ABOUT THE AUTHOR

Roopesh Kansara, MD, FRCPC

Dr. Roopesh Kansara is a staff Hematologist within the Department of Internal medicine, University of Manitoba. He is appointed as an assistant professor and is also the Program Director for Adult Hematology subspecialty program at the University of Manitoba. He pursued his Medicine and Hematology subspecialty training at the University of Manitoba followed by further training in Lymphoproliferative disorders at the British Columbia Cancer Agency (Vancouver). He treats both malignant and benign hematologic disorders but with special focus on Lymphoproliferative neoplasms especially CNS B-cell lymphomas.

MANAGEMENT OF FOLLICULAR LYMPHOMA AT FIRST RELAPSE

Follicular lymphoma (FL) is the most common subtype of indolent B-cell non-Hodgkin's lymphoma (NHL). Histologically, it is subcategorized as grade 1, 2, 3A or 3B[1]. FL, grade 3B is considered an aggressive form of the disease and is managed similar to diffuse large B-cell lymphoma (DLBCL). The intent of this article is to discuss the management of FL at first relapse. However, the knowledge of upfront management strategy is crucial in planning treatment in the event of a relapse.

FL lymphoma is an incurable disease except for small subset patients with limited stage disease (Stage I/II); with local radiotherapy, these patients may attain a 50 to 70% chance of cure[2]. For those with advanced stage disease (Stage III/IV), upfront management strategies include a wait and watch (WW) approach[3–6], monotherapy with rituximab[7] or a combination of anti-CD20 monoclonal antibodies and systemic chemotherapy/oral agents. WW and monotherapy with rituximab are typically pursued for patients with stage III/IV (including extensive limited stage not amenable to radiation) who are asymptomatic and do not meet criteria for treatment.

For patients meeting the indications for upfront treatment, several options are available that combine anti-CD20 monoclonal antibodies with either systemic chemotherapy or oral agents (lenalidomide). R-CHOP (rituximab, cyclophosphamide, vincristine, prednisone)[8], R-CVP (rituximab, cyclophosphamide, vincristine, prednisone)[9] and R-FM (rituximab, fludarabine, mitoxantrone)[10] have been widely used for upfront management of FL. Both R-CHOP and R-FM have demonstrated similar outcomes but superior 3-year progression free survival (PFS) and time to treatment failure (TTF) compared to R-CVP[11]. Trials comparing bendamustine and rituximab (BR) to R-CHOP and/or R-CVP show superior PFS and lesser toxicities with the BR[12,13] regimen. Therefore, BR is, the most preferred choice for upfront treatment of patients with FL, grades 1 to 2. Some centers have extrapolated the results of the STiL and BRIGHT trials to include FL, grade 3A (who were excluded in both of these studies) whereas some offer R-CHOP therapy to this subset of patients. The current body of data does not support upfront stem cell transplantation (SCT) following induction chemo-immunotherapy[14]. Instead, following upfront systemic therapy, maintenance rituximab (MR) is pursued for patients who attain a complete response (CR) or partial (PR) response to induction therapy based on improved PFS[15]. It should be noted that there are currently no definitive studies demonstrating an OS benefit with MR and there is a paucity of prospective data to support the use of MR versus observation following BR, however several retrospective studies support MR following BR[16].

The management of patients with untreated FL continues to evolve. In a multicenter, international, phase 3 superiority trial to evaluate rituximab plus lenalidomide, as compared with rituximab plus chemotherapy, in patients with previously untreated follicular lymphoma, patients were randomly assigned to receive one of the two regimens, followed by maintenance monotherapy with rituximab. Lenalidomide plus rituximab (R2) when compared to R-chemotherapy (BR,

R-CHOP, R-CVP) showed similar 3-year PFS between the two groups with the interim 3-year rate of progression-free survival being 77% (95% CI, 72 to 80) and 78% (95% CI, 74 to 82), in the R2 group compared with the R-chemotherapy group[17] making a new chemo-free treatment option available for patients with FL, grades 1 to 3A (**Table 1)**. This R2 regimen has not been approved for frontline use as the trial was not powered to show non-inferiority.

