REVIEW

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# Advancements in the Management of Follicular Lymphoma: A Comprehensive Review

## Foliküler Lenfoma Yönetiminde Gelişmeler: Kapsamlı Bir Derleme

Reid Merryman[1], Özgür Mehtap[2], Ann LaCasce[1]

[1]*Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA*
[2]*Kocaeli University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Kocaeli, Türkiye*

## Abstract

Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin lymphoma in Western countries. While FL is generally incurable, standard initial therapies are associated with high response rates and durable remissions for most patients. In addition, novel targeted agents and immunotherapies are changing the treatment algorithm for patients with relapsed or refractory disease. This review discusses the initial staging, prognosis, and treatment options for newly diagnosed and relapsed/refractory FL. Initial treatment options for FL include active surveillance, radiotherapy, rituximab monotherapy, and chemoimmunotherapy. Staging with positron emission tomography/computed tomography and bone marrow biopsy is crucial for identifying early-stage patients. Most patients with FL will receive chemoimmunotherapy as the initial treatment with options including rituximab or obinutuzumab plus cyclophosphamide, vincristine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone; bendamustine; or lenalidomide. No significant differences in overall survival have been observed in randomized studies comparing these regimens. Maintenance therapy with rituximab or obinutuzumab in responders to initial chemoimmunotherapy improves progression-free survival. For relapsed/refractory FL, treatment options include chemoimmunotherapy, lenalidomide-based regimens, tazemetostat, chimeric antigen receptor (CAR)-T cell therapy (axicabtagene ciloleucel and tisagenlecleucel), and CD3/CD20 bispecific antibodies (BsAbs). Given the encouraging outcomes obtained with CAR-T cell therapy and BsAbs, multiple trials are testing these highly active agents in earlier lines of therapy and among high-risk patients with early relapse after frontline chemoimmunotherapy. Additional studies and follow-up are needed to understand how these novel agents may further change treatment algorithms for FL.

**Keywords:** Follicular lymphoma, Treatment management, Review

## Öz

Foliküler lenfoma (FL), Batı ülkelerindeki indolent non-Hodgkin lenfomanın en yaygın alt türüdür. FL genellikle tedavi edilemez olsa da, standart başlangıç tedavileri çoğu hastada yüksek yanıt oranları ve sürdürülebilir remisyonlarla ilişkilidir. Ayrıca, yeni hedefli ajanlar ve immünoterapiler, relaps veya refrakter hastalığı olan hastaların tedavi algoritmalarını değiştirmektedir. Bu derleme, yeni tanı konmuş ve relaps/refrakter FL için başlangıç evrelemesi, prognoz ve tedavi seçeneklerini tartışmaktadır. FL için başlangıç tedavi seçenekleri arasında aktif gözetim, radyoterapi, rituksimab monoterapisi ve kemoimmünoterapi yer almaktadır. Pozitron emisyon tomografisi/bilgisayarlı tomografi ve kemik iliği biyopsisi ile evreleme, erken evre hastaları tanılamak için kritiktir. FL hastalarının çoğu, rituksimab veya obinutuzumab ile birlikte siklofosfamid, vinkristin, prednizon, siklofosfamid, doksorubisin, vinkristin, prednizon, bendamustin veya lenalidomid gibi seçenekleri içeren kemoimmünoterapiyi başlangıç tedavisi olarak alacaktır. Bu rejimleri karşılaştıran randomize çalışmalarda genel sağkalımda önemli farklar gözlemlenmemiştir. Rituksimab veya obinutuzumab ile idame tedavisi, başlangıç kemoimmünoterapisine yanıt veren hastalarda progresyonsuz sağkalımı artırır. Relaps/refrakter FL için tedavi seçenekleri, kemoimmünoterapi, lenalidomide tabanlı rejimler, tazemetostat, kimerik antijen reseptörü (CAR)-T-hücre terapisi (aksikabtagen sileulesel ve tisagenlecleucel) ve CD3/CD20 bispesifik antikorlar (BsAb) içermektedir. CAR-T hücre tedavisi ve BsAb'lerle umut verici sonuçlar alındığından, bu yüksek etkili ajanların tedavi algoritmalarını FL'nin ön tedaviden sonraki erken relapsı olan yüksek riskli hastalarda test etmek için birçok çalışma yapılmaktadır. Bu yeni ajanların FL için tedavi algoritmalarını nasıl daha fazla değiştirebileceğini anlamak için ek çalışmalar ve takip gereklidir.

**Anahtar Sözcükler:** Foliküler lenfoma, Tedavi yönetimi, Derleme

**Address for Correspondence/Yazışma Adresi:** Özgür Mehtap, M.D., Kocaeli University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Kocaeli, Türkiye
**Phone :** +90 262 303 70 03
**E-mail :** ozgurmehtap@gmail.com ORCID: orcid.org/0000-0002-5603-1178

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## Introduction

Follicular lymphoma (FL) represents the prevailing subtype among indolent lymphomas within Western nations, accounting for approximately 20%-30% of all non-Hodgkin lymphoma cases [1]. FL often manifests a protracted clinical course and is frequently diagnosed in advanced stages, with fewer than 10% of patients presenting at stage I-II upon diagnosis. Approximately 70% of patients have marrow involvement at diagnosis. In contrast to more aggressive lymphomas, the occurrence of B symptoms and elevated lactate dehydrogenase (LDH) levels is detected in fewer than 20% of patients [2].

FL arises within germinal centers and is characterized by the presence of t(14;18) translocation, which leads to aberrant BCL2 expression. Neoplastic cells express CD20, CD10, BCL2, and BCL6 by immunohistochemical staining. Histologically, FL is graded on a scale from 1 to 3, primarily based on the quantification of centroblasts. Grade 3 is further subclassified into A and B categories, with grade 3B being categorized and treated as diffuse large B-cell lymphoma (DLBCL). Typically, grade 1-2 FL exhibits an indolent clinical course. The outcome of patients with grade 3A disease is controversial, with some series demonstrating behavior similar to that of grade 1-2 and others suggesting a more aggressive course [3]. In the 5$^{th}$ classification of the World Health Organization, FL was divided into 3 groups: classic FL (cFL), follicular large B-cell lymphoma (FLBL), and FL with uncommon features [4]. The revised version of the World Health Organization's 5$^{th}$ classification no longer mandates grading given the unclear impact on clinical behavior; therefore, grade 1-3A disease is now classified as cFL [4]. Grade 3B FL is a distinct entity, typically lacking CD10 expression and t(14:18) [5], and it has a more aggressive clinical course. According to the World Health Organization, the subtype of FLBL is largely equivalent to FL grade 3B [4]. We will focus our discussion on cFL in this review.

Some uncommon FL subtypes are associated with unique presentations and clinical courses. FL with 1p36 deletion (typically in the absence of t[14;18] translocation) usually presents with diffuse follicular involvement, predominantly affecting the inguinal lymph nodes. Histologically, these cases primarily align with grade 1-2 structure and exhibit an indolent clinical course, thus warranting treatment in a manner similar to that for conventional FL [6]. Pediatric-type FL represents a distinct entity, frequently associated with localized head and neck lymph node involvement. Notably, these cases lack *BCL2* rearrangement and t(14;18) translocation, and they generally have a favorable prognosis [7].

FL is associated with a risk of transformation to DLBCL. In one large study, the risk of transformation within 5, 10, and 15 years was found to be 17%, 28%, and 37%, respectively [8]. At the time of transformation, patients often present with rapidly enlarging lymph nodes, elevated LDH levels, B symptoms, hypercalcemia, and extranodal involvement beyond the bone marrow. Biopsy is important to document transformation, and positron emission tomography (PET) imaging can be helpful in identifying sites to biopsy.

### Prognosis

The incorporation of rituximab into FL therapy has led to significant improvement in overall survival (OS), with an estimated 10-year survival rate of 80%. However, lymphoma-related mortality remains at 10% after a decade, likely reflecting histological transformation [9]. Multiple clinical scores have been established for prognostic assessment in FL, including the Follicular Lymphoma International Prognostic Index (FLIPI) and FLIPI-2 scores. The FLIPI-2 score is composed of 5 factors (age over 60 years, bone marrow involvement, hemoglobin levels below 12.0 g/dL, the largest diameter of the largest affected lymph node exceeding 6 cm, and serum β2-microglobulin [β2m] levels surpassing the upper limit of normal) and was specifically developed for patients receiving rituximab-based therapies while excluding patients on active surveillance [10,11]. Five-year progression-free survival (PFS) rates were 98%, 88%, and 77% for patients with low risk, intermediate risk, and high risk, respectively, based on the FLIPI-2 scoring system [11]. More recently, the m7-FLIPI score was devised to incorporate genomic alterations. Seven genes frequently mutated in FL (*EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP,* and *CARD11*) were identified as being of prognostic value in patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) or rituximab, cyclophosphamide, vincristine, and prednisone (RCVP). The 5-year failure-free survival rates were 77% for the low-risk group and 38% for the high-risk group [12]. However, the m7-FLIPI score lacks predictive utility in patients receiving bendamustine or obinutuzumab-based treatments, limiting its clinical applicability [13]. Another prognostic score comprising only 2 simple parameters (bone marrow involvement and β2m), called the PRIMA-Prognostic Index (PRIMA-PI), consists of 3 risk categories: high (β2m >3 mg/L), low (β2m ≤3 mg/L without bone marrow involvement), and intermediate (β2m ≤3 mg/L with bone marrow involvement). According to this index, 5-year PFS rates were found to be 69%, 55%, and 37% in the low-, intermediate-, and high-risk groups, respectively ($p<0.0001$) [14].

Numerous studies have evaluated the prognostic value of end-of-treatment PET, demonstrating its correlation with both PFS and OS in FL patients [15,16,17]. In one study of patients treated with RCHOP, those with negative end-of-treatment PET results achieved a 2-year OS rate of 100% in contrast to 88% in patients with positive PET/computed tomography (CT)

results [16]. Another study of 202 patients showed a 3-year PFS rate of 66% for those with negative PET/CT compared to 35% among PET-positive patients [17]. In addition to the prognostic importance of PET at the end of treatment, the relationship between total metabolic tumor volume (TMTV) calculated before treatment and PFS has been shown in some studies [18,19]. For FL patients enrolled in the FOLL12 trial, 5-year PFS was found to be significantly lower for patients with high versus low TMTV (60% vs. 75%, p<0.001) [18]. Similarly, in the RELEVANCE study, baseline TMTV was found to be predictive of PFS independently of the FLIPI score [19].

