Taylor & Francis
Taylor & Francis Group

Expert Review of Anticancer Therapy

ISSN: 1473-7140 (Print) 1744-8328 (Online) Journal homepage: http://www.tandfonline.com/loi/iery20

# Current and future therapeutic approaches for the treatment of follicular lymphoma

**Alessandro Pulsoni, Luca Vincenzo Cappelli, Laura Ballotta, Martina Canichella, Alessandra Serrao, Giorgia Annechini, Gianna Maria D'Elia & Robin Foà**

**To cite this article:** Alessandro Pulsoni, Luca Vincenzo Cappelli, Laura Ballotta, Martina Canichella, Alessandra Serrao, Giorgia Annechini, Gianna Maria D'Elia & Robin Foà (2018): Current and future therapeutic approaches for the treatment of follicular lymphoma, Expert Review of Anticancer Therapy, DOI: 10.1080/14737140.2018.1493926

**To link to this article:** https://doi.org/10.1080/14737140.2018.1493926

Accepted author version posted online: 04 Jul 2018.

**Publisher:** Taylor & Francis

**Journal:** *Expert Review of Anticancer Therapy*

**DOI:** 10.1080/14737140.2018.1493926

Review

# Current and future therapeutic approaches for the treatment of follicular lymphoma

Alessandro Pulsoni*[1], Luca Vincenzo Cappelli[1], Laura Ballotta[1], Martina Canichella[1], Alessandra Serrao[1], Giorgia Annechini[1], Gianna Maria D'Elia[1] and Robin Foà[1]

[1]Hematology, Department of Cellular Biotechnologies and Hematology, Sapienza University, Rome, Italy.

***Corresponding author:**
Alessandro Pulsoni,
Hematology, Sapienza University,
Via Benevento 6, 00161 Rome
Email: pulsoni@bce.uniroma1.it
Phone: +3906857951
Fax: +390644241984

**ABSTRACT**

**Introduction:** Nowadays follicular lymphoma (FL) is considered a virtually incurable disease. Nevertheless, an improvement of prognostic criteria must be pursued in order to achieve new treatment strategies based on a personalized approach.

**Areas covered:** Prognostic scores, old and recent, as well as innovative and experimental therapeutic approaches are constantly evaluated when it comes to discussing the proper approach to FL, due to its extremely variable presentation at diagnosis. For asymptomatic, low-tumor burden FL, a "watch & wait" policy is currently the first-choice approach, although possible alternatives are discussed. Early stage FL may be treated with local radiotherapy although the role of minimal residual disease in possible additional agents should be determined. The first line treatment for symptomatic FL is chemo-immunotherapy followed by two years maintenance therapy with anti-CD20 monoclonal antibodies. A deeper knowledge of FL biology has opened new perspectives regarding the timing of therapy and has offered new targets for the development of novel agents that aim to change the therapeutic scenario of FL management.

**Expert commentary:** The introduction of novel agents could question the incurability of FL and change the therapeutic goal from prolonging the complete remission state to eradicating the disease in young/fit patients, as well as improving quality of life in elderly/unfit patients. In the near future, combining new biologic agents and adoptive cell therapies could help in achieving these aims.

**Keywords:** follicular lymphoma, molecular biology, MRD, novel agents, PET, prognosis, stem-cell transplant

## 1. Background

Follicular lymphoma (FL) is the second most frequent subtype of nodal lymphoid malignancy in Western Europe affecting roughly 5/100.000 individuals per year[1]. The genetic hallmark of FL is the translocation t(14;18)(q32;q21) leading to overexpression of the anti-apoptotic B-cell lymphoma/leukemia 2 (*BCL2*) oncogene[2]. However, up to 50% of FL cases lack the t(14;18) translocation depending on disease stage[3]. The detailed mechanisms of FL ontogenesis were recently better clarified, opening the possibility to new therapeutic approaches[2]. Besides t(14;18) translocation, recurrent gene aberrations such as *TNFRSF14*, *EPHA7*, *EZH2*, *CREBBP*, *EP300*, *MLL2* and *MEF2B* have been identified[4]. A few t(14;18)-positive B cells can be detected in healthy subjects, and these B cells are reported to have their own biological features that are closely related to the pathogenesis of FL[5]. On the other hand, FL is characterized by a unique microenvironment, which allows the survival and development of FL subclones[6]. Diagnosis is based on the peculiar histologic nodular pattern, in which the relationship of centrocytes and centroblasts defines different grades from 1 to 3, the latter classification divided into 3A and 3B grades: 3B is almost completely composed of centroblasts with a nodular growth pattern and is considered similar to a diffuse large B cell lymphoma (WHO)[7]. The initial work-up for staging includes bone marrow biopsy and computed tomography (CT). Positron emission tomography (PET)-CT is used for pre-treatment tumor burden assessment, improving the accuracy of staging, as well as to evaluate the response to treatment. Also, its role in the identification of truly localized cases (Ann Arbor stage I/II) is essential[8]. Several prognostic algorithms were developed: "follicular lymphoma international prognostic index- FLIPI" created before rituximab introduction; post-rituximab era (FLIPI2) and more recently with the support of molecular biology m7-FLIPI[9,10,11]. Using micro-array profiling, Huet et al built a 23-gene expression-based predictor of progression free survival (PFS), able to identify those patients with a high risk of early progression[12]. These scores, although efficiently separating patients in different risk groups, are not currently used to choose different treatment strategies. The therapeutic approach still mainly depends on symptoms and stage. Around 10-20%

