Comparative effectiveness study of chemotherapy in follicular lymphoma patients in the rituximab era: a Japanese claims database study

Saaya Tsutsué^{*,1} , Kensei Tobinai², Jingbo Yi³ & Bruce Crawford³

¹ Celgene K.K., a Bristol Myers Squibb Company, JP Tower, 2-7-2 Marunouchi Chiyoda-ku, Tokyo 100-7010, Japan

² National Cancer Center Hospital, Tokyo, Japan

³ Syneos Health, Tokyo, Japan

*Author for correspondence: Tel.: +81 352 240 547; saaya.tsutsue@bms.com

Aim: To evaluate comparative effectiveness of rituximab (R)-based versus non-R-based therapies for follicular lymphoma patients in Japan, where limited studies have been reported. **Materials & methods:** Patients who received R-based index regimens were propensity score matched to those who did not receive R, based on patient baseline attributes and clinical characteristics using Japanese retrospective claims database to assess clinical and economic outcomes. **Results & conclusion:** A total of 1947 patients remained in the overall follicular lymphoma cohorts: 1294 receiving an R-based and 653 a non-R-based regimen. Patients on R-based therapy underwent fewer hospitalizations and had a shorter length of stay, but had higher costs during the first year of intensive R-based therapy. Improved clinical outcomes were associated with patients who were younger, female and chose R-based regimens in first index line.

First draft submitted: 14 August 2020; Accepted for publication: 22 September 2020; Published online: 6 October 2020

Keywords: comparative effectiveness • health economics • hematologic/lymphoma • pharmacoeconomics • real-world evidence

Follicular lymphoma (FL), which belongs to the subtype of non-Hodgkin lymphomas (NHL), accounts for approximately 20% of all lymphomas in the USA [1]. In Japan, FL is the second most common subtype of NHL, accounting for 13.5% of all NHL types, followed by diffuse large B-cell lymphoma [2,3]. In addition, FL is associated with approximately 30% lifetime risk of transforming to a more aggressive lymphoma, most commonly to diffuse large B-cell lymphoma [4,5].

The availability of rituximab (R) for FL patients in Japan since 2001 has substantially changed FL therapy, providing multiple treatment options for FL patients beyond ‘watch and wait’ and stem cell transplantation (SCT) [6]. Recommended treatment options for FL include R-based therapies (e.g., R plus bendamustine; R plus cyclophosphamide, doxorubicin, vincristine and prednisone; R plus cyclophosphamide, vincristine and prednisone or R-monotherapy). A recent clinical review [7] underscores the need to tailor treatment based on an individual patient’s disease state, risk status and genetic background for FL. There is no consensus for treatment of FL patients associated with multiplicity of relapse in course of disease progression. Therefore, the real-world evidence to clarify current treatment patterns, treatment-based economic and clinical outcomes on standard treatments is needed from comparative effectiveness perspective.

Five-year overall survival (OS) reported for FL patients in UK as 75.6% of Haematological Malignancy Research Network data, covering the period from 2007 to 2015 (n = 923 patients) [8]. In a database study of patients with FL from the USA (n = 1346) between 2008 and 2015, 2-year OS was reported as 86.9% after first-line (1L) treatment [9]. The economic burden of FL in the USA has been reported to be relatively high, with mean monthly costs per patient of US\$10,460 (USD) in total, including \$6482 of FL-related costs, based on a database study of 1595 patients who received 1L treatment for FL between 2008 and 2015 [10]. That study reported that over half of the patients (51.0%) had ≥1 inpatient visit and 57.2% had ≥1 emergency department visit.

Figure 1. Description of study and identification periods.

To date, however, there have been no comprehensive published studies describing treatment patterns, economic burden and survival outcomes of FL patients in Japan. Therefore, the objectives of our study are to describe treatment patterns, healthcare resource utilization (HCRU) and costs during each year of therapy for FL in Japan. Additionally, the study also aims to evaluate OS and time-to-next-treatment (TTNT) outcomes from the start of 1L treatment to better understand the clinical landscape for FL patients.

Materials & methods

Database & patient selection

Data for this administrative claims data study were analyzed using the Medical Data Vision (MDV) database (<http://www.mdv.co.jp/>), a Diagnosis Procedure Combination database comprising anonymized inpatient MDV database records and outpatient data from over 400 Japanese hospitals, covering approximately 22% of acute phase hospitals (including 187 cancer therapeutic facilities) and data for 26.77 million patient records as of December 2017. The identification period was from 1 October 2008 through 31 December 2017, with a minimum look-back period of 6 months by following previous MDV database study [3] and a minimum follow-up period 12 months relative to the patient index date, which from the start of 1L (defined as the first date of systemic treatment during the identification period). The identification and study periods are shown in Figure 1. Our study period continued until 31 December 2018 as last timing for patients who were still on the claims database record during the entire follow-up period based on our criteria of the 12 months minimum follow-up period.

The initial patient cohort included in the analysis were those treated for FL during the identification period and who had a claim with International Classification of Diseases (ICD)-10 diagnosis code for FL (C82.x) on the index date or during the 6-month look-back period. Patients excluded were those who did not have at least two claims (for any disorder) with at least 1-year follow-up (one claim every 6 months, unless they died within the first 6 months) or who did not have at least one claim (for any disorder) with a 6-month look-back period.

This initial cohort was further narrowed down through propensity score matching (PSM) using covariates as presented by Albarmawi *et al.* [11]. The covariates included patient demographic characteristics are based on age group (<66, 66–70, 71–75, 76–80, 81–85, 86+ years), sex, valid measure of disease severity including Charlson comorbidity index score (CCI) and index year (binary variable; before or after 27 October 2010, which was the launch date of bendamustine in Japan). Age and CCI group cutoffs were based similar cutoffs as presented by Albarmawi *et al.* [11] and slightly modified to include the elderly population in Japan and to account for the patients who by definition had a baseline CCI score of 2 (their FL diagnosis prior to treatment initiation contributes a score of 2).

PSM algorithm [12] was used to eliminate the potential selection bias from baseline covariates for making comparison between R and non-R-based index regimens. PSM was completed with a 2:1 ratio (R vs non-R-based for index regimen) using the nearest-neighbor algorithm and calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score with evaluation for each covariate using standardized mean difference of 0.1. A 2:1 ratio was chosen based on the number of patients in each group before the PSM to ensure that the non-R-based patients can also be sufficiently included in the match.