The most consistent predictor of OS in FL patients is progression of the disease within 24 months (POD-24) of initial therapy. After RCHOP treatment, the 5-year OS rate was 50% for patients experiencing early progression and 90% for those without early progression [20]. Transformation to aggressive lymphoma, which may be present at the time of initial therapy, contributes to poorer outcomes in patients with POD-24.

### Initial Therapy for Stage I/II FL

The initial treatment options for early-stage FL include active surveillance, radiotherapy, rituximab monotherapy, and chemoimmunotherapy. Importantly, no difference in survival has been observed among these treatment modalities in cases of early-stage disease.

Staging with PET/CT and bone marrow biopsy is important to identify early-stage patients before making treatment decisions [21]. Radiotherapy at doses of 24-30 Gy is a standard of care in early-stage FL with disease that can be targeted using a feasible radiotherapy field. The outcomes of patients with stage I disease are superior compared to stage II disease with estimated 5-year freedom from progression of 74.9% for stage I and 49.1% for localized stage II [22]. In the context of early-stage disease, 5-year and 10-year OS rates with radiotherapy are in the ranges of 82%-96% and 64%-83%, respectively [22,23,24,25,26,27,28,29]. The likelihood of disease recurrence after 10 years is low [23,25]. Tumor diameter is another significant factor influencing outcomes in patients receiving radiotherapy, with larger tumor sizes at the outset of radiotherapy associated with reduced PFS [24,25]. Although retrospective in nature, studies have indicated that the addition of rituximab to radiotherapy or chemotherapy with rituximab results in a notable improvement in PFS but has no discernible impact on OS [26,27,28,29,30].

Particularly in cases of non-contiguous stage II disease and other scenarios including abdominal disease, where radiotherapy may not be suitable, active surveillance, rituximab monotherapy, or chemoimmunotherapy are viable options [27,28,29]. Studies have shown that 7.5-year and 5-year OS are 100% with rituximab monotherapy in cases of early-stage disease [27,29]. On the other hand, the 7.5-year OS rate of 74% with chemoimmunotherapy shows that this treatment type is an option for this patient group [29]. In another study, the median PFS was not reached with chemoimmunotherapy after 57 months of follow-up [30].

Recent studies have also demonstrated that the "wait and watch" (W&W) strategy typically applied for patients with advanced-stage FL and low tumor burden can be extended to certain individuals with early-stage disease [29,30,31]. Advani et al. [31] reported 5-year and 10-year OS rates of 97% and 66%, respectively, for patients managed with the W&W approach.

In light of the collective data, radiotherapy emerges as a compelling choice for confirmed stage I disease. However, for other patients with early-stage FL, treatment decisions should be made on a case-by-case basis, taking into account various clinical factors and patient preferences [32].

### Initial Therapy for Advanced-Stage FL

For advanced-stage FL patients, immediate treatment decisions are often made based on tumor burden according to the criteria of the Groupe d'Etude des Lymphomes Folliculaires (GELF) (Table 1). Patients who meet one of the GELF criteria are considered to have high tumor burden. For asymptomatic patients with low tumor burden, the available evidence does not demonstrate the superiority of immediate treatment over active surveillance. The decision of when to treat patients with FL is subjective, as is the definition of low-burden disease [33].

### Active Surveillance

In a randomized phase III study with a median of 16 years of follow-up, chlorambucil did not impact OS compared to observation in asymptomatic patients [34]. Similarly, studies conducted with rituximab have concluded that asymptomatic patients can be safely observed without immediate treatment. In one prospective study, patients were randomized into 3 groups: follow-up without treatment, rituximab induction only, and rituximab induction plus maintenance. Three-year PFS was 60% (95% confidence interval [CI]: 49%-71%)

**Table 1. Criteria of the Groupe d'Etude des Lymphomes Folliculaires.**

| |
|---|
| Any mass of ≥7 cm in diameter |
| Involvement of ≥3 nodes, each ≥3 cm in diameter |
| Presence of B symptoms |
| Splenomegaly |
| Compression syndrome |
| Ascites or pleural effusion |
| Cytopenia |
| Leukemia (>5.0x$10^9$/L circulating malignant cells) |

in the rituximab induction group, which was significantly different from the other 2 arms with a hazard ratio of 0.53 (95% CI: 0.32-0.87, p=0.011) for the comparison between maintenance rituximab and rituximab induction and a hazard ratio of 0.55 (95% CI: 0.37-0.83, p=0.0034) for the comparison between rituximab induction and watchful waiting. However, there was no difference in 3-year OS rates (94%, 97%, and 96%, respectively) [35]. A retrospective study that included a majority of patients with low tumor burden (80%) found that the 5-year OS rates were similar for patients who did not receive treatment compared to those who received rituximab-based treatment [36]. A large retrospective analysis of 1754 patients showed no difference in PFS or OS following first- and second-line therapy in patients managed with active surveillance, rituximab monotherapy, or chemoimmunotherapy. Patients with grade 3 histology, anemia, elevated LDH, extranodal involvement, B symptoms, or performance status of ≥1 were more likely to have received chemoimmunotherapy [37]. The cumulative evidence presented in these studies strongly supports a W&W strategy as a favorable option for asymptomatic patients with low tumor burden.

In patients requiring treatment, the primary therapeutic approach typically involves combining chemotherapy with anti-CD20 therapy. Single-agent rituximab is also a reasonable therapeutic approach, particularly for patients with comorbidities or non-bulky disease and for those who prefer to delay or avoid exposure to cytotoxic chemotherapy. With regard to OS, no treatment approach demonstrates superiority over others. Therefore, the choice of initial therapy should be tailored based on individual patient factors.

### Chemoimmunotherapy

Initial chemoimmunotherapy options in FL (Table 2) include rituximab or obinutuzumab plus CVP, CHOP, bendamustine, or lenalidomide. None of the randomized studies comparing these regimens have demonstrated an improvement in OS, likely due to the availability of highly effective subsequent lines of therapy. However, RCHOP is associated with increased PFS compared to RCVP [38,39]. In a randomized study comparing RCHOP to bendamustine plus rituximab (BR) in the treatment of indolent B-cell lymphoma and mantle cell lymphoma, the median PFS with RCHOP was 31 months compared to 69 with BR (hazard ratio: 0.58, 95% CI: 0.44-0.74, p<0.0001) [40].

**Table 2. Treatments for patients with high tumor burdens.**

| Treatment [Ref.] | CRR/ORR (%) | Comment |
|---|---|---|
| RCVP vs. RCHOP vs. RFM [38,39] | RCVP 67/88<br>RCHOP 73/93<br>RFM 72/98 | - 3-year times to treatment failure were 46%, 62%, and 59% for the respective treatment groups<br>- 3-year PFS rates were 52%, 68%, and 63% (overall: p=0.011)<br>- 3-year OS was 95% for the whole series<br>- 8-year OS was 83% for the whole series<br>- RFM was significantly toxic<br>- Higher numbers of second malignancies with RFM<br>- Patients initially treated with RCVP had a higher risk of lymphoma progression compared to those receiving RCHOP |
| BR vs. RCHOP [40] | BR 40/93<br>RCHOP 30/91 | - With median follow-up of 45 months, median PFS was 69 months and 31 months (p<0.0001), respectively, for BR and RCHOP<br>- BR was associated with less neutropenia or fewer infections<br>- Secondary malignancy rate of 8% with BR and 9% with RCHOP<br>- 10-year OS of 71% and 66%, respectively, for BR and RCHOP |
| BR vs. RCHOP/RCVP [41,42] | BR 30/99<br>RCHOP/RCVP 25/94 | - Medians not reached for any of the time-to-event end points for either BR or RCHOP/RCVP<br>- PFS rates at 5 years were 65.5% in the BR and 55.8% in the RCHOP/RCVP group<br>- Difference in PFS was considered significant with a hazard ratio of 0.61<br>- Event-free survival and duration of response favored the BR regimen over RCHOP/RCVP<br>- OS was the same in both cohorts<br>- Higher rate of secondary malignancies with BR |
| R+Len vs. R+Chemo [43,44] | R+Len 48/61<br>R+Chemo 53/65 | - 6-year PFS was 60% and 59% for R+Len and R-Chemo, respectively<br>- 6-year OS was estimated to be 89% in both groups<br>- Median PFS and OS were not reached in either group<br>- Higher rates of grade 3 or 4 neutropenia and febrile neutropenia of any grade with R+Chemo<br>- Higher rates of grade 3 or 4 cutaneous reactions with R+Len<br>- R+Len was deemed an acceptable chemo-free alternative |

**Table 2. Continued.**

| Treatment [Ref.] | CRR/ORR (%) | Comment |
|---|---|---|
| O+Chemo vs. R+Chemo [45,46] | O+Chemo 19.5/88.5<br>R+Chemo 23.8/86.9 | - 7-year PFS was improved with O+Chemo (63.4%) versus R+Chemo (55.7%) (p=0.006)<br>- Time to the next line of treatment was improved with O+Chemo versus R+Chemo (hazard ratio: 0.71, p=0.001), and the proportion of patients who had not started their next treatment at 7 years was 74.1% and 65.4%, respectively<br>- Disease transformation was observed in 4.2% of patients with O+Chemo and 5.0% of patients with R+Chemo<br>- 7-year OS was similar in both arms at 88.5% with O+Chemo versus 87.2% with R+Chemo<br>- Incidence of serious adverse events was 48.9% with O+Chemo (28.2% and 24.4% during induction and maintenance, respectively) and 43.4% with R+Chemo (24.6% and 21.7%, respectively)<br>- Serious adverse events were much more common in patients who received bendamustine; it is important to be cautious during maintenance of O or R if patients receive bendamustine<br>- One of the important outcomes of the GALLIUM study was that O+Chemo reduced the risk of progression of the disease within 24 months by 34% compared to R+Chemo |

RCVP: Rituximab, cyclophosphamide, vincristine, and prednisone; RCHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RFM: rituximab, fludarabine, and mitoxantrone; BR: bendamustine plus rituximab; R: rituximab; Len: lenalidomide; O: obinutuzumab; Chemo: chemotherapy; CRR: complete response rate; ORR: overall response rate; PFS: progression-free survival; OS: overall survival.