of FL according to WHO occur with a limited stage (Ann Arbor stages I and II)[13] at diagnosis. These cases are mainly approached with involved-field radiotherapy (IF-RT)[14]. The role of R consolidation is under evaluation (see below). The advanced stages (Ann Arbor stages III and IV) are further divided in to asymptomatic-low-tumor burden patients and treatment requiring patients, as defined by the GELF criteria (table 4)[15]. These two entities have a different therapeutic strategy: for low-tumor burden, treatment is usually deferred due to the indolent course of the disease, until symptom occurrence or disease progression. For advanced stage symptomatic FL, an early treatment with combined regimens of chemo-immunotherapy is recommended[16,17]. The present paper aims to review the current literature on present and future therapeutic approaches for the treatment of FL.

### 1.1 Molecular detection of *BCL2/IGH* rearrangement

The t(14;18) translocation (q32;q21) causes the juxtaposition of the *BCL2* oncogene to the immunoglobulin heavy chain gene (*IGH*), resulting in an over-expression of the BCL2 protein and, consequently, in the clonal deregulation of cell cycle control and apoptosis[18,19]. This event is considered the first hit of a multistep process leading to the acquisition of a number of additional genetic or epigenetic events leading to FL development and/or progression[20]. The t(14;18) can be molecularly investigated in the peripheral blood (PB) and/or bone marrow (BM), providing a sensitive tool for minimal residual disease (MRD) detection after treatment and in the follow-up with prognostic implications. The European group BIOMED has developed polymerase chain reaction (PCR)-based protocols for the identification of the *BCL2/IGH* rearrangement[21]. The available markers are: MBR (major breakpoint region), mcr (minor cluster region)[22] and 3'MBR/5'mcr (minor BCL2 rearrangements)[23]. The real time TaqMan PCR approach (RQ-PCR) is used for the quantification of the MBR rearrangements, while no validated assay is yet available for the study of the other breakpoints. The third generation droplet digital PCR (ddPCR), has recently been tested in a few studies (including one from our team[24]) showing a comparable sensitivity and a

potentially greater accuracy for the detection and quantification of molecular targets[25]. The predictive role of MRD has already been established in advanced stage FL, by a large FIL (Federazione Italiana Linfomi) trial (FOLL05) which confirmed that MRD negativity after treatment was predictive of a better PFS compared to MRD positivity[26]. As regards early stage FL, in a previous work we showed that despite a negative bone marrow biopsy, tumour cells can contaminate the PB and/or BM in about 60% of patients at diagnosis[27]. This is relevant for lymphoma physiopathology and the definition of the disease extension at presentation[28]. Moreover, we reported that IF-RT on the primary site of the disease was able to clear *BCL2/IGH*+ cells from the PB and BM in more than 50% of the cases, when the basal level of circulating lymphoma cells was $<1x10^{-5}$ [27]. These findings have brought to the ongoing FIL trials (FOLL12 -EudraCT: 2012-003170-60- for advanced stage and MIRO' -EudraCT: 2012-001676-11- for early stage FL, respectively), in which MRD drives the post-induction treatment with anti-CD20 monoclonal antibodies (moAbs).

**1.2 FDG-PET in FL**

The role of F-fluorodeoxyglucose (FDG)-PET in diagnosis and staging of FL has been extensively studied and, since 2014, after the publication of the so called "Lugano Classification", it has entered the routine clinical practice[29,30]. In the field of indolent lymphomas, FL has a high avidity for FDG and, for this reason, PET has shown high rates of sensitivity and specificity when compared to CT alone[30]. Advantages are evident in defining both nodal and extranodal disease localizations, offering a reliable method for staging patients with FL[31]. In particular, as demonstrated by Luminari et al., the impact of PET on staging was higher for patients with early stage disease: in a population of 142 patients from the FOLL05 trial, 62% initially defined as stage II were actually upgraded to stage III or IV, with relevant prognostic and therapeutic implications[32]. However, PET has sub-optimal specificity and sensitivity in defining Bone Marrow Involvement (BMI) (20.3-28.9% sensitivity)[33]. As defined in the study of Perry et al., quantitative evaluation of SUV (Standardized Uptake Value)