Ethics approval & consent to participate

This was a retrospective study carried out using an existing hospital claims database with no primary data collection. Patients were informed that their data would be used for research (opt-out system) and their data were de-identified before addition to the database. Data from this database occur in an unlinked fashion. As the data had been anonymized, the Ethical Guidelines for Epidemiological Research in Japan, which require ethics approval and informed consent, are not applicable to this study. Based on the Ethical Guidelines on Biomedical Research Involving Human Subjects, pharmaco-epidemiological studies conducted on medical databases constitute research

carried out on pre-existing material and information not requiring any interaction with patients [13] and therefore obtaining written informed consent from patients was not required.

Outcome measures & data analyses

The outcome measures included: the proportion of patients who received either R-based or non-R-based FL therapy regimens within 30 days of the patient index date; treatment pattern; HCRU, including the use of radiation therapy and SCT; direct medical costs; and survival outcomes including OS and TTNT. R-based regimen categories during 1L included R plus cyclophosphamide, doxorubicin, vincristine and prednisone, R plus cyclophosphamide, vincristine and prednisone, R-bendamustine, other R-based chemotherapy and R-monotherapy. non-R-based regimens included any chemotherapy without R, immunotherapy/endocrine therapy and other treatments without R that were not otherwise specified. The first line captured during the identification period was designated as 1L; this regimen consisted of all drugs received during 30 days before and after the index date. Patients were considered to have a new line of therapy if they received a drug not included in the initial treatment regimen or had a gap of more than 90 days between any treatments. Measures of HCRU included number of outpatient visits, number of hospitalizations, length of hospital stay and number of emergency room visits during each year of follow-up.

In our study, nominal direct medical costs were obtained in Japanese yen (JPY) directly from the database and were totaled during the study period and then stratified by inpatient/outpatient status, cancer drug costs and other pharmacy costs. Direct unadjusted (nominal) medical costs are presented after converting from JPY to USD using the exchange rate based on the first month of every year in [Supplementary Table 3](#). Direct unadjusted (nominal) medical costs are then adjusted to direct adjusted medical costs with regard to Japanese inflation rate based on the calendar year average of Consumer Price Index by the reference year of 2018 [14,15].

OS was also calculated from the patient index date for all patients and stratified by demographic factors (i.e., age, sex and CCI) and treatment groups. In addition, TTNT was calculated from the index date to the next line of therapy, accounting for death as a competing risk.

Continuous variables that follow an approximately normal distribution were summarized using mean, standard deviation (SD), median, minimum and maximum. Categorical variables were summarized using frequency and percentage. For HCRU outcomes, differences between treatment groups were assessed using *t*-tests. For cost outcomes, differences between treatment groups were assessed using gamma generalized linear models with log-link function. For OS, Kaplan–Meier (KM) survival curves and their corresponding median and 95% CIs were generated for all patients and stratified by the specified groups. Corresponding median and 95% CI for hazard ratios were similarly generated using a cumulative incidence model with death as a competing risk from the Fine-Gray model [16,17]. Cumulative incidence function curves were also generated. All data analyses were performed using SAS® software version 9.4 or higher.

Results

Patient demographics & comorbidities

During the study identification period of 1 October 2008 through 31 December 2017, a total of 5037 patients were treated for NHL. Of these patients, 3928 had an FL diagnosis on the index date or during the 6-month look-back period before the index date. The remaining inclusion criteria were applied, which yielded 3593 patients who were subject to PSM. Of this prematched patient group, 2938 received a R-based regimen and 655 received a non-R-based regimen. After matching, 1947 patients remained in the overall patient sample, with 1294 receiving an R-based regimen and 653 receiving a non-R-based regimen. The flow of patient attrition is illustrated in [Figure 2](#). The groups were deemed balanced on all matching covariates as all had an absolute standardized mean difference of <0.1.

Patient characteristics are shown in [Table 1](#). The mean (SD) ages for patients with FL treated with R-based and non-R-based therapy were 66.3 (11.0) and 67.1 (10.7) years, respectively. In the R-based group, a total of 720 patients (55.6%) were ≥66 years of age and 107 (8.3%) were >80 years of age. The non-R-based group had 368 patients (56.4%) ≥66 years of age and 62 (9.5%) were >80 years of age. Almost exactly half of both regimen groups were male. The most common index year for both groups was 2015, with nearly half of patients in both groups initiating treatment on or after 2015. The mean follow-up time (SD) for R-based and non-R-based regimen patients was 1296.2 (685.0) days and 1134.2 (722.5), respectively. More non-R-based regimen patients had a death captured in the database compared with the R-based group (22.1 vs 9.7%). The most common comorbidities for R-based regimen patients and non-R-based regimen patients (other than malignancy in ~99% of both groups)

Table 1. Patient demographics and baseline characteristics (pre- and post propensity score matching).