A novel anti-CD20 monoclonal antibody, obinutuzumab (O), is now available in the first-line management of FL. A study from 2017 compared O-chemotherapy (BO, O-CHOP, O-CVP) followed by O-maintenance (MO) to R-chemotherapy (BR, R-CHOP, R-CVP) followed by MR in treatment of FL, grades 1-3A and demonstrated a significantly better 3-year PFS in the O-chemotherapy group with the estimated 3-year rate of progression-free survival at 80.0% in the O-chemotherapy group compared with 73.3% in the R-chemotherapy group (hazard ratio for progression, relapse, or death, 0.66; 95% confidence interval [CI], 0.51 to 0.85; P=0.001)[18]. Lenalidomide with obinutuzumab (GALEN) also appears to show efficacy in an upfront setting[19].

Variable	Rituximab-Lenalidomide Group (N= 513)	Rituximab-Chemotherapy Group (N=517)	Hazard Ratio (95%= CI)	P Value
Response status at 120 weeks, as assessed by independent review committee				
Overall response - no. (% [95% CI])	312 (61 [56-65])	336 (65 [61-69])		
Confirmed or unconfirmed complete response - no. (%[95% CI])	247 (48 [44-53])	274 (53 [49-57])		0.13
Complete response, confirmed - no. (%)	142(28)	169 (33)		
Complete response, unconfirmed - no. (%)	105 (20)	105 (20)		
Partial response - no. (%)	65 (13)	62 (12)		
Stable disease - no. (%)	2(<1)	0		
Progressive disease or death - no. (%)*	87 (17)	79 (15)		
Not evaluated or data missing - no. (%)	112 (22)	102(20)		
Response status at 120 weeks, as assessed by investigator				
Overall response - no. (% [95% CI])	335 (65 [61-69])	353 (68 [64-72])		
Confirmed or unconfirmed complete response - no. (%[95% CI)	283 (55 [51-60])	299 (58 [53-62])		0.38
Complete response, confirmed - no. (%)	201 (39)	242(47)		
Complete response, unconfirmed - no. (%)	82(16)	57(11)		
Partial response - no. (%)	52(10)	54(10)		
Stable disease - no. (%)	0	0		
Progressive disease or death - no. (%)*	90(18)	94(18)		
Not evaluated or missing -no. (%)	88(17)	70(14)		
Progression-free survival at 3 years				
Rate, as assessed by independent review committee - %(95% CI)	77(72-80)	78(74-82)	1.10 (0.85-1.43)	0.48
Rate, as assessed by investigator - % (95% CI)	77 (72-80)	78(74-81)	0.94 (0.73-1.22)	0.63
Overall survival rate at 3 years - % (95% CI)	94(91-96)	94(91-96)	1.16 (0.72-1.861	

Table 1. *Efficacy (Intention-to-Treat Population); adapted from Morschhauser F, 2018.*

Treatment at first relapse is determined by numerous factors including the patient's age, performance status, evidence of histologic transformation, first-line approach, type of monoclonal antibody received, whether a maintenance regimen was pursued and the time to first relapse. Among these variables, age and performance status allow for an assessment of eligibility for high dose systemic therapy/ SCT following second-line treatment. The time to relapse is also a critical determinant as patients who relapse within 2 years of initial therapy tend to have poorer overall outcomes requiring the consideration of more aggressive salvage therapies[20,21].