seems to correlate with BMI: in particular, a SUV <1.7 would exclude the BMI, on the contrary a SUV> 2.7 would confirm the BMI[34]. Despite these results, at present PET cannot replace Bone Marrow Biopsy (BMB) in defining BMI[32,35,36]. Another possible use of PET is to identify active disease, in the aim of selecting suitable lymph nodes to be biopsied, as well as areas of histologic transformation into aggressive disease. Recently, the focus has shifted to TMTV (Total Metabolic Tumor Volume), a functional parameter derived from PET at baseline, which has already shown a close correlation with the outcome in terms of PFS and overall survival (OS) in patients with high-tumor burden FL[35]. The role of TMTV as an independent prognostic factor in FL has recently been demonstrated by Meignan et al: by defining a TMTV cut-off of 510m$^3$, they observed as patients with TMTV ≤510m$^3$, compared to those with TMTV> 510m$^3$ had a better prognosis in terms of 5y-PFS and OS[35]. In the same study, the combination of TMTV and FLIPI-2 allowed to divide patients into three different groups in terms of prognosis. In conclusion, TMTV was defined to be a strong predictor of outcome and can be helpful in identifying patients with severe prognosis since diagnosis. The utility of PET in the evaluation of response after induction chemotherapy has been demonstrated by three retrospective studies: the LYSA PRIMA trial[36], FIL FOLL05 trial[37] and GOELAM trial[38]. These studies have highlighted that patients with negative PET after induction chemo-immunotherapy present higher rates of PFS and OS than patients with positive PET, as shown in Table 1-3. Post-induction PET evaluation is therefore strongly recommended in clinical practice.

## 2. Therapeutic approaches

### 2.1 Early stage FL

A minor part of FL (10 to 20 % according to WHO) are diagnosed as early stage according to the Ann-Arbor staging system (stage I-II)[8]. The correct definition of this particular entity is now more accurate with the use of PET/CT, which allows the identification of really localized disease[35]. Thus, this approach is especially recommended for localized FL staging. As regards the treatment of this

rare entity, despite the paucity of randomized clinical trials, radiation therapy (RT) is usually preferred, resulting in 10-year overall survival (OS) rates of 60–80%, with a median survival of approximately 19 years[39]. Alternatively, an initial observation strategy is also broadly employed with some authors reporting similar survival results[40]. Nevertheless, a recent analysis from the SEER registry, has demonstrated a clear OS advantage in patients with early stage FL treated with RT *vs* observation[41]. Despite the impact of R treatment on the outcome of advanced stage FL, as well as many other B-cell lymphomas, is established[42-44], its role in early stage FL is less clear, due to the rarity of the disease and its very indolent nature[45,46]. The current European Society of Medical Oncology (ESMO), as well as the National Comprehensive Cancer Network (NCCN) guidelines, suggest IF-RT as the preferred upfront treatment option in patients with early stage FL, reserving watchful waiting (or eventually R as single agent) only to selected cases[47]. Moreover, RT could induce systemic anti-tumor immune response and tumor regression also in sites distant from the irradiated ones, note as abscopal effect[48]. At present, the standard dose for IF-RT is 24 Gy which has been demonstrated in a randomized trial to be as effective as higher dosages[49]. However, these guidelines are still not universally followed, since many patients are not treated with IF-RT[46].

The addiction of R to IF-RT in stage I–II FL patients should be hypothesized in the aim of controlling distant subclinical disease outside the radiation fields and reducing the systemic relapse rate, without the toxicity reported with combined RT and chemotherapy[50,51]. The MIR (Mabthera® and Involved Field Radiation) study, prospective multicenter trial investigated this combination, demonstrating a safe toxicity profile and promising results.

We previously reported on the use of R consolidation in early stage patients with a positive MRD[52]. The results seem to be encouraging in improving PFS, but need to be confirmed in prospective trials.