Characteristic	Pre PSM		Post PSM		Standardized mean difference (post PSM) [†]
	R based (n = 2938)	Non R based (n = 655)	R based (n = 1294)	Non R based (n = 653)	
Mean age, years (SD)	64.5 (10.6)	67.2 (10.7)	66.3 (11.0)	67.1 (10.7)	0.0789
– Minimum, maximum, years	14.0, 94.0	28.0, 96.0	23.0, 94.0	28.0, 96.0	
Age group, n (%)					
– <66	1539 (52.4%)	285 (43.5%)	574 (44.4)	285 (43.6)	-
– 66–70	546 (18.6%)	120 (18.3%)	240 (18.5)	120 (18.4)	
– 71–75	401 (13.6%)	96 (14.7%)	194 (15)	96 (14.7)	
– 76–80	266 (9.1%)	91 (13.9%)	179 (13.8)	90 (13.8)	
– 81–85	144 (4.9%)	38 (5.8%)	69 (5.3)	38 (5.8)	
– Over 85	42 (1.4%)	25 (3.8%)	38 (2.9)	24 (3.7)	
Sex, n (%)					
– Female	1429 (48.6%)	325 (49.6%)	648 (50.1)	325 (49.8)	0.0061
– Male	1509 (51.4%)	330 (50.4%)	646 (49.9)	328 (50.2)	
Year of index date, n (%)					
– Before bendamustine date (27 October 2010)	169 (5.8%)	39 (6%)	72 (5.6)	38 (5.8)	0.011
– After bendamustine date (27 October 2010)	2769 (94.2%)	616 (94%)	1222 (94.4)	615 (94.2)	
Baseline CCI, n (%)					
– 0–2	1579 (53.74%)	292 (44.58%)	576 (44.5%)	292 (44.7%)	0.0065
– 3	318 (10.8%)	87 (13.3%)	170 (13.1%)	86 (13.2%)	
– 4	491 (16.7%)	111 (16.9%)	223 (17.2%)	111 (17.0%)	
– 5+	550 (18.7%)	165 (25.2%)	325 (25.1%)	164 (25.1%)	
Follow-up time (from index date until death or last patient record), days					
– Mean (SD)	1316.9 (693.7)	1137.9 (728.1)	1296.2 (685.0)	1134.2 (722.5)	0.2301
– Median (Q1, Q3)	1254.0 (827.0, 1725.0)	1050.0 (548.0, 1640.0)	1236.0 (802.0, 1698.0)	1050.0 (548.0, 1639.0)	
Other prior or concurrent primary cancer (C00–C96, except C77–C89 [‡]), n (%)					
– Yes	391 (13.3%)	163 (24.9%)	192 (14.8)	162 (24.8)	0.2521
– No	2547 (86.7%)	492 (75.1%)	1102 (85.2)	491 (75.2)	
Comorbidities, n (%)					
– Congestive heart failure	373 (12.7%)	116 (17.7%)	211 (16.3)	116 (17.8)	0.0388
– Dementia	16 (0.5%)	6 (0.9%)	9 (0.7)	6 (0.9)	0.025
– Chronic pulmonary disease	426 (14.5%)	139 (21.2%)	241 (18.6)	137 (21.0)	0.0591
– Rheumatologic disease	58 (2%)	15 (2.3%)	31 (2.4)	15 (2.3)	0.0065
– Mild liver disease	550 (18.7%)	134 (20.5%)	278 (21.5)	133 (20.4)	0.0274
– Diabetes with chronic complications	59 (2%)	19 (2.9%)	34 (2.6)	19 (2.9)	0.0172
– Hemiplegia or paraplegia	10 (0.3%)	3 (0.5%)	6 (0.5)	3 (0.5)	0.0006
– Renal disease	83 (2.8%)	31 (4.7%)	42 (3.3)	31 (4.8)	0.0767
– Any malignancy, including lymphoma and leukemia	2927 (99.6%)	647 (98.8%)	1289 (99.6)	645 (98.8)	0.0939
– Moderate or severe liver disease	6 (0.2%)	5 (0.8%)	3 (0.2)	5 (0.8)	0.0758
– Metastatic solid tumor	309 (10.5%)	82 (12.5%)	176 (13.6)	82 (12.6)	0.031
– HIV	2 (0.1%)	0 (0%)	0 (0)	0 (0)	NA

[†] Absolute value of the standardized mean difference is presented.

[‡] Codes from the ICD-10.

CCI: Charlson comorbidity index; FL: Follicular lymphoma; HIV: Human immunodeficiency virus; ICD-10: International Classification of Diseases, 10th revision; MDV: Medical Data Vision; NA: Not applicable; PSM: Propensity score matching; Q1, Q3: 1st and 3rd quartile; SD: Standard deviation.

Figure 2. Patient attrition for follicular lymphoma patients.

FL: Follicular lymphoma; ICD-10: International Classification of Diseases, 10th revision; MDV: Medical Data Vision; PSM: Propensity score matching; R: Rituximab.

were mild liver disease (21.5 vs 20.4%, respectively), chronic pulmonary disease (18.6 vs 21.0%) and congestive heart failure (16.3 vs 17.8%). Additional baseline statistics are listed in [Supplementary Table 1](#). Most patients with comorbid metastatic solid tumors were <66 years old. Over 80% of the cohort identified started their index treatment on or after 2013.

Treatment characterization

Treatment patterns ([Table 2](#)) showed that of patients who initially received R-based therapy, 35.0% switched to a non-R-based therapy as a second line (2L) of therapy. This proportion increased to 45.0% of the R-based group receiving non-R-based therapy in the third line of therapy (3L). For patients initially receiving a non-R-based regimen, 54.2% were still receiving non-R-based treatment by 2L and 69.9% by 3L. A higher proportion of R-based regimen patients received only 1 line of therapy (46.3%) compared with patients receiving non-R-based therapy (37.5%). The non-R-based regimen group had a consistently larger proportion of patients receiving multiple lines of therapy, from two lines to more than six lines. Treatment progression for lines 1–3 are illustrated in [Supplementary Figure 1](#) for those who initiated their 1L before and after the approval of bendamustine, respectively. For non-R-based regimens, the mean length of the index treatment was shorter than R-based regimens by more than 40 days

Table 2. Treatment patterns of follicular lymphoma.

Treatment patterns for FL (n = 1947)	R-based regimens (n = 1294)	Non-R-based regimens (n = 653)
Index regimen, n (%)		
– R-CHOP	534 (41.3)	(0)
– R-CVP	209 (16.2)	(0)
– R + bendamustine	273 (21.1)	(0)
– R + other chemotherapy or dexamethasone [†]	142 (11.0)	(0)
– R monotherapy	136 (10.5)	(0)
– Chemotherapy without R	(0)	276 (42.3)
– Other (immunotherapy, targeted therapy, hormone therapy) without R	(0)	29 (4.4)
– NOS	(0)	348 (53.3)
Subsequent regimen 2L, n (%)	n = 695 (100)	n = 408 (100)
– R-CHOP	51 (7.3)	42 (10.3)
– R-CVP	24 (3.5)	28 (6.9)
– R + bendamustine	154 (22.2)	62 (15.2)
– R + chemotherapy dexamethasone [‡]	70 (10.1)	37 (9.1)
– R monotherapy	153 (22.0)	18 (4.4)
– Chemotherapy without R	119 (17.1)	99 (24.3)
– Other (immunotherapy, targeted therapy, hormone therapy) without R	8 (1.2)	11 (2.7)
– NOS	116 (16.7)	111 (27.2)
Subsequent regimen 3L, n (%)	n = 387 (100)	n = 237 (100)
– R-CHOP	22 (5.7)	6 (2.5)
– R-CVP	6 (1.6)	4 (1.7)
– R + bendamustine	53 (13.7)	37 (15.6)
– R + chemotherapy dexamethasone [§]	54 (14.0)	21 (8.9)
– R monotherapy	78 (20.2)	14 (5.9)
– Chemotherapy without R	80 (20.7)	83 (35)
– Other (immunotherapy, targeted therapy, hormone therapy) without R	7 (1.8)	7 (3.0)
– NOS	87 (22.5)	65 (27.4)
Lines, n (%)		
– 1	599 (46.3)	245 (37.5)
– 2	308 (23.8)	171 (26.2)
– 3	174 (13.4)	96 (14.7)
– 4	80 (6.2)	55 (8.4)
– 5	51 (3.9)	36 (5.5)
– 6+	82 (6.3)	50 (7.7)
Duration of index regimen (days)		
– Mean (SD)	168.8 (197.3)	121.2 (288.7)
– Median (Q1, Q3)	128.0 (83.0, 169.0)	33.0 (8.0, 104.0)
– Minimum, maximum	1.0, 3058.0	1.0, 2757.0
Duration of 2L regimen (days)	n = 695 (100)	n = 408 (100)
– Mean (SD)	119.1 (182.5)	130.7 (205.4)
– Median (Q1, Q3)	59.0 (22.0, 141.0)	72.0 (26.0, 142.0)
– Minimum, maximum	1.0, 1583.0	1.0, 1493.0
Duration of 3L regimen (days)	n = 387 (100)	n = 237 (100)
Mean (SD)	97.2 (189.7)	122.7 (232.0)
– Median (Q1, Q3)	40.0 (9.0, 109.0)	55.0 (8.0, 126.0)
– Minimum, maximum	1.0, 1889.0	1.0, 1676.0
Patients using R maintenance therapy after 1L [†] , n (%)	85 (7.3)	0