In a study designed to show the superiority of lenalidomide plus rituximab over combination chemotherapy with the majority of patients receiving RCHOP, there was not a significant difference in PFS, with 6-year PFS being approximately 60% in both arms [43,44]. More recently, obinutuzumab plus chemotherapy was compared to rituximab plus chemotherapy, with all patients receiving maintenance therapy for 2 years. PFS at 7 years was 53% versus 57% in patients receiving obinutuzumab-containing regimens. Patients receiving bendamustine-containing regimens experienced higher rates of toxicity including infection during maintenance [45,46].

### Maintenance Therapy

Maintenance therapy with rituximab or obinutuzumab in patients responding to initial chemoimmunotherapy is associated with improved PFS, but it comes at the cost of increased toxicity in the form of delayed neutropenia and infection, and without evidence of superior OS [45,46,47,48,49]. In the PRIMA trial, FL patients who received chemoimmunotherapy followed by rituximab maintenance therapy achieved a median PFS of 10.5 years compared to 4.1 years in the observation arm (hazard ratio: 0.61, 95% CI: 0.52-0.73, p<0.001) [48]. In addition, a retrospective analysis of maintenance rituximab after BR in the BRIGHT study demonstrated a significant improvement in PFS with a trend towards improved OS [49]. In another study, the outcome of rituximab maintenance after BR treatment was examined retrospectively via real-world data. The authors of that study found that patients in complete remission did not exhibit an improved duration of response with rituximab maintenance compared to those who reached partial remission after ≥4 cycles of BR. The rates of 3-year duration of response for patients who achieved partial remission were 80% and 45% with and without rituximab maintenance, respectively [50]. Considering the retrospective nature of these studies, rituximab maintenance after BR treatment should be decided on a patient-by-patient basis. For patients who received obinutuzumab-based therapy during the induction phase, maintenance therapy with obinutuzumab for 2 years is also associated with improved PFS compared to rituximab [45].

### Single-Agent Rituximab

For patients with a lower burden of disease, comorbidities, or a preference of avoiding chemoimmunotherapy, single-agent rituximab is a reasonable therapeutic option. In a study that included both previously untreated and relapsed patients receiving rituximab for 4 weekly doses followed by an additional 4 doses of extended induction every 2 months, the treatment-naïve patients experienced median PFS of 6.6 years and 10-year PFS of 42% [51].

A recent study compared single-agent intravenous rituximab to the subcutaneous (SC) administration of rituximab in patients with low-burden FL. In both arms, patients received 4 weekly doses followed by extended induction with 4 doses every 2 months. Interestingly, SC administration was associated with improved PFS at 4 years of 58% versus 41% [52].

### Treatment of Relapsed/Refractory Disease

While frontline treatments for FL are associated with high response rates, most patients will eventually relapse. The time to relapse is an important prognostic marker. Approximately 20% of patients receiving frontline chemoimmunotherapy will progress within 24 months of the initial treatment (POD-24) and have inferior OS compared to other patients with FL [53]. Diagnostic confirmation at relapse to exclude transformation to an aggressive lymphoma is a critical consideration, particularly for patients with POD-24, who appear to be at higher risk of transformation [54].

There are multiple reasonable treatment options for relapsed/refractory FL. Asymptomatic patients can be managed with observation, similar to the frontline setting. Radiation is an appropriate treatment for selected patients with localized relapse or a single symptomatic site of recurrence. When systemic treatment is indicated, rituximab monotherapy or chemoimmunotherapy have been the historical standards. Rituximab retreatment is more likely to be effective among patients who had durable remissions with frontline therapy [55]. BR and RCHOP are the most commonly used chemoimmunotherapy regimens in the relapsed/refractory setting. For patients with rituximab-refractory disease, defined as no response to or progression following any rituximab-containing regimen within 6 months of the last rituximab dose, the use of obinutuzumab should be considered based on the phase III GADOLIN trial, which demonstrated improvement in OS with obinutuzumab-based chemoimmunotherapy [56]. Patients achieving complete or partial remission upon second-line or subsequent chemotherapy can be treated with rituximab therapy. In a phase III randomized trial involving patients with relapsed or resistant disease who responded to CHOP or RCHOP induction therapy, rituximab maintenance therapy significantly enhanced the median PFS compared to observation alone (4 years versus 1 year; $p<0.001$). After a median follow-up period of 6 years, the 5-year OS rate did not exhibit a statistically significant difference between the study arms, with rates of 74% and 64%, respectively [57]. In another study examining the efficacy of rituximab maintenance versus rituximab retreatment upon disease progression in patients with indolent lymphomas who had previously undergone chemotherapy (n=114), rituximab maintenance significantly extended the PFS compared to rituximab retreatment (31 months versus 7 months; $p=0.007$). However, despite the significant difference in PFS, the duration of benefit was similar between the treatment groups, with 31 months observed in the maintenance group and 27 months in the retreatment group [58]. Like rituximab, obinutuzumab can also be used for maintenance in relapsed/refractory patients. In the GADOLIN study, the implementation of obinutuzumab maintenance therapy subsequent to second-line treatment involving bendamustine plus obinutuzumab resulted in an enhancement of PFS among patients who had displayed refractoriness to rituximab [56].

### Stem Cell Transplantation

With the approval of multiple novel therapies, including chimeric antigen receptor (CAR)-T cells and bispecific antibodies (BsAbs), the use of stem cell transplantation has declined, particularly in countries where these newer agents are approved. Both autologous and reduced-intensity allogeneic stem cell transplantation have been used in relapsed/refractory settings. Consolidation in the second remission with autologous stem cell transplantation (ASCT) can also be considered for high-risk patients, such as those with POD-24. Two retrospective studies suggested an OS benefit for consolidative ASCT [59,60]; however, these studies were performed prior to the availability of many of the novel therapies to be discussed below. In a large retrospective study comparing the outcomes of 518 patients who were initially treated with rituximab-containing therapy between 2000 and 2012, autologous transplantation was associated with lower rates of non-relapse mortality but higher rates of relapse [61]. OS was improved with autologous transplant in the first 2 years, but allogeneic transplant resulted in superior survival and lower rates of secondary malignancies beyond 2 years [61]. For patients with chemotherapy-sensitive disease and adequate bone marrow reserve, ASCT may lead to durable disease control in a subset of patients. Allogeneic transplantation remains a therapeutic option for patients who have relapsed after the administration of CAR-T or other novel agents or in settings where these agents are not available.

The treatment of relapsed/refractory FL is rapidly changing with approval being granted for multiple novel targeted and immunotherapy agents.

### Novel Agents in Relapsed/Refractory Follicular Lymphoma

### Lenalidomide

Lenalidomide is an immunomodulatory agent that has multiple mechanisms of action including inducing changes in T-cell subsets and functions by reducing regulatory T-cells and activating CD8-positive cells [62]. As a single agent in relapsed/refractory FL, lenalidomide was associated with an overall response rate (ORR) of 27% and complete response rate (CRR) of 9%, with median PFS of 4.4 months in a small phase II study [63]. In combination with rituximab, responses are improved with ORRs of 65%-78% and CRRs of approximately 35%-40% [64,65]. In addition, the GALEN study tested lenalidomide plus obinutuzumab for 1 year, followed by maintenance lenalidomide for 1 year and obinutuzumab for 2 years [66]. The ORR and CRR were 79% and 38% with 2-year PFS of 65%.

The AUGMENT randomized phase III study established rituximab plus lenalidomide as a standard second-line approach in FL. In that study, 358 patients with FL (82%) or marginal zone lymphoma (MZL) (18%) received rituximab once weekly for 4 doses during cycle 1 followed by day 1 in cycles 2-5 in combination with lenalidomide (20 mg on days 1-21 of a 28-day cycle) or a placebo for 12 cycles. The median PFS strongly favored the lenalidomide arm at 39.4 versus 14.1 months. In terms of toxicity, leukopenia, rash, and infection were more common in the lenalidomide arm [67].

### Tazemetostat

*EZH2* is an epigenetic modifier that is important in the germinal center reaction. Approximately 20% of cases of FL harbor gain-of-function mutations in *EZH2*. Tazemetostat is an oral *EZH2* inhibitor tested in patients with relapsed/refractory FL in a multicenter phase II study. In the *EZH2*-mutated cohort (n=45), which included patients who had received a median of 2 prior lines of therapy, the ORR and CRR were 69% and 13%, respectively. In the *EZH2* wild-type group (n=54), patients had received a median of 3 prior lines of therapy, and they achieved ORR and CRR of 35% and 4%, respectively. Interestingly, the median PFS in the 2 groups was similar at 13.8 versus 11.1 months. High-grade cytopenia was rare and the serious adverse event rate was 4% [68].

Tazemetostat is a reasonable option for patients with non-bulky disease or those who are not candidates for more aggressive therapy. Given the drug's favorable toxicity profile, it is currently being studied in combination with other novel agents.

### PI3 Kinase Inhibitors

The PI3 kinase inhibitors idelalisib, which targets the delta isoform, and duvelisib, which targets the gamma and delta isoforms, were voluntarily withdrawn from the market in 2021 given safety concerns that arose in the long-term follow-up of clinical trials in patients with chronic lymphocytic leukemia. The contribution of these agents to excessive mortality is not clear, given the impact of subsequent lines of therapy, as well as COVID-19 infection. However, both agents have been associated with colitis and risk of infection. Their original approvals in FL were based on phase II studies that demonstrated ORR and CRR of 57% and 14% for idelalisib and 42% and 1% for duvelisib [69,70]. The median PFS rates were 11.8 and 9.5 months, respectively.

The only remaining drug in this class is copanlisib, a pan-PI3 kinase inhibitor, which unlike idelalisib and duvelisib is administered intravenously. In terms of efficacy, the ORR in a phase II study was 60% with a median PFS of 12.5 months [71]. The major toxicities of this agent are hypertension and hyperglycemia, which are typically managed with calcium channel blockers and metformin. For patients without diabetes or uncontrolled hypertension, copanlisib is generally well tolerated and it is an option for patients who can manage the frequency of infusions (weekly for 3 weeks with a 1-week break).

### Bruton Tyrosine Kinase Inhibitors

As single-agent therapy for relapsed/refractory FL, ibrutinib was associated with a disappointing ORR of 37.5% and CRR of 12.5% [72]. The median PFS was 14 months and the 2-year PFS rate was 20.4%. In combination with rituximab, however, the 30-month PFS was 67% [73]. In the recently published randomized phase II ROSEWOOD study, 217 patients received either obinutuzumab monotherapy or obinutuzumab plus zanubrutinib [74]. The ORR was 46% versus 69% with CRR of 19% versus 39%, respectively. The median PFS was 10.4 and 28 months, respectively. Rates of major bleeding and atrial fibrillation in the combination arm were low at 3% and 1%. Based on these results, the phase III MAHOGANY trial is now comparing zanubrutinib and obinutuzumab to lenalidomide and rituximab in patients with relapsed/refractory FL or MZL.