**2.2 Low-tumor burden FL**

Some patients with advanced stage FL (stage III-IV) are asymptomatic at diagnosis, not fulfilling the GELF criteria for the definition of treatment requiring disease (table 4). In this setting, no benefit of immediate treatment was recorded when compared with a watchful-waiting approach[60]. Delaying chemotherapy is important in order to avoid side effects, considering disease course. In the pre-rituximab era, no difference in OS and cause-specific survival (CSS) was found between the group of patients treated with chlorambucil and the observation group. In this last group, the median time to systemic treatment was 30 months and 19% of these patients did not require chemotherapy at 10 years follow-up (40% if older than 70 years)[61]. With the advent of anti-CD20 moAbs and their low toxicity profile, several trials have investigated the efficacy of R monotherapy in patients with low-tumor burden FL (LTBFL). In 2001, P. Colombat et al published the results of a clinical and molecular study performed on 50 patients who received R induction (375mg/m2 weekly for 4 weeks)[62]. The authors reported an overall response rate (ORR) of 73%, with 20% complete response (CR) and 6% unconfirmed CR (CRu). This study showed that R has a high clinical activity and a low toxicity inducing a complete molecular remission in this subgroup of patients. In 2012, an updated survival analysis of the same cohort was published, with a 7 years follow-up. This analysis confirmed the high efficacy of single-agent R: 52% of patients reached CR/CRu[63]. Moreover, MRD was confirmed to be a powerful prognostic tool for PFS. In support of a watchful waiting approach, in the F2 study P. Solal-Céligny et al. compared a group of patients with LTBFL who received a R based regimen (n=242) to another group of patients who were only observed (n=120)[64]. The 4-year freedom from treatment failure (FFTF) and the OS of the two groups were similar, suggesting that observation remains an appropriate approach in asymptomatic patients with LTBFL. In 2014, K. M. Ardeshna et al have compared the watchful waiting approach with immediate R treatment in a randomized trial involving 379 patients[65]. The authors concluded that in patients with LTBFL, immediate treatment with R monotherapy significantly delays disease progression and time until chemotherapy or radiotherapy compared with a watchful waiting approach. Progression-free

survival after maintenance R was significantly better than both watchful waiting and the use of R induction without maintenance. Nevertheless, no difference in OS was observed. Overall, R monotherapy was well tolerated with a better quality of life (QoL). Basing on these findings, the authors suggest R monotherapy for patients with asymptomatic LTBFL. As result, regarding the management of patients affected by LTBFL, the generically recommended approach of therapy abstention in these asymptomatic patients is surely agreeable, since it does not affect OS and the therapy-related toxicity is delayed. Nevertheless, the role of treatment on QoL is questionable: many patients show concern in living with cancer without receiving treatment[65]. Another relevant point is the risk of FL transformation to an aggressive lymphoma: there is not a clear-cut answer to the question whether the initiation of early treatment is protective against transformation. A huge number of patients collected by Federico et al, is currently been analysed retrospectively, attempting to demonstrate a possible increased risk of transformation in FL not receiving R in induction and/or maintenance.



**2.3 Treatment-requiring FL**

As stated above, patients fulfilling the GELF criteria require an immediate treatment. Currently the combination of R plus chemotherapy represents the standard of care for frontline treatment. Four prospective studies comparing different poli-chemotherapeutic regimens with or without R have shown a significant increase in PFS and OS in R arm[67-70]. No major adverse events were recorded with the addition of R. Whether any of the different chemotherapeutic regimens has clear advantages over the alternatives remains currently unanswered. The FOLL05 trial compared R-CVP (cyclophosfamide, vincristine, prednisone), R-CHOP (cyclophosfamide, doxorubicin, vincristine, prednisone) and R-FM (fludarabine, mitoxantrone), showing that R-CHOP and R-FM resulted in a superior PFS compared to R-CVP[71]. A 2017 update of the same study confirmed this result showing that R-CVP was associated with higher risk of lymphoma progression compared to R-CHOP[72]. More recently, another trial from Rummel et al investigated the role of bendamustine (B)-R as an alternative first line treatment in this subset of patients. Their results suggested an increase in PFS

in the BR arm, compared to R-CHOP (OR:92%, CR: 40% *vs* OR: 91%, CR: 30% respectively). A lower toxicity profile was also recorded[73]. The results of the BRIGHT study also confirmed the non-inferiority of BR compared to R-CHOP and R-CVP, with a better ORR in the BR arm (BR: 97% vs R-CHOP/R-CVP: 91%) and comparable safety profiles[74]. BR is currently the standard of care for first line treatment of FL in many centers, although some authors still prefer R-CHOP for high-risk patients. Grade 3a FL was not included in the analysis of the aforementioned studies; thus, there is no formal demonstration of non-inferiority (nor superiority) of BR over R-CHOP in this subset of patients. A recent retrospective study analyzed this point suggesting equal or more profound efficacy and less toxicity in the BR arm[75]. Nevertheless, these data need a prospective validation. Despite the improvement in ORR and OS brought by R-chemo in these patients, progression and/or relapse is a common event. Thus, to increase TTP, several strategies have been considered during years: consolidation with radio-immunotherapy or autologous stem cell transplantation in first-line did not prove to be useful (see below). Conversely, a maintenance with R has proven to be more attractive and gave better results. The PRIMA study, involving 1217 patients from more than 200 centres, is a randomized comparison of R maintenance vs observation[76]. R maintenance causes an improvement of the results inducing the conversion of more than 50% of patients obtaining a partial response (PR) after induction into CR. The update of the same analysis confirmed a significant increase in 6-years PFS in the R arm, irrespective of age, FLIPI risk, resulting in a higher rate of CR at the end of the 2-year maintenance period. No impact on OS was recorded[77]. Considering the low toxicity profile of R maintenance, the PRIMA trial aims to demonstrate a possible role of R maintenance for patients achieving remission after first-line treatment. Although an improvement in PFS has been demonstrated after R-CVP, R-CHOP and R-FCM, a role of R maintenance has still not been proved after BR. However, a sub-analysis of the BRIGHT study from the latest ASH-meeting suggested a significant PFS improvement in the BR arm treated with R maintenance *vs* observation[78]. Whether all subgroups of treatment-requiring FL take advantage from R-maintenance is currently being investigated by ongoing studies. More