[†] Maintenance therapy was explored in patients with R-based 1L regimens who continued therapy with R after 1L ended.

1L: First line; 2L: Second line; 3L: Third line; 4L: Fourth line; 5L: Fifth line; 6L: Sixth line; CHOP: Cyclophosphamide, doxorubicin, vincristine and prednisone; CVP: Cyclophosphamide, vincristine and prednisone; FL: Follicular lymphoma; Q1, Q3: 1st and 3rd quartile; NOS: Not otherwise specified; R: Rituximab; R-CHOP: Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP: Rituximab plus cyclophosphamide, vincristine and prednisone; SD: Standard deviation.

Table 2. Treatment patterns of follicular lymphoma (cont.).

Treatment patterns for FL (n = 1947)	R-based regimens (n = 1294)	Non-R-based regimens (n = 653)
Patients with stem cell transplant, n (%)		
– During index regimen (prior to 2L)	1 (0.1)	2 (0.3)
– During 2L (prior to 3L)	8 (0.6)	1 (0.2)
– During 3L (prior to 4L)	9 (0.7)	3 (0.5)
– During 4L (prior to 5L)	7 (0.5)	0 (0)
– During 5L (prior to 6L+)	5 (0.4)	1 (0.2)
Patients with radiation therapy, n (%)		
– During index regimen or within 30 days prior to initiation	64 (4.9)	33 (5.1)
– During entire patient follow-up period	127 (9.8)	74 (11.3)

† Maintenance therapy was explored in patients with R-based 1L regimens who continued therapy with R after 1L ended.
1L: First line; 2L: Second line; 3L: Third line; 4L: Fourth line; 5L: Fifth line; 6L: Sixth line; CHOP: Cyclophosphamide, doxorubicin, vincristine and prednisone; CVP: Cyclophosphamide, vincristine and prednisone; FL: Follicular lymphoma; Q1, Q3: 1st and 3rd quartile; NOS: Not otherwise specified; R: Rituximab; R-CHOP: Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP: Rituximab plus cyclophosphamide, vincristine and prednisone; SD: Standard deviation.

Table 3. Healthcare resource utilization during the follow-up period, overall.

HCRU outcome	All regimens		R-based regimens (n = 1294)		Non-R-based regimens (n = 653)		p-value
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	
Outpatient visits (n)	1899	49.7 (36.1)	1283	51.2 (35.1)	616	46.8 (38.1)	0.0168
Hospitalizations (n)	1819	3.8 (3.5)	1264	3.8 (3.6)	555	3.8 (3.4)	0.8648
LOS† days overall	1819	74.5 (83.9)	1264	70.9 (78.5)	555	82.8 (94.6)	0.0096
ICU admissions (n)	43	1.0 (0.2)	23	1.1 (0.3)	20	1.0 (0.0)	0.1619
ER visits (n)	68	2.9 (6.3)	39	2.8 (6.7)	29	3.0 (5.7)	0.9209
Stem cell transplants during follow-up (n)	37	1.0 (0.0)	30	1.0 (0.0)	7	1.0 (0.0)	NA
Radiation therapy procedures during follow-up (n)	201	20.0 (12.3)	127	20.5 (12.7)	74	19.1 (11.7)	0.4635

† Among hospitalized patients.
ER: Emergency room; HCRU: Healthcare resource utilization; ICU: Intensive care unit; LOS: Length of stay; NA: Not applicable; R: Rituximab; SD: Standard deviation.

(168.8 vs 121.2 days). The inverse trend was observed in lines 2 and 3, where patients with R-based index regimens had a shorter duration by more than 10 days. Slightly more patients receiving non-R-based regimens for FL also underwent radiation therapy compared with those receiving R-based treatment over the entire patient follow-up period (11.3 vs 9.8%).

Healthcare resource utilization & costs

HCRU during the follow-up period is shown in Table 3. Overall, the mean (SD) number of outpatient visits was 49.7 (36.1). Patients receiving R-based therapy had more outpatient visits compared with non-R-based therapy (51.2 vs 46.8). Mean number of hospitalizations was the same (3.8) for the entire FL patient group when stratified by R-based regimen. The mean length of stay for these hospitalizations was longer for patients receiving non-R-based therapy (82.8 days) compared with patients treated with R-based regimens (70.9 days). There was very little difference in the number of ICU or emergency room visits as well as the number of SCTs or radiation treatments performed regardless of R-based treatment status. Detailed HCRU by each year of follow-up are additionally reported in Supplementary Table 2.

Direct adjusted costs during the follow-up period are shown by overall and yearly costs in Table 4. The mean (SD) of total medical costs over the entire follow-up period was \$66,247.41 (\$51,950.18) and was significantly higher for R-based regimens compared with non-R-based regimens (\$69,601.68 vs 59,600.51; $p < 0.0001$). During the first year of follow-up the total mean (SD) costs for all regimens were \$39,481.78 (\$27,109.82). When stratified by treatment regimen type, mean first year costs were \$43,407.60 for R-based regimens and \$31,702.27 for non-R-based regimens ($p < 0.0001$). However, from the second year of follow-up, R-based regimens had lower

Table 4. Direct adjusted medical costs in US dollars during the follow-up period, overall and by year.