## Immunotherapies: CAR-T Cell Therapy and Bispecific Antibodies

Novel forms of immunotherapy are quickly changing the treatment landscape of relapsed/refractory FL. In the past 3 years, the Food and Drug Administration (FDA) approved 2 CD19 CAR-T cell products: axicabtagene ciloleucel (axi-cel) and tisagenlecleucel. In addition, the first CD3/CD20 BsAb, mosunetuzumab, was approved for FL earlier this year. Additional approvals for CAR-T cells and BsAbs in FL are expected soon, and numerous clinical trials are underway to determine the optimal treatment settings and strategies for the best use of these highly effective drugs.

### CAR-T Cell Therapies

While the initial FDA approvals for CD19-directed CAR-T cells were issued for patients with DLBCL, the ORRs among patients with FL have been consistently higher than those seen in DLBCL or other B-cell non-Hodgkin lymphomas. In addition, the rates of high-grade cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) also appear to be lower in FL [75,76,77,78,79]. ZUMA-5 was a phase II trial testing axi-cel in patients with either FL or MZL who had relapsed after 2 or more prior lines of therapy including a CD20 mAb and an alkylator. Among 124 patients with FL, the overall and complete metabolic response (CMR) rates were 92% and 77%, respectively [76]. CRS was observed in 78% of the patients, but grade 3+ CRS only occurred in 6%. ICANS was also observed frequently, but it was primarily low-grade (any grade of ICANS: 56%, grade 3+: 15%). Responses appear durable with a median PFS of 40.2 months, but longer follow-up is needed to determine whether some patients may be cured with this approach [80]. Tisa-cel was studied in a similar patient population in the phase II ELARA trial. Among 98 patients, the ORR was 86% and the CMR was 69%. Tisa-cel appeared to have a more favorable safety profile than axi-cel with lower rates of CRS (any grade: 49%, grade 3+: 0%) and ICANS (any grade: 37%, grade 3+: 4%) [81]. With a median follow-up of 28.9 months, the 2-year PFS in this trial was 57%. While lisocabtagene maraleucel (liso-cel) is not yet approved for FL, it has also demonstrated encouraging results in patients with relapsed/refractory FL. The phase II TRANSCEND-FL study tested liso-cel among patients with 2

or more prior lines of therapy or as second-line treatment in patients with POD-24. Among 107 patients receiving liso-cel as third-line or later therapy, the ORR and CMR were 97% and 94%, respectively. Results for patients with POD-24 receiving liso-cel as a second-line therapy have not yet been reported. CRS was observed in 58% of patients (including 1% with grade 3+ CRS), while only 15% of patients experienced ICANS (including 2% with grade 3+ ICANS). While the follow-up is still limited, responses appear to be durable with a 12-month PFS of 81% [82]. Longer follow-up is needed to determine if the higher CRRs observed with liso-cel compared to other CD19 CARs might translate into improved long-term disease control.

Based on the excellent outcomes in the phase II studies described above, randomized phase III studies are ongoing for axi-cel (NCT05371093) and tisa-cel (NCT05888493). These trials are comparing CAR-T cell therapy to standard-of-care treatment with either chemoimmunotherapy or lenalidomide-based treatment among patients with relapsed/refractory FL. It is likely that these trials will demonstrate superior PFS with CAR-T cell therapy, but absent an OS benefit, they still may not definitively confirm the optimal setting for CAR-T cell therapy in FL. Unlike in relapsed/refractory DLBCL, where lymphoma-related mortality is high and CAR-T cell therapy has a clear curative potential, patients with relapsed/refractory FL often have less aggressive disease and are fortunate to have other effective treatment options, including CD3/CD20 BsAbs. In the meantime, CAR-T cell therapy is an excellent option for patients with FL with aggressive clinical features, particularly if there are concerns about occult transformation, or for patients who favor a one-time intensive treatment option over continuous therapies.

### Bispecific Antibodies

Four different BsAbs targeting CD3 on T cells and CD20 on malignant FL cells are in active development for FL. CD3xCD20 BsAbs are associated with frequent CRS but significantly lower rates of ICANS compared to CAR-T cell therapy. To mitigate the risk of CRS, all 4 CD3xCD20 BsAbs employ step-up dosing and steroid premedication during treatment initiation, and with these approaches, rates of severe CRS are low at less than 5%. In addition, inpatient monitoring has been required in initial trials for all agents, except for mosunetuzumab. Mosunetuzumab, epcoritamab, and glofitamab have similar dose ramp-up schedules with dosing escalating weekly over 3 weeks, while odronextamab uses a more onerous step-up dosing schedule that currently requires 4 hospitalizations and twice weekly doses over a 4-week period [73,74,75,76,77,78,79,80,81,82,83,84,85,86]. Across all agents, the timing of CRS seems to be predictable with almost all events occurring during the first 1 or 2 cycles of therapy. Beyond CRS, other common adverse events with CD3xCD20 BsAbs include cytopenia and infections, which can be severe, including fatal cases of coronavirus disease-2019 (COVID-19) observed in several trials. In contrast, rates of ICANS and tumor lysis syndrome have been very low [73,74,75,76,77,78,79,80,81,82,83,84,85,86].

Initial trials have shown high response rates for all 4 agents, with ORRs ranging from 78% to 100% and CRRs ranging from 60% to 75% (Table 3) [83,84,85,86]. Importantly, high ORRs have been seen across different FL patient subgroups, including high-risk populations, like those with POD-24. Follow-up is still limited for these trials, but responses appear durable with the median PFS exceeding 18 months for both odronextamab and mosunetuzumab [84,86]. Similar to trials with CAR-T cell therapies, longer follow-up is needed to better understand the durability of responses for this therapy class.

Unlike CAR-T cell therapy, CD3xCD20 BsAbs do not require personalized manufacturing. Their easier availability and excellent efficacy and toxicity profiles make CD3xCD20 BsAbs attractive candidates for combination approaches. Epcoritamab has been combined with lenalidomide and rituximab ($R^2$) among relapsed/refractory FL patients with encouraging results. Among 111 treated patients with relapsed/refractory FL, the ORR and CRR were 98% and 87%, respectively, and the 1-year PFS was 78%. The same combination was tested in a smaller population of patients with untreated FL (n=41) and also yielded very high response rates (ORR: 94%, CMR: 86%) [87,88]. In both trials, treatment was well tolerated without new safety signals, supporting the feasibility of BsAb combinations in FL.

Based on these encouraging results, BsAb-based combinations are being tested across all lines of therapy in FL (Table 4). There are ongoing confirmatory randomized phase III trials for epcoritamab and mosunetuzumab (NCT05409066 and NCT04712097). These trials have similar designs, which will determine whether the addition of a CD3xCD20 BsAb to lenalidomide-based treatment can improve PFS among patients with relapsed/refractory FL. There are also 7 ongoing phase II trials testing BsAbs as part of frontline therapy, either as monotherapy or with various combinations including CD20 mAbs, polatuzumab, lenalidomide, and tazemetostat.

Key questions remain about how to best incorporate BsAbs into the treatment paradigm for FL. Should BsAbs be used alone or in combination? What agents are optimal combination partners? Can we identify biomarkers to predict high-grade CRS, and, if so, is inpatient hospitalization necessary for most patients during dose escalation? What is the optimal duration of treatment with BsAbs and does it vary based on treatment setting? Will

**Table 3. Results from trials of bispecific antibodies in the treatment of follicular lymphoma.**

| Bispecific antibody [Ref.] | Trial | Eligibility | Number of patients | ORR, CRR | PFS, OS | CRS | Neurotoxicity | Notes |
|---|---|---|---|---|---|---|---|---|
| Mosunetuzumab [84] | Phase II | 2+ prior lines including CD20 and an alkylator | 90 | 78%, 60% | 24-month PFS: 51.4% | 44% any grade | 5% of any grade, no grade 3+ | |
| Epcoritamab [83] | EPCORE NHL-1 | | 128 | ORR: 82% | | | | Based on press release only |
| | Phase I | | 12 | 90%, 50% | | | | |
| Glofitamab [85] | Phase I/II | R/R FL grade 1-3A, 1+ prior lines of therapy | 72<br>53 (monotherapy)<br>19 (glofitamab + obinutuzuma) | 81%, 70%<br><br>100%, 74% | Limited follow-up | In glofit + obin, 79% any grade, 0% grade 3; 1 case of grade 3 CRS among all patients | None | High response rates seen across high-risk patient subgroups |
| Odronextamab [86] | ELM-2, phase II | R/R FL grade 1-3A, 2+ prior lines including CD20 mAb and alkylator | 96 | 81%, 75%, consistent across different patient subgroups | Median PFS was 20.2 months | CRS of any grade 51%, no grade 3+ | No ICANS reported with final dose ramp-up strategy | More involved dose escalation with doses on cycle 1's days 1-2, 8-9, and 15-16 and cycle 2's day 1; 4 hospitalizations required |
| **Combinations** | | | | | | | | |
| Epcoritamab + $R^2$ [87,88,89] | Untreated | | 41 | 94%, 86% | Early follow-up | 51% any grade, no grade 3+ | No ICANS | |
| | R/R | | 111 | 98%, 87%, similar across high-risk subgroups | 1-year PFS: 78% | Any grade: 48%, grade 3+: 2% | 2% | |

$R^2$: Rituximab plus lenalidomide; R/R: relapsed/refractory; FL: follicular lymphoma; mAb: monoclonal antibody; ORR: overall response rate; CRR: complete response rate; PFS: progression-free survival; OS: overall survival; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome.