promising in improving the already good results of first line treatment in FL is the introduction of other drugs acting with alternative mechanisms to chemotherapy, including novel MoAbs. Several trials are exploring these options as illustrated in the dedicated section. One of these, obinutuzumab (GA101; G), has currently entered the clinical practice. G is a glycoengineered type II anti-CD20 mAb which showed a greater direct cell death induction and ADCC/ADCP activity compared to R[79]. It also proved active in association with chemotherapy in patients with NHL who had previously received R. Few studies attempted to verify whether a more efficient MoAb could improve the already good results obtained by R in combination with chemotherapy. The GALLIUM study is a randomized phase III trial which investigated the role of G as a substitute to R both in induction (plus chemo) and in maintenance[79]. At the end of the trial, OS and response rates (CR and ORR) were mostly comparable between the two arms, whilst investigator-assessed PFS showed to be significantly superior in the experimental arm (G-chemo) compared with the standard one (R-chemo). Whether G will eventually consolidate as the new standard of care and a potential substitute to R is still to be established. Moreover, new chemo-free regimens like Lenalidomide and Rituximab and others are under evaluation, as discussed below.

**2.4 Relapsed-Refractory FL**

With the introduction of new agents and their combinations, the available options for relapsed-refractory FL are rapidly increasing. Several trials have investigated the role of novel agents in prolonging the outcome of this subset of patients: B monotherapy[80], ofatumumab monotherapy[81], idelalisib monotherapy[82]. The GADOLIN study was conducted on patients with R-refractory NHL, comparing an experimental arm, based on G + B in induction followed by G maintenance with a standard arm of single agent B in induction without maintenance[83]. The updated results of this study confirmed that G-B induction plus G maintenance significantly reduces risk of progressive disease showing a small advantage also in OS in comparison with B alone [84]. This combination is a therapeutic option for patient relapsing after R containing first-line treatments. Thus, the choice of

several treatment options for relapsed/refractory FL patients, ranging from watch and wait to very aggressive approaches, as well as new biologic agents, is influenced by factors such as: age, comorbidities, duration of previous CR, amount of previous treatments, current tumor burden and biologic features of the disease. In general, in a young and fit FL patient, the aim is a deep and long-lasting CR and, potentially, the disease eradication. Conversely, in elderly patients and/or with comorbidities, the aim could be to obtain a good quality of life with a co-existing disease.

**2.5 Role of transplant**

Hematopoietic cell transplantation (HCT), both autologous (auto-) and allogeneic (allo-), has long been considered as salvage therapy for relapsed/refractory FL patients. However, the lack of randomized trials that compare current treatments with HCT, are questioning the role and the timing of transplantation in general and of allo-HCT in particular. Three randomized trials from the pre-rituximab era[85-87] and one from the rituximab era[88] evaluated the role of upfront auto-HCT consolidation versus observation in patients with advanced stage FL who were in remission after first-line therapies. Despite a consistent PFS benefit, suggesting some disease control effect of dose intensification, none of these studies observed an OS benefit with auto-HCT consolidation. Based on these results, auto-HCT is not recommended as consolidation in first remission in FL. In relapsed/refractory FL, auto-HCT is largely used in fit patients, although perspective comparison studies with conventional salvage chemotherapy are rather weak. The National LymphoCare Study (NLCS) recently reported that patients with FL who experience relapse within 2 years of starting first-line immune-chemotherapy represent a biologically high-risk cohort with an extremely poor prognosis[89]. On the basis of these observations, the Center for International Blood and Marrow Transplant Research (CIBMTR) and NLCS recently investigated the role of auto-HCT in patients with FL who experience an early failure of immune-chemotherapy. A preliminary report of this analysis demonstrated that the early application of auto-HCT—that is, within 1 year of experiencing early failure—in patients with NLCS-defined high risk FL, was associated with an OS benefit

