety (2)

- **Summary of safety profiles (More than 20% in either arm)**

	indolent non-Hodgkin lymphoma		follicular lymphoma	
	GAZ + Ben (n=194)	Bendamustine (n=198)	GAZ + Ben (n=155)	Bendamustine (n=163)
Number of patients	191 (98.5%)	194 (98.0%)	154 (99.4%)	159 (97.5%)
Infusion reaction	125 (64.4%)	115 (58.1%)	103 (66.5%)	99 (60.7%)
Nausea	104 (53.6%)	121 (61.1%)	82 (52.9%)	102 (62.6%)
Fatigue	76 (39.2%)	66 (33.3%)	62 (40.0%)	58 (35.6%)
Neutropenia	68 (35.1%)	57 (28.8%)	53 (34.2%)	41 (25.2%)
Fever	54 (27.8%)	36 (18.2%)	40 (25.8%)	31 (19.0%)
Cough	54 (27.8%)	34 (17.2%)	42 (27.1%)	31 (19.0%)
Diarrhea	53 (27.3%)	60 (30.3%)	41 (26.5%)	47 (28.8%)
Vomiting	43 (22.2%)	54 (27.3%)	33 (21.3%)	47 (28.8%)
Constipation	41 (21.1%)	38 (19.2%)	30 (19.4%)	34 (20.9%)
Thrombocytopenia	29 (14.9%)	47 (23.7%)	24 (15.5%)	37 (22.7%)

The terms used in the aggregation were according to the MedDRA v17.1.

Data cut off: September 1, 2014

The approved indication of GAZYVA is CD20-positive follicular lymphoma. (as of July, 2018)

Safety (3)

- **Summary of safety profiles* (More than 2% in any arm of iNHL patients)**

	indolent non-Hodgkin lymphoma		follicular lymphoma	
	GAZ + Ben (n=194)	Bendamustine (n=198)	GAZ + Ben (n=155)	Bendamustine (n=163)
Number of patients	74 (38.1%)	65 (32.8%)	54 (34.8%)	52 (31.9%)
Febrile neutropenia	8 (4.1%)	6 (3.0%)	6 (3.9%)	4 (2.5%)
Sepsis	6 (3.1%)	7 (3.5%)	4 (2.6%)	5 (3.1%)
Neutropenia	6 (3.1%)	1 (0.5%)	6 (3.9%)	0
Infusion reaction	6 (3.1%)	3 (1.5%)	5 (3.2%)	2 (1.2%)
Pneumonia	5 (2.6%)	10 (5.1%)	3 (1.9%)	7 (4.3%)
Fever	5 (2.6%)	3 (1.5%)	2 (1.3%)	2 (1.2%)
Thrombocytopenia	4 (2.1%)	0	3 (1.9%)	0
Diarrhea	0	4 (2.0%)	0	3 (1.8%)

The terms used in the aggregation were according to the MedDRA v17.1.

* Serious adverse events were defined as an event that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect in newborns or infants born from mothers exposed to the investigational drug, and is determined by a primary physician to be a medically important event.

Data cut off: September 1, 2014

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Conclusions

- **GALLIUM Study results showed the prolongation of PFS with a statistically significant difference for GAZYVA plus chemotherapy compared with R-Chemo, the standard therapy for patients with initial FL[1)].**

- **GADOLIN Study results revealed that GAZYVA plus bendamustine therapy significantly prolonged PFS compared with bendamustine monotherapy, a representative treatment for rituximab-refractory iNHL[2)].**

- **In terms of safety, G-Chemo frequently causes infusion reactions and infections compared with R-Chemo; thus, attention should be paid to the management of these adverse reactions[1), 2)].**

1) Marcus R, et al.: N Engl J Med 377: 1331 (2017)
2) Sehn LH, et al.: Lancet Oncol 17: 1081 (2016)

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