**Table 4. Selected ongoing bispecific antibody trials.**

| | Treatment regimen | Trial size | Trial type | NCT number |
|---|---|---|---|---|
| **Untreated patients** | | | | |
| Epcoritamab | Rituximab, epcoritamab | n=35 | Phase II | NCT05783609 |
| Glofitamab | Obinutuzumab, glofitamab | n=35 (FL), n=12 MZL) | Phase II | NCT05783596 |
| Mosunetuzumab | Mosunetuzumab monotherapy | n=53 | Phase II | NCT05389293 |
| Mosunetuzumab | Mosunetuzumab and polatuzumab | n=34 | Phase II | NCT05410418 |
| Mosunetuzumab | Mosunetuzumab and tazemetostat | n=50 | Phase II | NCT05994235 |
| Mosunetuzumab | Mosunetuzumab and lenalidomide | n=52 | Phase II | NCT04792502 |
| Mosunetuzumab | Mosunetuzumab monotherapy with addition of obinutuzumab and polatuzumab vedotin for non-complete responders | n=42 | Phase II | NCT05169658 |
| **POD-24** | | | | |
| Epcoritamab | Epcoritamab-lenalidomide | n=60 | Phase II | NCT04663347 |
| Mosunetuzumab (MERLIN) | Mosunetuzumab monotherapy | n=80 | Phase II | NCT05849857 |

**Table 4. Continued.**

| | Treatment regimen | Trial size | Trial type | NCT number |
|---|---|---|---|---|
| **R/R FL** | | | | |
| Epcoritamab | Epcoritamab + $R^2$ versus $R^2$ | n=520 | Phase III | NCT05409066 |
| Mosunetuzumab | Mosunetuzumab and lenalidomide versus rituximab-lenalidomide | n=400 | Phase III | NCT04712097 |
| Mosunetuzumab | Mosunetuzumab and tiragolumab (anti-TIGIT) with or without atezolizumab | n=118 | Phase II (including both FL and DLBCL) | NCT05315713 |

POD-24: Progression of the disease within 24 months; R/R: relapsed/refractory; FL: follicular lymphoma; Len: lenalidomide; $R^2$: rituximab plus lenalidomide; MZL: marginal zone lymphoma; DLBCL: diffuse large B-cell lymphoma; NCT: National Clinical Trial.

patients who receive time-limited treatment with BsAbs benefit from retreatment at the time of progression? Answering these questions and others will be critical in maximizing the potential benefit of BsAbs for patients with FL.

## Conclusion

The treatment landscape for FL is evolving rapidly with multiple novel target agents and immunotherapies approved in recent years. The optimal selection and sequencing of these agents is not yet defined and should be personalized based on individual patient characteristics and preferences. The ongoing exploration of BsAbs and CAR-T cell therapies has the potential to further transform FL management. However, important questions remain, underscoring the need for continued clinical research.

### Authorship Contributions

Concept: R.M., Ö.M., A.L.; Design: R.M., Ö.M., A.L.; Data Collection or Processing: R.M., Ö.M., A.L.; Analysis or Interpretation: R.M., Ö.M., A.L.; Literature Search: R.M., Ö.M., A.L.; Writing: R.M., Ö.M., A.L.

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## References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th Edition. Lyon, IARC Press, 2017.
2. Freedman A. Follicular lymphoma: 2018 update on diagnosis and management. Am J Hematol 2018;93:296-305.
3. Koch K, Hoster E, Ziepert M, Unterhalt M, Ott G, Rosenwald A, Hansmann ML, Bernd W, Stein H, Pöschel V, Dreyling M, Trümper L, Löffler M, Schmitz N, Hiddemann W, Pfreundschuh M, Klapper W. Clinical, pathological and genetic features of follicular lymphoma grade 3A: a joint analysis of the German low-grade and high-grade lymphoma study groups GLSG and DSHNHL. Ann Oncol 2016;27:1323-1329.
4. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, Bhagat G, Borges AM, Boyer D, Calaminici M, Chadburn A, Chan JKC, Cheuk W, Chng WJ, Choi JK, Chuang SS, Coupland SE, Czader M, Dave SS, de Jong D, Du MQ, Elenitoba-Johnson KS, Ferry J, Geyer J, Gratzinger D, Guitart J, Gujral S, Harris M, Harrison CJ, Hartmann S, Hochhaus A, Jansen PM, Karube K, Kempf W, Khoury J, Kimura H, Klapper W, Kovach AE, Kumar S, Lazar AJ, Lazzi S, Leoncini L, Leung N, Leventaki V, Li XQ, Lim MS, Liu WP, Louissaint A Jr, Marcogliese A, Medeiros LJ, Michal M, Miranda RN, Mitteldorf C, Montes-Moreno S, Morice W, Nardi V, Naresh KN, Natkunam Y, Ng SB, Oschlies I, Ott G, Parrens M, Pulitzer M, Rajkumar SV, Rawstron AC, Rech K, Rosenwald A, Said J, Sarkozy C, Sayed S, Saygin C, Schuh A, Sewell W, Siebert R, Sohani AR, Tooze R, Traverse-Glehen A, Vega F, Vergier B, Wechalekar AD, Wood B, Xerri L, Xiao W. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 2022;36:1720-1748.
5. Horn H, Schmelter C, Leich E, Salaverria I, Katzenberger T, Ott MM, Kalla J, Romero M, Siebert R, Rosenwald A, Ott G. Follicular lymphoma grade 3B is a distinct neoplasm according to cytogenetic and immunohistochemical profiles. Haematologica 2011;96:1327-1334.
6. Siddiqi IN, Friedman J, Barry-Holson KQ, Ma C, Thodima V, Kang I, Padmanabhan R, Dias LM, Kelly KR, Brynes RK, Kamalakaran S, Houldsworth J. Characterization of a variant of t(14;18) negative nodal diffuse follicular lymphoma with CD23 expression, 1p36/TNFRSF14 abnormalities, and STAT6 mutations. Mod Pathol 2016;29:570-581.
7. Louissaint A Jr, Schafernak KT, Geyer JT, Kovach AE, Ghandi M, Gratzinger D, Roth CG, Paxton CN, Kim S, Namgyal C, Morin R, Morgan EA, Neuberg DS, South ST, Harris MH, Hasserjian RP, Hochberg EP, Garraway LA, Harris NL, Weinstock DM. Pediatric-type nodal follicular lymphoma: a biologically distinct lymphoma with frequent MAPK pathway mutations. Blood 2016;128:1093-1100.
8. Montoto S, Davies AJ, Matthews J, Calaminici M, Norton AJ, Amess J, Vinnicombe S, Waters R, Rohatiner AZ, Lister TA. Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. J Clin Oncol 2007;25:2426-2433.
9. Sarkozy C, Maurer MJ, Link BK, Ghesquieres H, Nicolas E, Thompson CA, Traverse-Glehen A, Feldman AL, Allmer C, Slager SL, Ansell SM, Habermann TM, Bachy E, Cerhan JR, Salles G. Cause of death in follicular lymphoma in the first decade of the rituximab era: a pooled analysis of French and US cohorts. J Clin Oncol 2019;37:144-152.
10. Solal-Céligny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, Au WY, Bellei M, Brice P, Caballero D, Coiffier B, Conde-Garcia E, Doyen C, Federico M, Fisher RI, Garcia-Conde JF, Guglielmi C, Hagenbeek A, Haïoun C, LeBlanc M, Lister AT, Lopez-Guillermo A, McLaughlin P, Milpied N, Morel P, Mounier N, Proctor SJ, Rohatiner A, Smith P, Soubeyran P, Tilly H, Vitolo U, Zinzani PL, Zucca E, Montserrat E. Follicular Lymphoma International Prognostic Index. Blood 2004;104:1258-1265.
11. Federico M, Bellei M, Marcheselli L, Luminari S, Lopez-Guillermo A, Vitolo U, Pro B, Pileri S, Pulsoni A, Soubeyran P, Cortelazzo S, Martinelli G, Martelli M, Rigacci L, Arcaini L, Di Raimondo F, Merli F, Sabattini E, McLaughlin P, Solal-Céligny P. Follicular Lymphoma International Prognostic Index 2: a new prognostic index for follicular lymphoma developed by the International Follicular Lymphoma Prognostic Factor Project. J Clin Oncol 2009;27:4555-4562.

12. Pastore A, Jurinovic V, Kridel R, Hoster E, Staiger AM, Szczepanowski M, Pott C, Kopp N, Murakami M, Horn H, Leich E, Moccia AA, Mottok A, Sunkavalli A, Van Hummelen P, Ducar M, Ennishi D, Shulha HP, Hother C, Connors JM, Sehn LH, Dreyling M, Neuberg D, Möller P, Feller AC, Hansmann ML, Stein H, Rosenwald A, Ott G, Klapper W, Unterhalt M, Hiddemann W, Gascoyne RD, Weinstock DM, Weigert O. Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. Lancet Oncol 2015;16:1111-1122.

13. Jurinovic V, Passerini V, Oestergaard MZ, Knapp A, Mundt K, Araf S, Richter J, Fitzgibbon J, Klapper W, Marcus RE, Davies A, Herold M, Hiddemann W, Unterhalt M, Hoster E, Weigert O. Evaluation of the m7-FLIPI in patients with follicular lymphoma treated within the gallium trial: EZH2 mutation status may be a predictive marker for differential efficacy of chemotherapy. Blood 2019;134(Suppl 1):122.

14. Bachy E, Maurer MJ, Habermann TM, Gelas-Dore B, Maucort-Boulch D, Estell JA, Van den Neste E, Bouabdallah R, Gyan E, Feldman AL, Bargay J, Delmer A, Slager SL, Gomes da Silva M, Fitoussi O, Belada D, Maisonneuve H, Intragumtornchai T, Ansell SM, Lamy T, Dartigues P, Link BK, Seymour JF, Cerhan JR, Salles G. A simplified scoring system in de novo follicular lymphoma treated initially with immunochemotherapy. Blood 2018;132:49-58.

15. Le Dortz L, De Guibert S, Bayat S, Devillers A, Houot R, Rolland Y, Cuggia M, Le Jeune F, Bahri H, Barge ML, Lamy T, Garin E. Diagnostic and prognostic impact of 18F-FDG PET/CT in follicular lymphoma. Eur J Nucl Med Mol Imaging 2010;37:2307-2314.

16. Dupuis J, Berriolo-Riedinger A, Julian A, Brice P, Tychyj-Pinel C, Tilly H, Mounier N, Gallamini A, Feugier P, Soubeyran P, Colombat P, Laurent G, Berenger N, Casasnovas RO, Vera P, Paone G, Xerri L, Salles G, Haioun C, Meignan M. Impact of [$^{18}$F]fluorodeoxyglucose positron emission tomography response evaluation in patients with high-tumor burden follicular lymphoma treated with immunochemotherapy: a prospective study from the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS. J Clin Oncol 2012;30:4317-4322.