compared to similar patients who did not undergo auto-HCT. Contrary to auto-HCT, allo-HCT is potentially curative for patients with FL. The lower risk of relapse and durable remissions in patients with FL who underwent allo-HCT are due to graft-*vs*-lymphoma (GVL) effect. Registry data from the CIBMTR and the European Group for Blood and Marrow Transplantation (EBMT) demonstrate that a plateau in relapse risk occurs 2 to 3 years after allografting for FL, which indicates that a substantial proportion of these patients can be cured with allo-HCT[90-91]. Many prospective single-arm studies have evaluated the role of allo-HCT in relapsed/refractory FL employing reduced-intensity conditioning (RIC) regimen. RIC regimen provides disease control while facilitating donor cell engraftment, which allows the subsequent eradication of disease via the effects of GVL. RIC regimen is also safer in older and sicker patients. However, the majority of FL patients is >60 years at diagnosis and often present with comorbidities that can contraindicate allo-HCT even with the RIC regimen. Choosing between auto and/or allo-HCT remains a controversial issue. The benefits of auto-HCT include relatively low morbidity and mortality. However, allo-HCT can be a reasonable alternative for patients who are candidates but have a contraindication for auto-HCT, i.e: heavy marrow involvement or a difficulty to mobilize an adequate number of peripheral stem cells. CIBMTR conducted a registry study that compared auto-HCT with RIC allo-HCT in patients with FL who received R-based therapies before undergoing transplantation[92]. This analysis suggested that auto-HCT and allo-HCT, when applied as the first transplantation approach, provided comparable outcomes—PFS and OS—in relapsed/refractory FL. However, the risk of relapse was substantially lower after allo-HCT (even though the mortality was significantly higher). EBMT recently reported the outcomes of patients with FL who underwent RIC allo-HCT after auto-HCT failure[93]. The 5-year OS and PFS were 48% and 51%, respectively, and mortality was 27% at 2 years, which suggests that RIC allo-HCT can be an effective salvage strategy in patients with FL who experience disease recurrence after prior auto-HCT. These results suggest that, in young and fit patients relapsing after several lines of immune-chemotherapy (and eventually auto-HCT), allogenic transplant is a powerful and potentially curable weapon. Nevertheless, for unfit/elderly

patients, other strategies should be considered with the aim of delaying progression and keeping the disease under control. With the advent of novel biological agents, the timing and the role of transplantation are dramatically changing: although disease eradication with the new drugs is not a reliable option at the moment, these can play a role in obtaining a better response both in clinical and molecular terms, deferring or even deterring the need for auto/allo-HCT. In addition, CAR-T cells, by eliciting a specific and durable immunologic response against tumor cells, could assume in the next future an alternative role to allo-HCT.

**2.6 Novel therapeutic approaches in FL**

The availability of agents targeting several other biological pathways is currently modifying the treatment algorithm for FL. Some of these have already been tested in first-line approaches, whereas the majority of data are available for relapsed/refractory FL. In this setting we are reviewing the most relevant ones.

**Lenalidomide** is an oral immunomodulatory agent, derived from thalidomide, which has already shown activity toward Non Hodgkin Lymphomas (NHL) both a single agents as well as in combination. Fowler et al. have studied the role of lenalidomide and rituximab (R2) in untreated, advanced-stage NHL, including patients with FL (n=45), and reported an exciting ORR of 90%, with 87% CR (76% CR and 11% CRu) and 11% PR. The PFS at 3y was 78.5%[94]. Similar results have been obtained by Martin et al. in the ALLIANCE study, with an ORR of 95% (72% CR); at 2y and 5y PFS was respectively 86% and 70% and the 5y OS was 100%[95]. Nevertheless, a definitive answer about R2 effectiveness is awaited upon the results of the randomized RELEVANCE trial (Clinical Trails.gov - NCT01650701), which compares R2 *vs* the available standard chemotherapy (R-CHOP, BR, R-CVP). At the time of writing the results are not yet available, although they will be presented soon. The role of lenalidomide in maintenance is object of the MAGNIFY study (Clinical Trails.gov - NCT01996865), a phase 3b, multicenter, open-label study on patients with grade 1-3b or transformed FL. After an induction period, which includes 12 cycles of lenalidomide

plus R, patients are randomized to maintenance lenalidomide plus R or R alone. The primary endpoint is to evaluate the PFS and safety of this regimen. Within relapsed/refractory FL, Tuscano et al have shown that the R2 combination can produce durable clinical response: in 22 FL patients with a median of 3 prior lines of treatment treated with R2, the reported ORR was 77% (41% CR/CRu 41% and 36% PR)[96]. In another study (CALB 50401, Alliance) comparing lenalidomide alone *vs* R2, Leonard et al. showed that R2 was more active with an ORR respectively of 76.1% *vs* 53.3%, CR 39.1% *vs* 20% and PR 37% *vs* 33.3%[97]. In the GALEN phase I trial, Morschhauser et al combined G and lenalidomide in patients with relapsed/refractory FL: in 20 patients, the ORR was 68% with 54% CR.[98]. The recommended dose of lenalidomide and the efficacy of the combination of lenalidomide and G for relapsed FL is now object of another study (Clinical gov trial - NCT01582776).