Alternate combination chemotherapy is usually the treatment of choice at relapse. Bendamustine as a second-line treatment option for patients without prior exposure to bendamustine may be considered provided there is no histologic transformation. In a study from 2010, 161 patients were enrolled with a median of 2 previous chemotherapy regimens. Histologies included follicular (68%), small lymphocytic (20%), marginal zone (11%), and lymphoplasmacytic (1%) lymphoma. Sixty patients (34.1%) were refractory to their last chemotherapy, 53 (30.1%) were alkylating agent refractory. The overall response rate (ORR) was 76% with a median 10-month duration of response[22]. Considering monoclonal antibodies are widely available, bendamustine can be combined with rituximab (if not refractory) or obinituzumab (if refractory to rituximab). The use of BR in the treatment of patients with relapsed indolent or mantle cell lymphoma (excluding rituximab refractory patients) produced superior median PFS with BR compared to fludarabine-rituximab (FR) (54.5 months versus 22.9 months, respectively, p= 0.01)[23]. For patients who are rituximab-refractory, bendamustine may be combined with obinutuzumab (BO) based on the outcomes seen in the GADOLIN trial that included patients with indolent B-cell NHL, including FL, grades 1 to 3A[24]. In this study, patients were randomized to receive either BO followed by MO or to bendamustine monotherapy. After a median observation time of 32.6 months (range 0.4 to 65.9) in the obinutuzumab plus bendamustine group and 29.3 months (0 to 65.1) in the bendamustine monotherapy group, progression-free survival was significantly longer with obinutuzumab plus bendamustine (median 25.3 [95% CI 17.4 - 36 months) than with bendamustine monotherapy (14 months [11.3-15.3]; hazard ratio 0.52 [95% CI 0.39-0.69]; p=0.0001). It also showed an OS benefit in the obinutuzumab-arm (Not estimate able versus 53.9 months, p= 0.0061)[24]. Another study recently compared the efficacy of bendamustine in combination with ofatumumab, a second generation anti-CD20 antibody, to bendamustine monotherapy in patients with rituximab-refractory indolent NHL (including FL, grades 1-3A)[25]. Unlike the results seen in the GADOLIN trial, this study showed no benefit to the addition ofatumumab to bendamustine with median IRC-assessed PFS at 16.7 and 13.8 months in the combination and monotherapy arms respectively [hazard ratio (HR) = 0.82; P = 0.1390]. Additionally, the median overall survival (OS) was 58.2 and 51.8 months in the combination and monotherapy arms respectively (HR = 0.89, P = 0.4968). For patients who had already received BR as initial therapy but were not refractory, retreatment with BR may be a reasonable approach at the time of first relapse. Both the StilNHL2 and GADOLIN trials allowed retreatment with bendamustine in the relapse setting if patients were deemed to have been responsive to bendamustine. However, further research is needed to better understand the cumulative long-term effects of re-exposure to bendamustine, and as a result, retreatment is rare.

Given that many patients may have received first-line BR followed by MR, many clinicians choose alternate second-line options such as CHOP, CVP or lenalidomide in combination with rituximab or obinutuzumab (depending on rituximab-refractory status). A small phase II study showed a median time to progression of approximately 47 months for patients with relapsed FL treated with RCHOP[26]. The CALGB 50401 trial comparing lenalidomide with rituximab (LR) to lenalidomide alone (L) showed that LR produced a superior median time to progression (TTP) compared to L alone (2 years versus 1.1 years, respectively)[27]. The same group published results from the AUGMENT trial in which patients with recurrent iNHL (including FL, grades 1 to 3A) were randomized to either the LR arm or the placebo-rituximab arm. The results from this study showed superior PFS in the LR arm compared to the placebo-rituximab arm (**Figure 1**) with a secondary analysis showing favorable OS for FL patients who received LR (hazard ratio 0.45, p= 0.02)[28]. It should be noted that this subgroup analysis was not powered to assess definite OS benefit. Lenalidomide-based combinations have not yet received regulatory approval from Health Canada.

Lenalidomide in combination with obinutuzumab (LO) has also been studied in patients with recurrent FL, grades 1 to 3A. A phase II trial treated recurrent FL patients with LO followed by 1 year of L and 2 years of MO and showed an ORR at the end of induction in the 86 evaluable patients of 79% (95% CI 69–87) with 38% of subjects achieving a CR (95% CI 28–50)[29].

In the event of evident transformed relapsed FL, a CHOP regimen (with R) would be standard for DLBCL[30–32] histology and dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)

(with R) may be used if the histology shows high-grade B-cell lymphoma with double or triple hit gene rearrangements[33]. Management of these patients however becomes challenging if the patients experience transformed FL after initial treatment with R-CHOP. In this scenario such patients may be managed with salvage combination agents utilized in the management of DLBCL such as GDP (gemcitabine, dexamethasone, cisplatin)[34], ICE (ifosfamide, carboplatin, etoposide)[35], DHAP (dexamethasone, high dose cytarabine, cisplatin)[34,35] with or without monoclonal antibodies. In patients who have experienced transformed FL after initial treatment with R-CHOP, salvage therapy followed by ASCT may be considered.