17. Luminari S, Biasoli I, Versari A, Rattotti S, Bottelli C, Rusconi C, Merli F, Spina M, Ferreri AJ, Zinzani PL, Gallamini A, Franceschetto A, Boccomini C, Franceschetti S, Salvi F, Raimondo FD, Carella AM, Micol Q, Balzarotti M, Musto P, Federico M. The prognostic role of post-induction FDG-PET in patients with follicular lymphoma: a subset analysis from the FOLL05 trial of the Fondazione Italiana Linfomi (FIL). Ann Oncol 2014;25:442-447.

18. Luminari S, Guerra L, Minoia C, Chauvie S, Anastasia A, Cavallo F, Corradini P, Rattotti S, Durmo R, Ghiggi C, Olivieri J, Ferrero S, Casaluci GM, Nassi L, Stelitano C, Ricci F, Zilioli VR, Pinto A, Zanni M, Silvia B, Patti C, Merli M, Chiarenza A, Musuraca G, Tosi P, Federico M, Versari A. Total metabolic tumor volume is confirmed as independent prognostic factor in treatment naïve follicular lymphoma patients and can be combined with FLIPI2 to improve prognostic accuracy. A FOLL12 Substudy by the Fondazione Italiana Linfomi. Blood 2022;140(Suppl 1):1313-1315.

19. Cottereau AS, Rebaud L, Trotman J, Feugier P, Nastoupil LJ, Bachy E, Flinn IW, Haioun C, Ysebaert L, Bartlett NL, Tilly H, Casasnovas O, Ricci R, Portugues C, Buvat I, Meignan M, Morschhauser F. Metabolic tumor volume predicts outcome in patients with advanced stage follicular lymphoma from the RELEVANCE trial. Ann Oncol 2024;35:130-137.

20. Casulo C, Byrtek M, Dawson KL, Zhou X, Farber CM, Flowers CR, Hainsworth JD, Maurer MJ, Cerhan JR, Link BK, Zelenetz AD, Friedberg JW. 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;33:2516-2522.

21. Luminari S, Biasoli I, Arcaini L, Versari A, Rusconi C, Merli F, Spina M, Ferreri AJ, Zinzani PL, Gallamini A, Mastronardi S, Boccomini C, Gaidano G, D'Arco AM, DiRaimondo F, Carella AM, Santoro A, Musto P, Federico M. The use of FDG-PET in the initial staging of 142 patients with follicular lymphoma: a retrospective study from the FOLL05 randomized trial of the Fondazione Italiana Linfomi. Ann Oncol 2013;24:2108-2112.

22. Brady JL, Binkley MS, Hajj C, Chelius M, Chau K, Balogh A, Levis M, Filippi AR, Jones M, Mac Manus M, Wirth A, Oguchi M, Vistisen AK, Andraos TY, Ng AK, Aleman BMP, Choi SH, Kirova Y, Hardy S, Reinartz G, Eich HT, Bratman SV, Constine LS, Suh CO, Dabaja B, El-Galaly TC, Hodgson DC, Ricardi U, Yahalom J, Hoppe RT, Mikhaeel NG. Definitive radiotherapy for localized follicular lymphoma staged by $^{18}$F-FDG PET-CT: a collaborative study by ILROG. Blood 2019;133:237-245.

23. MacManus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. J Clin Oncol 1996;14:1282-1290.

24. Wilder RB, Jones D, Tucker SL, Fuller LM, Ha CS, McLaughlin P, Hess MA, Cabanillas F, Cox JD. Long-term results with radiotherapy for stage I-II follicular lymphomas. Int J Radiat Oncol Biol Phys 2001;51:1219-1227.

25. Campbell BA, Voss N, Woods R, Gascoyne RD, Morris J, Pickles T, Connors JM, Savage KJ. Long-term outcomes for patients with limited stage follicular lymphoma: involved regional radiotherapy versus involved node radiotherapy. Cancer 2010;116:3797-3806.

26. MacManus M, Fisher R, Roos D, O'Brien P, Macann A, Davis S, Tsang R, Christie D, McClure B, Joseph D, Jayamohan J, Seymour JF. Randomized trial of systemic therapy after involved-field radiotherapy in patients with early-stage follicular lymphoma: TROG 99.03. J Clin Oncol 2018;36:2918-2925.

27. Janikova A, Bortlicek Z, Campr V, Kopalova N, Benesova K, Belada D, Prochazka V, Pytlik R, Vokurka S, Pirnos J, Duras J, Mocikova H, Mayer J, Trneny M. Radiotherapy with rituximab may be better than radiotherapy alone in first-line treatment of early-stage follicular lymphoma: is it time to change the standard strategy? Leuk Lymphoma 2015;56:2350-2356.

28. Ruella M, Filippi AR, Bruna R, DiRusso A, Magni M, Caracciolo D, Passera R, Matteucci P, DiNicola M, Corradini P, Parvis G, Gini G, Olivieri A, Ladetto M, Ricardi U, Tarella C, Devizzi L. Addition of rituximab to involved-field radiation therapy prolongs progression-free survival in stage I-II follicular lymphoma: results of a multicenter study. Int J Radiat Oncol Biol Phys 2016;94:783-791.

29. Michallet AS, Lebras LL, Bauwens DD, Bouafia-Sauvy FF, Berger FF, Tychyj-Pinel CC, D'Hombres AA, Salles GG, Coiffier BB. Early stage follicular lymphoma: what is the clinical impact of the first-line treatment strategy? J Hematol Oncol 2013;6:45.

30. Friedberg JW, Byrtek M, Link BK, Flowers C, Taylor M, Hainsworth J, Cerhan JR, Zelenetz AD, Hirata J, Miller TP. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National Lympho Care Study. J Clin Oncol 2012;30:3368-3375.

31. 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;22:1454-1459.

32. Binkley MS, Brady JL, Hajj C, Chelius M, Chau K, Balogh A, Levis M, Filippi AR, Jones M, Ahmed S, MacManus M, Wirth A, Oguchi M, Vistisen AK, Andraos TY, Ng AK, Aleman BMP, Choi SH, Kirova YM, Hardy S, Reinartz G, Eich HT, Bratman SV, Constine LS, Suh CO, Dabaja B, El-Galaly TC, Hodgson DC, Ricardi U, Yahalom J, Mikhaeel NG, Hoppe RT. Salvage treatment and survival for relapsed follicular lymphoma following primary radiation therapy: a collaborative study on behalf of ILROG. Int J Radiat Oncol Biol Phys 2019;104:522-529.

33. Brice P, Bastion Y, Lepage E, Brousse N, Haïoun C, Moreau P, Straetmans N, Tilly H, Tabah I, Solal-Céligny P. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1997;15:1110-1117.

34. Ardeshna KM, Smith P, Norton A, Hancock BW, Hoskin PJ, MacLennan KA, Marcus RE, Jelliffe A, Vaughan G, Hudson, Linch DC; British National Lymphoma Investigation. 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;362:516-522.