**Ibrutinib** is an oral inhibitor of Bruton's tyrosine kinase which has already shown a certain grade of activity in relapsed/refractory FL. Advani et al. reported an ORR of 45.5% (27% CR) in 16 FL patients treated with ibrutinib[99]. Not very encouraging results also derived from the recent update of CONSORTIUM clinical trial: in 40 patients with relapsed FL, the treatment with ibrutinib single agent (560mg/day) resulted in an ORR of 37.5%, with 12.5% CR, a median PFS of 14 months and 2-years PFS of 20.4%. Interestingly, the activity of Ibrutinib was higher in patients not refractory to R; by next generation sequencing approach, authors have identified CARD11 somatic mutation as a predictor of poor response to Ibrutinib[100]. In the future, this information may be useful to develop targeted therapies. More promising results are emerging from the combination of ibrutinib with other drugs: Fowler et al. combined ibrutinib with R in previously untreated FL patients (Clinical gov trial - NCT01980654). Patients received oral ibrutinib 560mg/die until progressive disease combined with 4 weekly doses of R (375 mg/m$^2$). Preliminary data on 60 patients with a median follow-up of 10.2 months suggest an important clinical activity of the two agents with an ORR of 82%, with a 27% CR and 55% PR. The use of chemo-free regimens does not mean toxicity-free: in

the same study the authors observed bleeding events in 32% of patients (only one Grade 2), atrial fibrillation in 5% and secondary malignancies in 7%.

**Idelalisib** was the first phosphoinositide 3-kinase (PI3K) inhibitor approved by FDA (Food and Drug Administration) for the treatment of relapsed FL as monotherapy for patients who have received at least two prior systemic therapies[101]. In the phase II study that led to the registration of idelalisib for FL, Gopal et al. have shown antitumor activity in patients with indolent NHL who had received extensive prior treatments and became refractory to R and alkylating agents. In 72 patients with FL, after a median duration of treatment of 6.6 months, ORR was 57%, with 7% CR and 50% PR. The median duration of response (DOR) was 12.5 months with a PFS of 11 months. The most common adverse events were: serum elevation of hepatic aminotransferase level in 47% patients, grade 3 transaminitis in 13%, grade 3 colitis or diarrhea in 13%[102]. A retrospective post hoc analysis demonstrated that idelalisib is also effective in high risk patients with FL: 37 patients with early progressive disease (PD) treated with idelalisib showed an ORR of 56.8% (13.5% CR and 43.2% PR). The DOR was 11.8 months[101]. Based on these results, within high risk refractory patients, idelalisib may represent a valid opportunity though other propsective studies are necessary. Nevertheless, caution should be advised for the occurrence of unexpected toxicity: an excessive mortality was observed compared to placebo[103]. Thus, an adequate Pneumocystis prophylaxis and Cytomegalovirus monitoring are recommended. A phase-I clinical trial investigated the combination of idelalisib and R2 in relapsed/refractory FL and mantle cell lymphoma (MCL). Unfortunately, this combination showed excessive toxicities including grade 3 or higher transaminitis, hypotension, rash, sepsis syndrome, and pulmonary infiltrates, leading to interruption of the study[103]. The results of phase-III BRIDALVEIL trial investigating the combination of Idelalisib plus BR are awaited (Clinical gov trial - NCT01732926).

**Copanlisib**[104] is an intravenous pan-class PI3K inhibitor with predominant and potent activity against the PI3K-α and PI3K-δ isoforms, recently approved by FDA for the treatment of patients with relapsed FL who have received at least two prior systemic therapies. A phase II study has

demonstrated the activity of Copanlisib: in 104 FL patients the ORR was 59% with 12% CR, DOR was 22.6 months and PFS 11.2 months[105].

Other PI3K inhibitors (i.e. Duvelisib and others) are also currently being investigated for the treatment of relapsed FL, with promising results[106].

The emerging role of **check point inhibitors** in the treatment of B-cell Lymphomas is now object of study. Nivolumab is a fully human IgG4 PD-1 (Programmed Death-1) immune checkpoint inhibitor antibody that binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function.[107]. The efficacy of Nivolumab is related to PD-1 levels of intratumoral T cells; in FL, PD-1 is highly expressed[108] and preliminary results of phase-Ib study seem to demonstrate some activity of Nivolumab in previously treated patients with FL. In this study the ORR was 40% in FL (10 patients), with 10% CR, 30% PR and 60% SD with manageable toxicity[109]. Other studies are necessary to confirm these data and to evaluate the duration of response. The use of checkpoint inhibitors seems to be more promising in combination with other agents: an open-label, non-randomized, single institution, phase II trial has tested pembrolizumab combined with R for the treatment of R/R NHL. The ORR was 80% with 60% CR, and a reported acceptable toxicity profile[110].

Despite the constitutive BCL2 expression represents one of the hallmark pathogenic pathways in FL, BCL2 inhibitors did not show equivalent efficacy as observed in CLL and other hematologic malignancies. **Venetoclax** is an oral highly selective BCL2 inhibitor which was reported to restore the apoptotic ability of malignant cells[111]. A phase I study, investigating the effect of Venetoclax monotherapy in 29 patients with R/R FL, reported an ORR of 38%, with 14% CR and 24% PR[112].