Cost outcome	All regimens		R-based regimens		Non-R-based regimens		p-value
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	
Total costs	1947	66247.41 (51950.18)	1294	69601.68 (47772.04)	653	59600.51 (58844.37)	<0.0001
– During year 1	1947	39481.78 (27109.82)	1294	43407.60 (24498.76)	653	31702.27 (30201.01)	<0.0001
– During year 2	1749	11479.23 (18257.54)	1204	10673.01 (16803.02)	545	13260.31 (21026.33)	0.0011
– During year 3	1451	9942.44 (17699.58)	1007	9343.04 (15954.74)	444	11301.88 (21087.02)	0.0120
– During year 4	1091	7656.07 (14563.08)	774	7037.73 (13689.12)	317	9165.85 (16429.58)	0.0049
– During year 5	693	7735.84 (16743.66)	484	7378.23 (16410.84)	209	8563.99 (17502.42)	0.2295
Inpatient cost, total	1819	40641.86 (43082.93)	1264	38761.14 (41087.79)	555	44925.14 (47073.23)	0.0027
– During year 1	1732	27716.82 (28096.16)	1237	26647.76 (27250.16)	495	30388.36 (29968.82)	0.0078
– During year 2	486	20257.99 (23687.21)	287	19563.60 (22567.20)	199	21259.45 (25239.66)	0.3781
– During year 3	355	19747.00 (23879.19)	221	18953.22 (21052.81)	134	21056.15 (27960.62)	0.3422
– During year 4	234	19183.11 (19246.13)	153	19589.32 (18869.24)	81	18415.80 (20035.62)	0.6424
– During year 5	139	19725.05 (22044.04)	97	20034.39 (23271.70)	42	19010.62 (19151.56)	0.7864
ICU cost, total	43	3272.53 (3694.49)	23	3633.46 (3924.72)	20	2857.46 (3463.74)	0.3892
– During year 1	27	3729.72 (4165.77)	13	4318.08 (4336.26)	14	3183.38 (4084.47)	0.3895
– During year 2	4	1958.62 (1793.21)	4	1958.62 (1793.21)	N/A	N/A	N/A
– During year 3	3	1786.71 (638.92)	N/A	NA	3	1786.71 (638.92)	N/A
– During year 4	4	4268.72 (4018.84)	4	4268.72 (4018.84)	N/A	N/A	N/A
– During year 5	4	1614.87 (1546.43)	2	831.93 (0.00)	2	2397.80 (2173.11)	0.0851
Outpatient cost, total	1899	28992.19 (27440.65)	1283	32011.29 (25609.92)	616	22704.02 (29967.44)	<0.0001
– During year 1	1897	15216.39 (12610.15)	1282	18101.52 (12428.92)	615	9202.19 (10729.98)	<0.0001
– During year 2	1724	5934.91 (8252.08)	1192	6070.09 (8134.45)	532	5632.03 (8509.75)	0.2111
– During year 3	1439	5153.78 (8156.46)	1000	5219.78 (7962.84)	439	5003.44 (8588.70)	0.5316
– During year 4	1082	3571.10 (7033.20)	768	3190.15 (5827.06)	314	4502.85 (9295.53)	<0.0001
– During year 5	689	3801.39 (9712.27)	481	3384.05 (8237.68)	208	4766.48 (12442.69)	0.0015
Cancer treatment costs, total	1947	28140.88 (25996.49)	1294	32550.86 (23327.81)	653	19401.96 (28684.68)	<0.0001
– During year 1	1947	18534.91 (14093.38)	1294	22242.60 (12025.52)	653	11187.66 (14989.65)	<0.0001
– During year 2	690	11086.66 (11477.29)	435	12667.05 (10838.92)	255	8390.70 (12042.18)	0.0007
– During year 3	531	10088.82 (11479.65)	350	11213.96 (11106.71)	181	7913.15 (11900.64)	0.0131
– During year 4	281	9158.41 (11033.03)	175	9916.25 (9912.92)	106	7907.25 (12618.61)	0.2441
– During year 5	157	11094.19 (14857.14)	98	12470.84 (15204.10)	59	8807.54 (14091.68)	0.2036
Other pharmacy costs, total	1947	11037.70 (17232.02)	1294	10432.08 (15521.03)	653	12237.80 (20158.44)	0.0043
– During year 1	1946	5835.15 (9176.37)	1294	5809.53 (8151.29)	652	5885.98 (10936.65)	0.8173
– During year 2	1622	2355.98 (6022.64)	1115	1975.70 (5219.14)	507	3192.30 (7430.39)	<0.0001
– During year 3	1299	2163.90 (6157.91)	899	1810.86 (5028.44)	400	2957.36 (8095.59)	<0.0001
– During year 4	904	1886.86 (4985.90)	628	1641.09 (4624.90)	276	2446.08 (5692.84)	0.0003
– During year 5	575	1997.70 (6073.57)	394	1783.58 (5599.27)	181	2463.78 (6990.15)	0.0279
Cost of stem cell transplants	37	3473.29 (1306.75)	30	3404.61 (1275.98)	7	3767.67 (1500.49)	0.4442
Cost of radiation therapy procedures	201	3132.88 (2142.77)	127	3195.95 (2229.50)	74	3024.63 (1995.26)	0.5641

ICU: Intensive care unit; R: Rituximab; SD: Standard deviation.

total costs compared with non-R-based regimens (\$10,673.01 vs 13,260.31; $p = 0.0011$). This trend continued, with statistically significant differences, until the 5th year of follow-up (\$7378.23 vs 8563.99; $p = 0.2295$).

Similarly, overall mean costs for R-based regimens were higher for ICU compared with non-R-based regimens (\$3633.46 vs 2857.46), outpatient (\$32,011.29 vs 22,704.02) and cancer treatment (\$32,550.86 vs 19,401.96) across all years. Cancer treatment costs were consistently lower for non-R-based therapy in each year of follow-up, while outpatient costs became significantly lower for R-based regimens compared with non-R-based therapy in the fourth (\$3190.15 vs 4502.85; $p < 0.0001$) and fifth year (\$3384.05 vs 4766.48; $p = 0.0015$). In contrast, the overall inpatient costs accrued with R-based regimens were lower than non-R-based (\$38,761.14 vs 44,925.14) ($p = 0.0027$). The lower inpatient costs of R-based regimens remained constant for each of the 5 years of follow-

Table 5. Overall survival and time-to-next-treatment outcomes.