35. Ardeshna KM, Qian W, Smith P, Braganca N, Lowry L, Patrick P, Warden J, Stevens L, Pocock CF, Miall F, Cunningham D, Davies J, Jack A, Stephens R, Walewski J, Ferhanoglu B, Bradstock K, Linch DC. 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;15:424-435.
36. Solal-Céligny P, Bellei M, Marcheselli L, Pesce EA, Pileri S, McLaughlin P, Luminari S, Pro B, Montoto S, Ferreri AJ, Deconinck E, Milpied N, Gordon LI, Federico M. Watchful waiting in low-tumor burden follicular lymphoma in the rituximab era: results of an F2-study database. J Clin Oncol 2012;30:3848-3853.
37. Nastoupil LJ, Sinha R, Byrtek M, Ziemiecki R, Zhou X, Taylor M, Friedberg JW, Link BK, Cerhan JR, Dawson K, Flowers CR. Outcomes following watchful waiting for stage II-IV follicular lymphoma patients in the modern era. Br J Haematol 2016;172:724-734.
38. Federico M, Luminari S, Dondi A, Tucci A, Vitolo U, Rigacci L, Di Raimondo F, Carella AM, Pulsoni A, Merli F, Arcaini L, Angrilli F, Stelitano C, Gaidano G, Dell'olio M, Marcheselli L, Franco V, Galimberti S, Sacchi S, Brugiatelli M. 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;31:1506-1513.
39. Luminari S, Ferrari A, Manni M, Dondi A, Chiarenza A, Merli F, Rusconi C, Tarantino V, Tucci A, Vitolo U, Kovalchuk S, Angelucci E, Pulsoni A, Arcaini L, Angrilli F, Gaidano G, Stelitano C, Bertoldero G, Cascavilla N, Salvi F, Ferreri AJM, Vallisa D, Marcheselli L, Federico M. 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;36:689-696.
40. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C, Kofahl-Krause D, Heil G, Welslau M, Balser C, Kaiser U, Weidmann E, Dürk H, Ballo H, Stauch M, Roller F, Barth J, Hoelzer D, Hinke A, Brugger W; Study group indolent Lymphomas (StiL). 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;381:1203-1210.
41. Flinn IW, van der Jagt R, Kahl BS, Wood P, Hawkins TE, Macdonald D, Hertzberg M, Kwan YL, Simpson D, Craig M, Kolibaba K, Issa S, Clementi R, Hallman DM, Munteanu M, Chen L, Burke JM. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood 2014;123:2944-2952.
42. Flinn IW, van der Jagt R, Kahl B, Wood P, Hawkins T, MacDonald D, Simpson D, Kolibaba K, Issa S, Chang J, Trotman J, Hallman D, Chen L, Burke JM. First-line treatment of patients with indolent non-Hodgkin lymphoma or mantle-cell lymphoma with bendamustine plus rituximab versus R-CHOP or R-CVP: results of the BRIGHT 5-year follow-up study. J Clin Oncol 2019;37:984-991.
43. Morschhauser F, Fowler NH, Feugier P, Bouabdallah R, Tilly H, Palomba ML, Fruchart C, Libby EN, Casasnovas RO, Flinn IW, Haioun C, Maisonneuve H, Ysebaert L, Bartlett NL, Bouabdallah K, Brice P, Ribrag V, Daguindau N, Le Gouill S, Pica GM, Martin Garcia-Sancho A, López-Guillermo A, Larouche JF, Ando K, Gomes da Silva M, André M, Zachée P, Sehn LH, Tobinai K, Cartron G, Liu D, Wang J, Xerri L, Salles GA; RELEVANCE Trial Investigators. Rituximab plus lenalidomide in advanced untreated follicular lymphoma. N Engl J Med 2018;379:934-947.
44. Morschhauser F, Nastoupil L, Feugier P, Schiano de Colella JM, Tilly H, Palomba ML, Bachy E, Fruchart C, Libby EN, Casasnovas RO, Flinn IW, Haioun C, Maisonneuve H, Ysebaert L, Bartlett NL, Bouabdallah K, Brice P, Ribrag V, Le Gouill S, Daguindau N, Guidez S, Pica GM, García-Sancho AM, López-Guillermo A, Larouche JF, Ando K, Gomes da Silva M, André M, Kalung W, Sehn LH, Izutsu K, Cartron G, Gkasiamis A, Crowe R, Xerri L, Fowler NH, Salles G. Six-year results from RELEVANCE: lenalidomide plus rituximab ($R^2$) versus rituximab-chemotherapy followed by rituximab maintenance in untreated advanced follicular lymphoma. J Clin Oncol 2022;40:3239-3245.
45. Marcus R, Davies A, Ando K, Klapper W, Opat S, Owen C, Phillips E, Sangha R, Schlag R, Seymour JF, Townsend W, Trněný M, Wenger M, Fingerle-Rowson G, Rufibach K, Moore T, Herold M, Hiddemann W. Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med 2017;377:1331-1344.
46. Townsend W, Hiddemann W, Buske C, Cartron G, Cunningham D, Dyer MJS, Gribben JG, Phillips EH, Dreyling M, Seymour JF, Grigg A, Trotman J, Lin TY, Hong XN, Kingbiel D, Nielsen TG, Knapp A, Herold M, Marcus R. Obinutuzumab versus rituximab immunochemotherapy in previously untreated iNHL: final results from the GALLIUM Study. Hemasphere 2023;7:e919.
47. Seymour JF, Marcus R, Davies A, Gallop-Evans E, Grigg A, Haynes A, Herold M, Illmer T, Nilsson-Ehle H, Sökler M, Dünzinger U, Nielsen T, Launonen A, Hiddemann W. Association of early disease progression and very poor survival in the GALLIUM study in follicular lymphoma: benefit of obinutuzumab in reducing the rate of early progression. Haematologica 2019;104:1202-1208.
48. Bachy E, Seymour JF, Feugier P, Offner F, López-Guillermo A, Belada D, Xerri L, Catalano JV, Brice P, Lemonnier F, Martin A, Casasnovas O, Pedersen LM, Dorvaux V, Simpson D, Leppa S, Gabarre J, da Silva MG, Glaisner S, Ysebaert L, Vekhoff A, Intragumtornchai T, Le Gouill S, Lister A, Estell JA, Milone G, Sonet A, Farhi J, Zeuner H, Tilly H, Salles G. Sustained progression-free survival benefit of rituximab maintenance in patients with follicular lymphoma: long-term results of the PRIMA Study. J Clin Oncol 2019;37:2815-2824.
49. Kahl B, Burke J, van der Jagt R, Assessment of maintenance rituximab after first-line bendamustine-rituximab in patients with follicular lymphoma: an analysis from the BRIGHT trial. Blood 2017;130(Suppl 1):484.
50. Hill BT, Nastoupil L, Winter AM, Becnel MR, Cerhan JR, Habermann TM, Link BK, Maurer MJ, Fakhri B, Reddy P, Smith SD, Mukhija D, Jagadeesh D, Desai A, Alderuccio JP, Lossos IS, Mehra P, Portell CA, Goldman ML, Calzada O, Cohen JB, Hussain MJ, Ghosh N, Caimi P, Tiutan T, Martin P, Kodali A, Evens AM, Kahl BS. Maintenance rituximab or observation after frontline treatment with bendamustine-rituximab for follicular lymphoma. Br J Haematol 2019;184:524-535.
51. Martinelli G, Schmitz SF, Utiger U, Cerny T, Hess U, Bassi S, Okkinga E, Stupp R, Stahel R, Heizmann M, Vorobiof D, Lohri A, Dietrich PY, Zucca E, Ghielmini M. Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98. J Clin Oncol 2010;28:4480-4484.
52. Cartron G, Bachy E, Tilly H, Daguindau N, Pica GM, Bijou F, Mounier C, Clavert A, Damaj GL, Slama B, Casasnovas O, Houot R, Bouabdallah K, Sibon D, Fitoussi O, Morineau N, Herbaux C, Gastinne T, Fornecker LM, Haioun C, Launay V, Araujo C, Benbrahim O, Sanhes L, Gressin R, Gonzalez H, Morschhauser F, Ternant D, Xerri L, Tarte K, Pranger D. Randomized phase III trial evaluating subcutaneous rituximab for the first-line treatment of low-tumor burden follicular lymphoma: results of a LYSA study. J Clin Oncol 2023;41:3523-3533.
53. Casulo C, Byrtek M, Dawson KL, Zhou X, Farber CM, Flowers CR, Hainsworth JD, Maurer MJ, Cerhan JR, Link BK, Zelenetz AD, Friedberg JW. 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;33:2516-2522.
54. Freeman CL, Kridel R, Moccia AA, Savage KJ, Villa DR, Scott DW, Gerrie AS, Ferguson D, Cafferty F, Slack GW, Farinha P, Skinnider B, Connors JM, Sehn LH. Early progression after bendamustine-rituximab is associated with high risk of transformation in advanced stage follicular lymphoma. Blood 2019;134:761-764.
55. Kahl BS, Jegede OA, Peterson C, Swinnen LJ, Habermann TM, Schuster SJ, Weiss M, Fishkin PA, Fenske TS, Williams ME. Long-term follow-up of the

RESORT Study (E4402): a randomized phase III comparison of two different rituximab dosing strategies for low-tumor burden follicular lymphoma. J Clin Oncol 2024;42:774-778.

56. Cheson BD, Chua N, Mayer J, Dueck G, Trněný M, Bouabdallah K, Fowler N, Delwail V, Press O, Salles G, Gribben JG, Lennard A, Lugtenburg PJ, Fingerle-Rowson G, Mattiello F, Knapp A, Sehn LH. 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;36:2259-2266.
57. van Oers MH, Van Glabbeke M, Giurgea L, Klasa R, Marcus RE, Wolf M, Kimby E, van t Veer M, Vranovsky A, Holte H, Hagenbeek A. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. J Clin Oncol 2010;28:2853-2858.
58. Hainsworth JD, Litchy S, Shaffer DW, Lackey VL, Grimaldi M, Greco FA. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma--a randomized phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2005;23:1088-1095.
59. Casulo C, Friedberg JW, Ahn KW, Flowers C, DiGilio A, Smith SM, Ahmed S, Inwards D, Aljurf M, Chen AI, Choe H, Cohen J, Copelan E, Farooq U, Fenske TS, Freytes C, Gaballa S, Ganguly S, Jethava Y, Kamble RT, Kenkre VP, Lazarus H, Lazaryan A, Olsson RF, Rezvani AR, Rizzieri D, Seo S, Shah GL, Shah N, Solh M, Sureda A, William B, Cumpston A, Zelenetz AD, Link BK, Hamadani M. 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;24:1163-1171.
60. Jurinovic V, Metzner B, Pfreundschuh M, Schmitz N, Wandt H, Keller U, Dreger P, Dreyling M, Hiddemann W, Unterhalt M, Hoster E, Weigert O. 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;24:1172-1179.
61. Klyuchnikov E, Bacher U, Kröger NM, Hari PN, Ahn KW, Carreras J, Bachanova V, Bashey A, Cohen JB, D'Souza A, Freytes CO, Gale RP, Ganguly S, Hertzberg MS, Holmberg LA, Kharfan-Dabaja MA, Klein A, Ku GH, Laport GG, Lazarus HM, Miller AM, Mussetti A, Olsson RF, Slavin S, Usmani SZ, Vij R, Wood WA, Maloney DG, Sureda AM, Smith SM, Hamadani M. Reduced-intensity allografting as first transplantation approach in relapsed/refractory grades one and two follicular lymphoma provides improved outcomes in long-term survivors. Biol Blood Marrow Transplant 2015;21:2091-2099.
62. Gribben JG, Fowler N, Morschhauser F. Mechanisms of action of lenalidomide in B-cell non-Hodgkin lymphoma. J Clin Oncol 2015;33:2803-2811.
63. Witzig TE, Wiernik PH, Moore T, Reeder C, Cole C, Justice G, Kaplan H, Voralia M, Pietronigro D, Takeshita K, Ervin-Haynes A, Zeldis JB, Vose JM. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's lymphoma. J Clin Oncol 2009;27:5404-5409.
64. Chong EA, Ahmadi T, Aqui NA, Svoboda J, Nasta SD, Mato AR, Walsh KM, Schuster SJ. Combination of lenalidomide and rituximab overcomes rituximab resistance in patients with indolent B-cell and mantle cell lymphomas. Clin Cancer Res 2015;21:1835-1842.
65. Leonard JP, Jung SH, Johnson J, Pitcher BN, Bartlett NL, Blum KA, Czuczman M, Giguere JK, Cheson BD. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance). J Clin Oncol 2015;33:3635-3640.
66. Morschhauser F, Le Gouill S, Feugier P, Bailly S, Nicolas-Virelizier E, Bijou F, Salles GA, Tilly H, Fruchart C, Van Eygen K, Snauwaert S, Bonnet C, Haioun C, Thieblemont C, Bouabdallah R, Wu KL, Canioni D, Meignin V, Cartron G, Houot R. Obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma (GALEN): a multicentre, single-arm, phase 2 study. Lancet Haematol 2019;6:e429-e437.
67. Leonard JP, Trneny M, Izutsu K, Fowler NH, Hong X, Zhu J, Zhang H, Offner F, Scheliga A, Nowakowski GS, Pinto A, Re F, Fogliatto LM, Scheinberg P, Flinn IW, Moreira C, Cabeçadas J, Liu D, Kalambakas S, Fustier P, Wu C, Gribben JG; AUGMENT Trial Investigators. AUGMENT: A phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol 2019;37:1188-1199.
68. Morschhauser F, Tilly H, Chaidos A, McKay P, Phillips T, Assouline S, Batlevi CL, Campbell P, Ribrag V, Damaj GL, Dickinson M, Jurczak W, Kazmierczak M, Opat S, Radford J, Schmitt A, Yang J, Whalen J, Agarwal S, Adib D, Salles G. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol 2020;21:1433-1442.
69. Gopal AK, Kahl BS, Flowers CR, Martin P, Ansell SM, Abella-Dominicis E, Koh B, Ye W, Barr PM, Salles GA, Friedberg JW. Idelalisib is effective in patients with high-risk follicular lymphoma and early relapse after initial chemoimmunotherapy. Blood 2017;129:3037-3039.
70. Flinn IW, Miller CB, Ardeshna KM, Tetreault S, Assouline SE, Mayer J, Merli M, Lunin SD, Pettitt AR, Nagy Z, Tournilhac O, Abou-Nassar KE, Crump M, Jacobsen ED, de Vos S, Kelly VM, Shi W, Steelman L, Le N, Weaver DT, Lustgarten S, Wagner-Johnston ND, Zinzani PL. DYNAMO: A phase II study of duvelisib (IPI-145) in patients with refractory indolent non-Hodgkin lymphoma. J Clin Oncol 2019;37:912-922.
71. Dreyling M, Santoro A, Mollica L, Leppä S, Follows G, Lenz G, Kim WS, Nagler A, Dimou M, Demeter J, Özcan M, Kosinova M, Bouabdallah K, Morschhauser F, Stevens DA, Trevarthen D, Munoz J, Rodrigues L, Hiemeyer F, Miriyala A, Garcia-Vargas J, Childs BH, Zinzani PL. Long-term safety and efficacy of the PI3K inhibitor copanlisib in patients with relapsed or refractory indolent lymphoma: 2-year follow-up of the CHRONOS-1 study. Am J Hematol 2020;95:362-371.
72. Bartlett NL, Costello BA, LaPlant BR, Ansell SM, Kuruvilla JG, Reeder CB, Thye LS, Anderson DM, Krysiak K, Ramirez C, Qi J, Siegel BA, Griffith M, Griffith OL, Gomez F, Fehniger TA. Single-agent ibrutinib in relapsed or refractory follicular lymphoma: a phase 2 consortium trial. Blood 2018;131:182-190.
73. Fowler NH, Nastoupil L, De Vos S, Knapp M, Flinn IW, Chen R, Advani RH, Bhatia S, Martin P, Mena R, Davis RE, Neelapu SS, Eckert K, Ping J, Co M, Beaupre DM, Neuenburg JK, Palomba ML. The combination of ibrutinib and rituximab demonstrates activity in first-line follicular lymphoma. Br J Haematol 2020;189:650-660.
74. Zinzani PL, Mayer J, Flowers CR, Bijou F, De Oliveira AC, Song Y, Zhang Q, Merli M, Bouabdallah K, Ganly P, Zhang H, Johnson R, Martín García-Sancho A, Provencio Pulla M, Trněný M, Yuen S, Tilly H, Kingsley E, Tumyan G, Assouline SE, Auer R, Ivanova E, Kim P, Huang S, Delarue R, Trotman J. ROSEWOOD: A phase II randomized study of zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy in patients with relapsed or refractory follicular lymphoma. J Clin Oncol 2023;41:5107-5117.
75. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, Braunschweig I, Oluwole OO, Siddiqi T, Lin Y, Timmerman JM, Stiff PJ, Friedberg JW, Flinn IW, Goy A, Hill BT, Smith MR, Deol A, Farooq U, McSweeney P, Munoz J, Avivi I, Castro JE, Westin JR, Chavez JC, Ghobadi A, Komanduri KV, Levy R, Jacobsen ED, Witzig TE, Reagan P, Bot A, Rossi J, Navale L, Jiang Y, Aycock J, Elias M, Chang D, Wiezorek J, Go WY. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377:2531-2544.
76. Jacobson CA, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, Munshi PN, Casulo C, Maloney DG, de Vos S, Reshef R, Leslie LA, Yakoub-Agha I, Oluwole OO, Fung HCH, Rosenblatt J, Rossi JM, Goyal L, Plaks V, Yang Y, Vezan R, Avanzi MP, Neelapu SS. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol 2022;23:91-103.
77. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, Mehta A, Purev E, Maloney DG, Andreadis C, Sehgal A, Solomon SR, Ghosh N, Albertson TM, Garcia J, Kostic A, Mallaney M, Ogasawara K, Newhall K, Kim Y, Li D, Siddiqi T. Lisocabtagene maraleucel for patients with relapsed