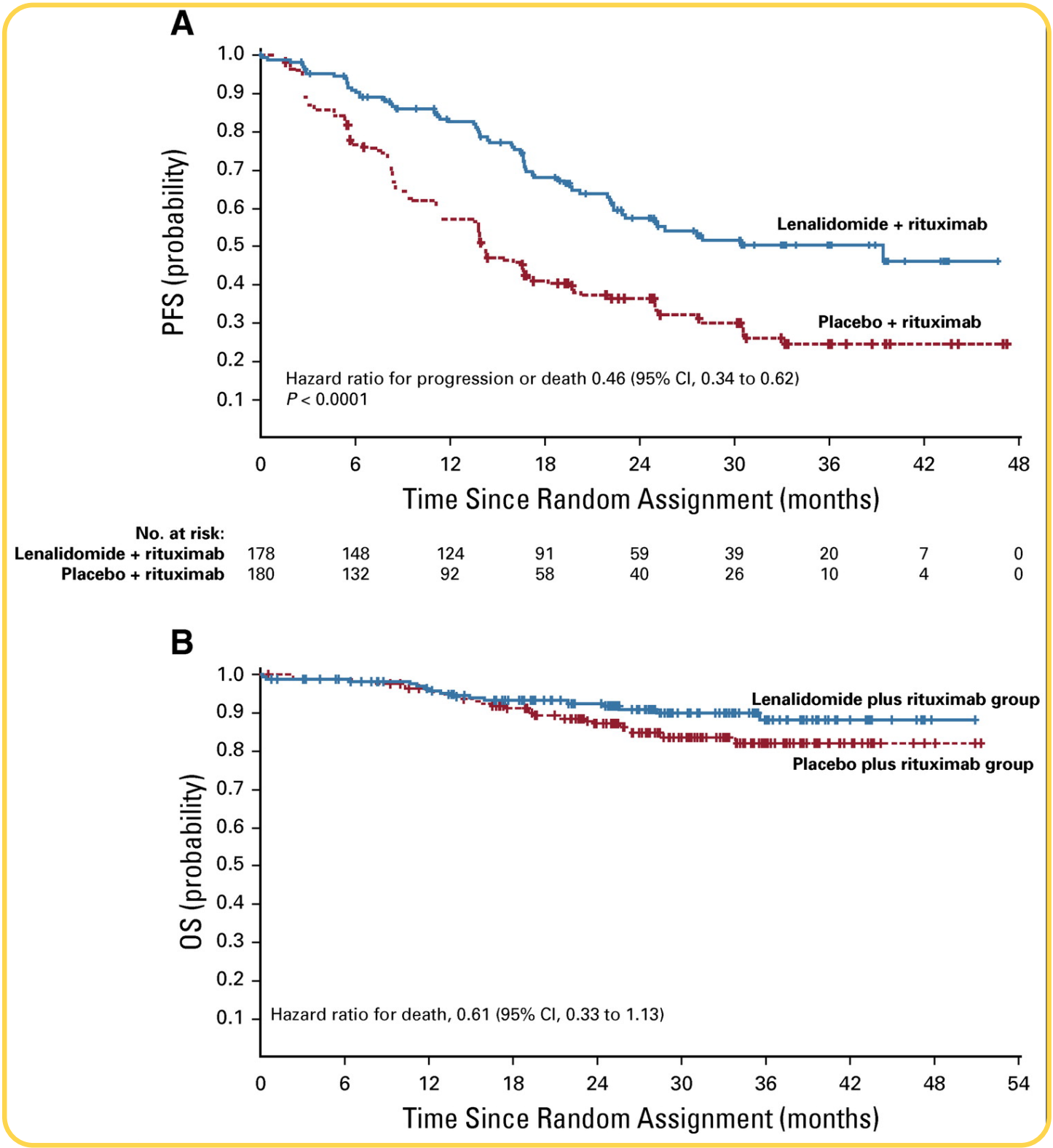

Figure 1. *Progression-free survival (PFS) and overall survival (OS) as assessed by independent review committee in the intention-to-treat population: (A) progression-free survival; (B) overall survival. Adapted from Leonard, JP et al, 2019*