Characteristics	All regimens (n = 1947)	R-based regimens (n = 1284)	Non-R-based regimens (n = 653)
Deaths (n [%])	270 (13.9%)	126 (9.7%)	144 (22.1%)
KM OS estimate			
– Median (95% CI)	Not reached	Not reached	Not reached
Number of patients with next treatment (n [%])	1103 (56.7%)	695 (53.7%)	408 (62.5%)
Number of patients with next treatment or death (n [%])	1161 (59.6%)	709 (54.8%)	452 (69.2%)
TTNT estimate, death as competing risk			
– HR (95% CI)		0.702 (0.620, 0.796)	Ref

HR: Hazard ratio; KM: Kaplan–Meier; OS: Overall survival; R: Rituximab; TTNT: Time to next treatment.

Figure 3. Kaplan–Meier plot for overall survival stratified by R-based and non R-based regimen.
1L: First line; R: Rituximab.

up. Both the overall and yearly costs for other pharmacy costs were also consistently lower in R-based regimens compared with non-R-based regimens (overall average cost: \$10,432.08 vs 12,237.80) ($p = 0.0043$). The costs of SCTs and radiation therapy procedures during follow-up were similar between the treatment groups. The nominal costs prior to adjusting for inflation are also presented in [Supplementary Table 3](#).

Overall survival

Overall, there were 270 deaths (13.9% of patients) over the analysis period for the entire group of patients with FL. Among patients receiving non-R-based regimens for FL, mortality was roughly double that of R-based patients (22.1 vs 9.7%, respectively) ([Table 5](#)). Based on the OS KM curve, R-based regimens had significantly better survival ($p < 0.0001$), although a median was not reached in either group ([Figure 3](#)). A significantly better OS was

Figure 4. Kaplan-Meier plot for overall survival stratified by patient baseline attributes. Kaplan-Meier plot for overall survival for (A) all follicular lymphoma patients and stratified by (B) age group, (C) sex, (D) CCI score. CCI: Charlson comorbidity index.

also found with lower age, female and lower CCI score (Figure 4). Detailed summary statistics on OS are reported in Supplementary Table 4.

Time to next treatment

There were a total 1103 patients (56.7%) who progressed to subsequent lines of therapy and 1161 (59.6%) who either progressed in treatment or died (Table 5). Patients who received R-based therapy during 1L marked a significant reduction in risk of progressing to subsequent therapy compared with those who received non-R-based therapy (HR: 0.702; 95% CI: 0.620–0.796). The cumulative incidence function plot stratified by treatment group is shown in Figure 5. The risk of treatment progression was also significantly reduced in younger age groups (Figure 6), although no differences were observed in terms of sex and CCI score. Detailed summary statistics on TTNT can also be found in Supplementary Table 4.

Discussion

To our knowledge, this is the first study to comprehensively evaluate treatment patterns, cost, HCRU and clinical outcomes among patients with FL in Japan using a propensity score-matched cohort. The identified baseline demographics (i.e., age and sex) were comparable to FL patients characterized by Morrison *et al.* in the USA [9].

Figure 5. Cumulative incidence function plot for time-to-next-treatment stratified by R-based regimen and non R-based regimen.

1L: First-line; R: Rituximab.

For FL patients who were eligible for PSM in the present analysis, about two-thirds of patients received an R-based regimen. This is a distribution that is similar to prior real-world evidence of FL treatment patterns, suggesting that the regimens identified reflect FL treatment patterns. In terms of comorbidities, less than 1% of patients had a CCI score of 0 and almost half of both treatment groups had a CCI of 2. Over half of patients had a CCI score of 3 or higher. Interpretation of CCI score distribution could be explained by our patient selection definition, which required them to have a diagnosis of any malignancy (part of the CCI definition) on or prior to their index date, thus the diagnosis of FL itself was included in the CCI. Approximately a fifth of the patients had the following commonly observed comorbidities: chronic pulmonary disease, mild liver disease and congestive heart failure. Physicians report that they take comorbid conditions into account when deciding NHL treatment intensity but evidence remains poor and heterogeneous about the comorbidities and outcomes in FL [18]. It is possible that the utilization of R-based regimens is affected depending on the treating physicians' experience with comorbidities and FL.

According to the clinical guidelines, chemo-immunotherapy is the recommended treatment for FL patients across all stages for patients who are not otherwise 'watch-and-wait' or radiation therapy recipients. These results are mostly consistent with the Japanese Society of Hematology guidelines [19], with chemo-immunotherapy observed in 72.4% of patients and R alone in 9.3% of patients.

Notably, patients on R-based regimens had a significantly higher number of outpatient visits compared with therapies without R due to the possibility that patients might be receiving R-maintenance therapy, although the direction of effect was reversed on and after year 2. The 7% of patients on R-based regimens with R maintenance therapy after their index treatment could potentially contribute to the high number of outpatient visits during the first year. Patients on R-based regimens also marked a significantly lower overall length of stay and number of hospitalizations in year 1. However, overall number of hospitalizations, ER visits and ICU visits were comparable between the groups.

Total costs for FL patients in Japan in this study were found to vary widely, with a mean (SD) of \$66,247.41 (\$51,950.18) USD. The heterogeneity of these costs may reflect the heterogeneity inherent in the FL patient

Figure 6. Cumulative incidence function plot for time-to-next treatment stratified by patient baseline characteristics. Cumulative incidence function plot for time-to-next-treatment stratified by (A) age group, (B) sex, (C) CCI score. CCI: Charlson comorbidity index.

population itself. Patients with R-based 1L regimens had significantly higher overall medical costs but we observed a lower yearly cost on and after year 3. The first-year costs found in this study (\$39,481.78) was similar to that was reported by another US study, which found the first-year economic burden in FL patients to be \$36,000 [20]. Patients with R-based 1L regimens had significantly higher outpatient costs, but we observed a reversed direction of effect in years 4. Longer treatment may significantly increase healthcare expenditure, as R is priced at JPY 22,553 (\$210.80 USD) per 100 mg vial [21]. Additionally, R-based regimens require multiple days of injections, which may contribute to the higher outpatient utilization for patients on R-based therapies.

Although the cancer pharmacy and outpatient costs were higher for R-based regimens, the inpatient costs were significantly lower. These findings show the high costs of outpatient and pharmacy burden driven by R; however, it has also shown the potential effect of longer-term benefits. A retrospective study of the National Health Service (UK) in 2018 also found a wide range of costs and survival outcomes [22] and recommended future cost modeling based on a lifetime horizon approach, as results from restricted time horizons may not be appropriate in all scenarios.

In previous studies [22–25], R-based therapies have shown to be relatively cost-effective options compared with non-R therapy in the use of R in induction monotherapy, combination with chemotherapy and as maintenance therapy.