or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet 2020;396:839-852.

78. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, Jäger U, Jaglowski S, Andreadis C, Westin JR, Fleury I, Bachanova V, Foley SR, Ho PJ, Mielke S, Magenau JM, Holte H, Pantano S, Pacaud LB, Awasthi R, Chu J, Anak Ö, Salles G, Maziarz RT; JULIET Investigators. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 2019;380:45-56.
79. Shah BD, Ghobadi A, Oluwole OO, Logan AC, Boissel N, Cassaday RD, Leguay T, Bishop MR, Topp MS, Tzachanis D, O'Dwyer KM, Arellano ML, Lin Y, Baer MR, Schiller GJ, Park JH, Subklewe M, Abedi M, Minnema MC, Wierda WG, DeAngelo DJ, Stiff P, Jeyakumar D, Feng C, Dong J, Shen T, Milletti F, Rossi JM, Vezan R, Masouleh BK, Houot R. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. Lancet 2021;398:491-502.
80. Neelapu SS, Chavez JC, Sehgal AR, Epperla N, Ulrickson ML, Bachy E, Munshi PN, Casulo C, Maloney DG, Vos S, Reshef R, Leslie LA, Oluwole OO, Yakoub-Agha I, Khanal R, Rosenblatt J, Yan J, Song Q, Peng W, Lui C, Wulf J, Shen RR, Poddar S, Miao H, Beygi S, Jacobson CA. 3-Year follow-up analysis of ZUMA-5: a phase 2 study of axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL). Transplant Cell Ther 2023;29(Suppl 2):s374.
81. Fowler NH, Dickinson M, Dreyling M, Martinez-Lopez J, Kolstad A, Butler J, Ghosh M, Popplewell L, Chavez JC, Bachy E, Kato K, Harigae H, Kersten MJ, Andreadis C, Riedell PA, Ho PJ, Pérez-Simón JA, Chen AI, Nastoupil LJ, von Tresckow B, Ferreri AJM, Teshima T, Patten PEM, McGuirk JP, Petzer AL, Offner F, Viardot A, Zinzani PL, Malladi R, Zia A, Awasthi R, Masood A, Anak O, Schuster SJ, Thieblemont C. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat Med 2022;28:325-332.
82. Morschhauser F, Dahiya S, Palomba ML, Garcia-Sancho AM, Reguera Ortega JL, Kuruvilla J, Jager U, Cartron G, Izutsu K, Dreyling M, Kahl B, Ghesquieres H, Ardeshna K, Goto H, Barbui AM, Abramson JS, Borchmann P, Fleury I, Mielke S, Farazi T, Fasan O, Lymp J, Vedal M, Nishii R, Avilion A, Papuga J, Nastoupil LJ. TRANSCEND FL: Phase 2 study results of lisocabtagene maraleucel (LISO-CEL) in patients (PTS) with relapsed/refractory (R/R) follicular lymphoma (FL). Hematol Oncol 2023;41(S2):877-880.
83. Hutchings M, Mous R, Clausen MR, Johnson P, Linton KM, Chamuleau MED, Lewis DJ, Sureda Balari A, Cunningham D, Oliveri RS, Elliott B, DeMarco D, Azaryan A, Chiu C, Li T, Chen KM, Ahmadi T, Lugtenburg PJ. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. Lancet 2021;398:1157-1169.
84. Budde LE, Sehn LH, Matasar M, Schuster SJ, Assouline S, Giri P, Kuruvilla J, Canales M, Dietrich S, Fay K, Ku M, Nastoupil L, Cheah CY, Wei MC, Yin S, Li CC, Huang H, Kwan A, Penuel E, Bartlett NL. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. Lancet Oncol 2022;23:1055-1065.
85. Morschhauser F, Carlo-Stella C, Dickinson M, Phillips T, Houot R, Offner F, Haioun C, Corradini P, Hutchings M, Sureda A, Martínez-López J, Wrobel T, Wu SJ, Lundberg L, Mulvihill E, Perez-Callejo D, Relf J, Panchal A, Humphrey K, Bachy E. Glofitamab as monotherapy and in combination with obinutuzumab induces high complete response rates in patients (pts) with multiple relapsed or refractory (R/R) follicular lymphoma (FL). Blood 2021;138(Suppl 1):128.
86. Min Kim T, Taszner M, Cho SG, Novelli S, Le Gouill S, Poon M, Villasboas J, Champion R, Bachy E, Guidez S, Alonso Alonso A, Jagadeesh D, Merli M, Tucker D, Cai J, Leite de Oliveira C, Zhu M, Chaudhry A, Mohamed H, Ambati S, Luminari S. Odronextamab in patients with relapsed/refractory (R/R) follicular lymphoma (FL) grade 1-3a: results from a prespecified analysis of the pivotal phase II study ELM-2. Blood 2022;140(Suppl 1):2280-2282.
87. Merryman R, Belada D, Sureda A, Leppa S, Vermaat J SP, Holte H, Hutchings M, Lugtenburg P, Vos S, Abrisqueta P, Nijland M, Christensen JH, Wahlin BE, Linton KM, Wang L, Abbas A, Rana A, Quadri S, Falchi L. Epcoritamab + $R^2$ regimen and responses in high-risk follicular lymphoma, regardless of POD24 status. J Clin Oncol 2023;41(Suppl 16):7506.
88. Falchi L, Leslie LA, Belada D, Kopeckova K, Offner F, Brody J, Canales M, García-Sancho AM, Nijland M, Andersson P-O, Awan FT, Christensen JH, Drott K, Hellström M, Lewerin C, Narkhede M, Snauwaert S, Wahlin BE, Rana A, Abbas A, Wang L, Dinh M, Vermaat JSP, Abrisqueta P. Subcutaneous epcoritamab in combination with rituximab + lenalidomide ($R^2$) for first-line treatment of follicular lymphoma: initial results from phase 1/2 trial. Blood 2022;140(Suppl 1):1471-1473.
89. Falchi L, Abrisqueta P, Nijland M, Leppä S, Hutchings M, Holte H, Reid W Merryman RW, Lugtenburg P, Vos S, Cheah CY, Christensen JH, Luca Arcaini L, Drott K, Hellström M, Leslie LA, Vitolo U, Rana A, Abbas A, Wang L, Dinh M, Belada D. Subcutaneous epcoritamab with rituximab + lenalidomide in patients with relapsed or refractory follicular lymphoma: phase 1/2 trial update. Blood 2022;140(Suppl 1):1464-1466.