Following systemic second-line chemo-immunotherapy, further consolidative strategies may be pursued such as SCT or maintenance therapy if patients are deemed to be eligible. If patients are candidates for stem cell transplant therapy, then autologous stem cell transplant (ASCT) or allogeneic stem cell transplant (alloSCT) is considered--especially for those with early relapse. The CUP trial demonstrated significant improvement in PFS and OS for patients who received ASCT compared to chemotherapy alone[36]. The benefit of ASCT was also demonstrated at first relapse in both rituximab-naïve and rituximab re-treated patients[37] in the GELA/GOELAMS FL2000 study which showed a 3-year OS of 92% (95%CI 78-97%) versus 63% (95%CI 51-72%) (P=0.0003), for those that received ASCT versus chemotherapy alone. There is also retrospective evidence demonstrating a survival benefit with early transplant in patients with early treatment failure[38–40]. It should be noted that the benefit of ASCT in the modern era is unclear and there may be varied practices across different centers. In our center we pursue ASCT following second-line therapy at first relapse especially for patients who relapsed within 24 months of first-line treatment. AlloSCT can offer a potential cure due to its graft versus lymphoma (GVL) effect however only few patients would be eligible. Several studies have demonstrated a benefit to alloSCT over ASCT but with higher transplant related mortality (TRM)[41–43]. For patients with early treatment failure both ASCT and matched sibling alloSCT produce a similar 5-year OS (~70%) but with a higher rate of TRM in the alloSCTgroup[44]. The role of alloSCT even in a few select young patients with refractory/relapsed FL, is unclear in the modern era of emerging therapeutic agents. The optimal transplant strategy thus continues to remain unclear.

For patients who are not transplant candidates, maintenance therapy with monoclonal antibodies following salvage chemo-immunotherapy is recommended if maintenance has not been previously given or was administered using a different monoclonal antibody. Maintenance should also be considered post-ASCT if warranted. MR following (R)-salvage therapy in patients with relapsed/refractory FL significantly improved PFS[15]. Even though evidence is lacking on the utility of MR post-ASCT, a recent consensus publication on maintenance therapy after ASCT recommended post-autologous maintenance rituximab for chemo-sensitive, rituximab-naïve patients with FL at relapse[45]. Clinicians may consider the use of MO in patients who received O-chemotherapy followed by ASCT for rituximab refractory FL patients. However, there are no prospective trials to inform this potential therapeutic approach, nor any evidence about potential post-SCT toxicities.

The management at first relapse will continue to evolve as more and more novel therapies are studied in a first relapse setting. Novel chimeric antigen receptor T-cell therapy (CAR-T) is showing promising results in patients with relapsed FL[46]. Additionally, data is also beginning to emerge on the use of bispecific antibodies in FL[47]. In the end, the management of FL at first relapse will undoubtedly consider advances in management strategies as clinicians continue to strive for optimal outcomes for their relapsed FL patients.

References

1. Swerdlow SH, Campo E, Harris NL. WHO Classification of Tumors. Vol 2. WHO Press

2. Brady JL, Binkley MS, Hajj C, et al. Definitive radiotherapy for localized follicular lymphoma staged by 18F-FDG PET-CT: a collaborative study by ILROG. Blood. 2019;133(3):237-245. doi:10.1182/blood-2018-04-843540

3. El-Galaly TC, Bilgrau AE, de Nully Brown P, et al. A population-based study of prognosis in advanced stage follicular lymphoma managed by watch and wait. Br J Haematol. 2015;169(3):435-444. doi:10.1111/bjh.13316

4. Solal-Céligny P, Bellei M, Marcheselli L, et al. Watchful waiting in low-tumor burden follicular lymphoma in the rituximab era: results of an F2-study database. J Clin Oncol. 2012;30(31):3848-3853. doi:10.1200/JCO.2010.33.4474

5. Ardeshna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet. 2003;362(9383):516-522. doi:10.1016/s0140-6736(03)14110-4

6. Advani R, Rosenberg SA, Horning SJ. Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. J Clin Oncol. 2004;22(8):1454-1459. doi:10.1200/JCO.2004.10.086

7. Ardeshna KM, Qian W, Smith P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncol. 2014;15(4):424-435. doi:10.1016/S1470-2045(14)70027-0

8. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2005;106(12):3725-3732. doi:10.1182/blood-2005-01-0016

9. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol. 2008;26(28):4579-4586. doi:10.1200/JCO.2007.13.5376

10. Federico M, Luminari S, Dondi A, et al. R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. J Clin Oncol. 2013;31(12):1506-1513. doi:10.1200/JCO.2012.45.0866