The FL patients identified in this study generally had long survival, with only 13.9% who died during the follow-up period, or a presumed survival rate of 86.1%. These results are very similar to the findings in another Japanese study of FL patients who showed 5-year OS rates ranging from 84.4 to 93.5% [26]. These results were cited in a systematic review by Monga *et al.* [27], who described a 5-year OS range from 48.9 to 93.5% in the most elderly population as well. In this study, OS findings were stratified, further characterizing this patient population.

More specifically, stratified our OS KM survival analyses showed worse survival with increasing age, male sex and chemotherapy regimens without R. Although all other groups had similar survival curves, in contrast, R-based therapies performed better than regimens in the chemotherapy without R group. In this study, slightly higher OS was observed compared with the 2019 US database study by Morrison *et al.* (90.6% 3-year OS vs 86.9% 2-year survival) [9,28].

Our TTNT results were in favorable agreement in trend with the above OS analysis results. As patients who have progressive disease were found to have significantly higher frequencies of outpatient visits, laboratory procedures, acute care visits and intensive chemotherapy [29], it is paramount that 1L therapy is effective to delay disease progression and thus, minimize HCRU and direct costs.

The findings herein should be interpreted in light of several limitations. First, the MDV database does not indicate the disease treated with each drug claim, therefore treatment groupings were made in consultation with the clinical experts based on the relevance from clinical plausibility perspective. The complete treatment history of the included patients is not recorded in this database, therefore their 1L regimen may or may not be their true first line of therapy. Analysis was based on a patient's first treatment during the identification period and required at least 6 months of look-back with a FL diagnosis. An assumption was made that most patients were treatment naive and the distribution of the 1L regimens was consistent with the prior literature. Also, 'watch and wait' was difficult to define during this study, therefore we did not include it as part of the scope of this study. Further, mortality data were captured only through patient's hospital discharge records, limiting the robustness of OS calculations.

In our study, we observed no impact of obinutuzumab (Gazyva), approved for naive and relapsed/refractory FL in Japan in July 2018, due to our data study period (2008–2017) occurring prior to its approval. We also observed no impact of the R subcutaneous injection formulation. In Western countries, the subcutaneous injection formulation of R, especially used in maintenance therapy, was approved in the USA in June 2017. However, it has not been approved in Japan yet. Several R biosimilar drugs have been launched in Japan for B cell NHL in recent years. R biosimilar obtained approval in September 2017, but was not available as a treatment option in real-world practice until January 2018. Similarly, R biosimilar approval in Japan was obtained in September 2019 following US approval in July 2019. These treatment options were not included in the scope of our study due to the data available during the study period.

Although it was not possible to fully capture all cases of mortality, the randomness inherent in this variable should make the comparison between groups still clinically plausible.

Conclusion & future perspective

This study revealed that patients with FL in Japan typically experienced multiple lines of therapy with diverse treatment patterns due to little consensus of FL treatment and had relatively long survival outcomes. In general, our findings report the mean (SD) total medical cost during first year was significantly higher for R-based regimens but the trend reversed on and after year 2.

Clinical outcomes, measured by OS and TTNT, were better in patients with R-based therapies, in order of decreasing age and female. Our results underscore the superiority of R-based therapy over other regimens as the 1L treatment option in balanced consideration from comparative effectiveness perspectives of clinical outcomes, with regard to mid to long-term economic burden of FL care.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-0832

Summary points

- Newly diagnosed follicular lymphoma patients who were on rituximab (R)-based treatment had more outpatient visits compared with patients on non-R-based treatment (51.2 vs 46.8).
- The mean length of stay for hospitalizations was longer for patients receiving non-R-based therapy (82.8) compared with patients treated with R-based regimens (70.9).
- The mean (standard deviation) total medical costs were significantly higher for R-based regimens compared with non-R-based regimens (\$69,601.68 vs 59,600.51).
- The mean (standard deviation) total medical cost during first year was also significantly higher for R-based regimens (\$43,407.60 vs 31,702.27) but the trend reversed on and after year 2.
- Cancer treatment costs were consistently lower for non-R-based therapy in each year of follow-up, while outpatient costs became significantly higher for non-R-based therapy in years 4 and 5.
- In contrast, the overall inpatient costs accrued with R-based regimens were lower than with non-R-based regimens (\$38,761.14 vs 44,925.14).
- Overall costs for ICU (\$3633.46 vs 2857.46), outpatient (\$32,011.29 vs 22,704.02) and cancer treatment (\$32,550.86 vs 19,401.96) were lower for non-R-based therapy compared with R-based therapy.
- Stratified Kaplan–Meier survival analyses showed worse survival with increasing age, male sex and chemotherapy regimens without R.
- Patients who received R-based therapy during 1L marked a significant reduction in the risk of progressing to subsequent therapy compared with those who received a non-R-based therapy.
- As the treatment of follicular lymphoma continues to evolve with upcoming innovative therapies, the economic impact and healthcare resource utilization need to be further investigated in these populations who receive R, non-R and other types of innovative therapies.

Financial & competing interests disclosure

S Tsutsué is current employee of Celgene KK. B Crawford and J Yi are current employee of Syneos Health Japan. K Tobinai served as a consultant for Mundi Pharma, Takeda Pharmaceutaical, Celgene, Ono pharmaceutical, Janssen Pharmaceutical, HUYA Bioscience, Zenyaku Kogyo, Daiichi Sankyo, Eisai, Chugai Pharmaceutical, outside of the submitted work. K Tobinai received honaria from Solasia, Mundi Pharma, Takeda Pharmaceutaical, Ono pharmaceutical, Yakult, Meiji Seika, Janssen Pharmaceutical, BMS, HUYA Bioscience, Zenyaku Kogyo, DS, Eisai, Chugai Pharmaceutical, Verastem, Kyowa Kirin, outside of the submitted work. K Tobinai received research funding from Mundi Pharma, Takeda Pharmaceutaical, Celgene, Ono pharmaceutical, Yakult, Janssen Pharmaceutical, Eisai, Chugai Pharmaceutical, outside of the submitted work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. PDQ Adult Treatment Editorial Board. Adult non-Hodgkin lymphoma treatment (PDQ®): health professional version. (2002). <https://pubmed.ncbi.nlm.nih.gov/26389492/>
2. Chihara D, Ito H, Matsuda T *et al.* Differences in incidence and trends of haematological malignancies in Japan and the United States. *Br. J. Haematol.* 164(4), 536–545 (2014).
3. Tsutsué S, Tobinai K, Yi J, Crawford B. Nationwide claims database analysis of treatment patterns, costs and survival of Japanese patients with diffuse large B-cell lymphoma. *PLoS ONE* 15(8), e0237509 (2020).
- **Reports treatment patterns and cost analysis of diffuse large B-cell lymphoma using nationwide retrospective claims database in Japan.**
4. Krysiak K, Gomez F, White BS *et al.* Recurrent somatic mutations affecting B-cell receptor signaling pathway genes in follicular lymphoma. *Blood* 129(4), 473–483 (2017).
5. Casulo C, Burack WR, Friedberg JW. Transformed follicular non-Hodgkin lymphoma. *Am. Soc. Hematol.* (2015). <https://ashpublications.org/blood/article-pdf/125/1/40/1382839/40.pdf>
6. Luminari S, Bellei M, Biasoli I, Federico M. Follicular lymphoma – treatment and prognostic factors. *Associação Brasileira de Hematologia e Hemoterapia* doi:10.5581/1516-8484.20120015 (2012).

7. Matasar MJ, Luminari S, Barr PM *et al.* Follicular lymphoma: recent and emerging therapies, treatment strategies and remaining unmet needs. *Oncologist* 24(11), (e1236–e1250 2019). <https://pubmed.ncbi.nlm.nih.gov/31346132/>
- **Reports current landscape for treatment of follicular lymphoma and identifies the unmet need to understand first line treatments in practice.**
8. Smith A, Crouch S, Lax S *et al.* Lymphoma incidence, survival and prevalence 2004–2014: sub-type analyses from the UK's Haematological Malignancy Research Network. *Br. J. Cancer* 112(9), 1575–1584 (2015).
- **Reports overall survival of various sub-types of hematological malignancy in UK.**
9. Morrison VA, Shou Y, Bell JA *et al.* Treatment patterns and survival outcomes in patients with follicular lymphoma: a 2007 to 2015 humedica database study. *Clin. Lymphoma, Myeloma Leuk.* 19(4), e172–e183 (2019).
- **Reports data for follicular lymphoma treatment patterns and survival outcomes in the USA.**
10. Ren J, Asche CV, Shou Y, Galaznik A. Economic burden and treatment patterns for patients with diffuse large B-cell lymphoma and follicular lymphoma in the USA. *J. Comp. Eff. Res.* 8(6), 393–402 (2019).
11. Albarmawi H, Nagarajan M, Sun K *et al.* Costs associated with follicular lymphoma among individuals diagnosed with non-Hodgkin lymphoma: a longitudinal analysis using SEER-Medicare data. *Leuk. Lymphoma* 61(1), 75–83 (2020).
- **Reports a longitudinal analysis of follicular lymphoma patients using SEER-Medicare data in USA.**
12. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 70(1), 41–55 (1983).
13. International ethical guidelines for biomedical research involving human subjects. *Bull. Med. Ethics* (182), 17–23 (2002).
14. 'Consumer Price Index 2015-base consumer price index annual report yearly 2019 | file | browse statistics | portal site of official statistics of Japan'. <https://www.e-stat.go.jp/en/stat-search/files?page=1&layout=datalist&toukei=00200573&tstat=000001084976&cycle=7&year=20190&month=0&class1=000001085975>
15. Statistics Bureau of Japan. 'Statistics Bureau home page/consumer price index'. <https://www.stat.go.jp/english/data/cpi/index.html>
16. Zhang Z. Survival analysis in the presence of competing risks. *Ann. Transl. Med.* (2017). <http://circ.ahajournals.org/lookup/doi/10.1161/CIRCULATIONAHA.115.017719>
17. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 133(6), 601–609 (2016).
18. Terret C, Albrand G, Rainfray M, Soubeyran P. Impact of comorbidities on the treatment of non-Hodgkin's lymphoma: a systematic review. Expert Reviews Ltd (2015). <https://pubmed.ncbi.nlm.nih.gov/25771832/>
19. Nagai H. [Revision of JSH guideline for tumors of hematopoietic and lymphoid tissues 2018: lymphoma]. *Rinsho Ketsueki* 59(10), 2146–2152 (2018).
20. Gleeson M, Carolina R, Danese M, Knopf KB. Cost of follicular lymphoma (FL) in Medicare patients. *J. Clin. Oncol.* 26(Suppl. 15), 6634–6634 (2008).
21. Ministry of Health, Labor and Welfare of Japan. Various information of medical fee. Pharmaceutical Master Search 2020'. <https://www.pmda.go.jp/files/000235661.pdf>
22. Wang HI, Roman E, Crouch S *et al.* A generic model for follicular lymphoma: predicting cost, life expectancy and quality-adjusted-life-year using UK population-based observational data. *Value Heal.* 21(10), 1176–1185 (2018).
23. Soini EJO, Martikainen JA, Nousiainen T. Treatment of follicular non-Hodgkin's lymphoma with or without rituximab: cost-effectiveness and value of information based on a 5-year follow-up. *Ann. Oncol.* 22(5), 1189–1197 (2011).
24. Ray JA, Carr E, Lewis G, Marcus R. An evaluation of the cost-effectiveness of rituximab in combination with chemotherapy for the first-line treatment of follicular non-hodgkin's lymphoma in the UK. *Value Heal.* 13(4), 346–357 (2010).
25. Auweiler PWP, Miller D, Stock S, Gerber A. Cost effectiveness of rituximab for non-hodgkins lymphoma: a systematic review. *Pharmacoeconomics* (2012). <https://pubmed.ncbi.nlm.nih.gov/22612993/>
26. Hirayama Y, Ishitani K, Ota S *et al.* Long-term survey of survival time, histological transformation and secondary malignancies in Japanese patients with advanced-stage follicular lymphoma in the rituximab era: Hokkaido Hematology Study Group. *Int. J. Hematol.* 100(3), 281–289 (2014).
27. Monga N, Nastoupil L, Garside J *et al.* Burden of illness of follicular lymphoma and marginal zone lymphoma. *Ann. Hematol.* 98(1), 175–183 (2019).
28. Morrison VA, Bell JA, Hamilton L *et al.* Economic burden of patients with diffuse large B-cell and follicular lymphoma treated in the USA. *Futur. Oncol.* 14(25), 2627–2642 (2018).
- **Reports economic burden of Follicular lymphoma treatments in USA.**
29. Beveridge R, Satram-Hoang S, Sail K *et al.* Economic impact of disease progression in follicular non-Hodgkin lymphoma. *Leuk. Lymphoma* 52(11), 2117–2123 (2011).
- **Reports the burden of disease progression of follicular lymphoma patients.**