11. Luminari S, Ferrari A, Manni M, et al. Long-Term Results of the FOLL05 Trial Comparing R-CVP Versus R-CHOP Versus R-FM for the Initial Treatment of Patients With Advanced-Stage Symptomatic Follicular Lymphoma. J Clin Oncol. 2018;36(7):689-696. doi:10.1200/JCO.2017.74.1652

12. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014;123(19):2944-2952. doi:10.1182/blood-2013-11-531327

13. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381(9873):1203-1210. doi:10.1016/S0140-6736(12)61763-2

14. Bruna R, Benedetti F, Boccomini C, et al. Prolonged survival in the absence of disease-recurrence in advanced-stage follicular lymphoma following chemo-immunotherapy: 13-year update of the prospective, multicenter randomized GITMO-IIL trial. Haematologica. 2019;104(11):2241-2248. doi:10.3324/haematol.2018.209932

15. Vidal L, Gafter-Gvili A, Salles G, et al. Rituximab maintenance improves overall survival of patients with follicular lymphoma-Individual patient data meta-analysis. Eur J Cancer. 2017;76:216-225. doi:10.1016/j.ejca.2017.01.021

16. Roschewski M, Hill BT. One Size Does Not Fit All: Who Benefits From Maintenance After Frontline Therapy for Follicular Lymphoma? Am Soc Clin Oncol Educ Book. 2019;39:467-476. doi:10.1200/EDBK_239065

17. Morschhauser F, Fowler NH, Feugier P, et al. Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma. N Engl J Med. 2018;379(10):934-947. doi:10.1056/NEJMoa1805104

18. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med. 2017;377(14):1331-1344. doi:10.1056/NEJMoa1614598

19. Bachy E, Houot R, Feugier P, et al. Obinutuzumab plus lenalidomide (GALEN) in advanced, previously untreated follicular lymphoma in need of systemic therapy. Blood. Published online December 22, 2021:blood.2021013526. doi:10.1182/blood.2021013526

20. Maurer MJ, Bachy E, Ghesquières H, et al. Early event status informs subsequent outcome in newly diagnosed follicular lymphoma. Am J Hematol. 2016;91(11):1096-1101. doi:10.1002/ajh.24492

21. Casulo C, Byrtek M, Dawson KL, et al. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. J Clin Oncol. 2015;33(23):2516-2522. doi:10.1200/JCO.2014.59.7534

22. Cheson BD, Friedberg JW, Kahl BS, Van der Jagt RH, Tremmel L. Bendamustine produces durable responses with an acceptable safety profile in patients with rituximab-refractory indolent non-Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk. 2010;10(6):452-457. doi:10.3816/CLML.2010.n.079

23. Rummel M, Kaiser U, Balser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial. Lancet Oncol. 2016;17(1):57-66. doi:10.1016/S1470-2045(15)00447-7

24. Cheson BD, Chua N, Mayer J, et al. Overall Survival Benefit in Patients With Rituximab-Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study. J Clin Oncol. 2018;36(22):2259-2266. doi:10.1200/JCO.2017.76.3656

25. Rummel MJ, Janssens A, MacDonald D, et al. A phase 3, randomized study of ofatumumab combined with bendamustine in rituximab-refractory iNHL (COMPLEMENT A + B study). Br J Haematol. 2021;193(6):1123-1133. doi:10.1111/bjh.17420

26. Czuczman MS, Weaver R, Alkuzweny B, Berlfein J, Grillo-López AJ. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J Clin Oncol. 2004;22(23):4711-4716. doi:10.1200/JCO.2004.04.020

27. Leonard JP, Jung SH, Johnson J, et al. Randomized Trial of Lenalidomide Alone Versus Lenalidomide Plus Rituximab in Patients With Recurrent Follicular Lymphoma: CALGB 50401 (Alliance). J Clin Oncol. 2015;33(31):3635-3640. doi:10.1200/JCO.2014.59.9258

28. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. J Clin Oncol. 2019;37(14):1188-1199. doi:10.1200/JCO.19.00010

29. Morschhauser F, Le Gouill S, Feugier P, et al. Obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma (GALEN): a multicentre, single-arm, phase 2 study. Lancet Haematol. 2019;6(8):e429-e437. doi:10.1016/S2352-3026(19)30089-4

30. Pfreundschuh M, Kuhnt E, Trümper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol. 2011;12(11):1013-1022. doi:10.1016/S1470-2045(11)70235-2

31. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol. 2008;9(2):105-116. doi:10.1016/S1470-2045(08)70002-0

32. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol. 2006;24(19):3121-3127. doi:10.1200/JCO.2005.05.1003

33. Dunleavy K, Fanale MA, Abramson JS, et al. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. Lancet Haematol. 2018;5(12):e609-e617. doi:10.1016/S2352-3026(18)30177-7

34. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014;32(31):3490-3496. doi:10.1200/JCO.2013.53.9593

35. Hagberg H, Gisselbrecht C, CORAL study group. Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study. Ann Oncol. 2006;17 Suppl 4:iv31-32. doi:10.1093/annonc/mdj996

36. Schouten HC, Kvaloy S, Sydes M, Qian W, Fayers PM. The CUP trial: a randomized study analyzing the efficacy of high dose therapy and purging in low-grade non-Hodgkin's lymphoma (NHL). Ann Oncol. 2000;11 Suppl 1:91-94.

37. Le Gouill S, De Guibert S, Planche L, et al. Impact of the use of autologous stem cell transplantation at first relapse both in naive and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study. Haematologica. 2011;96(8):1128-1135. doi:10.3324/haematol.2010.030320

38. Manna M, Lee-Ying R, Davies G, et al. Autologous transplantation improves survival rates for follicular lymphoma patients who relapse within two years of chemoimmunotherapy: a multi-center retrospective analysis of consecutively treated patients in the real world. Leuk Lymphoma. 2019;60(1):133-141. doi:10.1080/10428194.2018.1473576

39. Casulo C, Friedberg JW, Ahn KW, et al. Autologous Transplantation in Follicular Lymphoma with Early Therapy Failure: A National LymphoCare Study and Center for International Blood and Marrow Transplant Research Analysis. Biol Blood Marrow Transplant. 2018;24(6):1163-1171. doi:10.1016/j.bbmt.2017.12.771

40. Jurinovic V, Metzner B, Pfreundschuh M, et al. Autologous Stem Cell Transplantation for Patients with Early Progression of Follicular Lymphoma: A Follow-Up Study of 2 Randomized Trials from the German Low Grade Lymphoma Study Group. Biol Blood Marrow Transplant. 2018;24(6):1172-1179. doi:10.1016/j.bbmt.2018.03.022

41. Khouri IF, Milton DR, Gulbis AM, et al. Nine-Year Follow-up of Patients with Relapsed Follicular Lymphoma after Nonmyeloablative Allogeneic Stem Cell Transplant and Autologous Transplant. Clin Cancer Res. 2021;27(21):5847-5856. doi:10.1158/1078-0432.CCR-21-1377

42. Hosing C, Saliba RM, McLaughlin P, et al. Long-term results favor allogeneic over autologous hematopoietic stem cell transplantation in patients with refractory or recurrent indolent non-Hodgkin's lymphoma. Ann Oncol. 2003;14(5):737-744. doi:10.1093/annonc/mdg200

43. van Besien K, Loberiza FR, Bajorunaite R, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood. 2003;102(10):3521-3529. doi:10.1182/blood-2003-04-1205

44. Smith SM, Godfrey J, Ahn KW, et al. Autologous transplantation versus allogeneic transplantation in patients with follicular lymphoma experiencing early treatment failure. Cancer. 2018;124(12):2541-2551. doi:10.1002/cncr.31374

45. Kanate AS, Kumar A, Dreger P, et al. Maintenance Therapies for Hodgkin and Non-Hodgkin Lymphomas After Autologous Transplantation: A Consensus Project of ASBMT, CIBMTR, and the Lymphoma Working Party of EBMT. JAMA Oncol. 2019;5(5):715-722. doi:10.1001/jamaoncol.2018.6278

46. Hirayama AV, Gauthier J, Hay KA, et al. High rate of durable complete remission in follicular lymphoma after CD19 CAR-T cell immunotherapy. Blood. 2019;134(7):636-640. doi:10.1182/blood.2019000905

47. Assouline SE, Kim WS, Sehn LH, et al. Mosunetuzumab Shows Promising Efficacy in Patients with Multiply Relapsed Follicular Lymphoma: Updated Clinical Experience from a Phase I Dose-Escalation Trial. Blood. 2020;136:42-4