**Chimeric Antigen Receptor (CAR) T cells** are emerging as a novel treatment for patients with NHL resistant to standard therapies, as well as other lymphoproliferative diseases. Different clinical trials have demonstrated an important activity of anti-CD19 CAR T-cells against some types of NHL including refractory FL. A recent trial by Schuster et al. investigated the activity of autologous T cells expressing CD19-directed CAR (CTL019) in patients with relapsed or refractory DLBCL

and FL[113]. A total of 28 patients (14 with FL) received CTL019 cells and the ORR was 64%, with 71% CR in patients with FL. Notably, with a median follow-up of 28.6 months, 89% of patients had maintained the response. CAR-T cells however are associated with potential toxic effects including cytokine release syndrome (CRS) that in this trial occurred in 5 patients (18%) and encephalopathy that occurred in 3 patients with 1 fatal case. CAR T cells seem to be a promising therapeutic approach for NHL, especially for patients who are refractory to multiple lines of chemotherapy, exhibiting a remarkable ability in obtaining durable CR. On the other hand, it is necessary to improve the security profile. In terms of management, IL6 is thought to be the main driver of CRS and for that reason the IL6-R antagonist, tocilizumab has been FDA-approved to mitigate this toxicity.

**Biosimilar drugs:** Despite the introduction of new MoAbs as potential substitutes to R, it is widely accepted that R remains the standard anti-CD20 moAb for the treatment of FL because of its established long-term efficacy. However, composition-of-matter patent of R is currently expired and this has opened the way to new cost-effective compounds. Moreover, many countries with restricted resources still do not have access to patented R. For these reasons, new biosimilar drugs have been introduced[114]. "Biosimilar" refers to a biologic product that is highly similar to an approved product, except for minor differences in clinically inactive components, and for which there are no clinically meaningful differences in potency, purity, or safety. Some of the newly developed biosimilars for FL are: CT-P10 (Celltrion), GP2013 (Sandoz), PF-05280586 (Pfizer) and ABP 798 (Amgen). A randomized non-inferiority phase III trial investigated the use of CT-P10 compared with R in patients with untreated advanced stage FL. This study successfully confirmed the non-inferior efficacy, pharmacokinetics and safety of CT-P10[115]. Another biosimilar (Truxima™) has recently been granted approval for the treatment of NHL and CLL. A clinical study in patients with previously untreated FL showed therapeutic equivalence in ORR and similar efficacy, pharmacokinetic, and pharmacodynamic between GP-2013 and R[116]. Other biosimilars in development for FL are: ABP 798 (for CD20-positive B-cell NHL; ClinicalTrials.gov -

NCT02747043), BI-695500 (for LTBFL; ClinicalTrials.gov - NCT01950273), and PF-05280586 (for LTBFL; ClinicalTrials.gov - NCT02213263). The final development of one or more R-biosimilars will be crucial to solve the lack of access to R in some countries and generate cost savings for health care systems worldwide.

## 3. Expert Commentary and 5-year view

In localized stage FL, the current recommendation is a local irradiation of the involved lymph node(s), although it is not always attended by the physicians. Nevertheless, this approach achieves eradication of the disease only in about half of patients. An accurate identification of patients at high risk of relapsing, could address to a specific consolidation. Stringent evaluation of MRD with novel biomolecular techniques could be useful to lead an appropriate treatment in this subset of patients.

Patients with asymptomatic, advanced stage, LTBFL, that are currently managed with a watch and wait approach, represent an heterogeneous group: some of them will not require therapy for 10 years after diagnosis, while many other necessitate the initiation of an early treatment. More accurate prognostic scoring systems could help to identify a more appropriate and personalized approach.

Several weakness points are still evident also in management of treatment-requiring patients affected by FL. The available prognostic systems do not fully allow to identify high risk patients at diagnosis. The methods which incorporate molecular biology such as m7-FLIPI or gene expression profiling have improved the stratification, however the best indicator is POD24, available only after the induction treatment, 2 years from diagnosis. Thus, at present, the best applicable strategy is to modify the therapeutic approach on the base of the evaluation of the response to induction, using highly predictive methods such as: PET TMTV, MRD. The Italian FOLL12 ongoing trial will evaluate the efficacy of a personalized post-induction strategy based on these methods, compared to the standard of care.

The second weakness point in the management of the disease is that currently adopted therapeutic strategies have been based on several subsequent studies aimed at prolonging the response to therapy of a virtually incurable disease. Although this approach is surely agreeable in elderly ones, in young and fit patients it is probably time to persecute the goal of disease eradication. Indeed, in the experience of physicians managing FL, a minority of patients never relapse following modern treatment strategies. Hence, a change of strategy in this direction is nowadays to be considered. The quality of response evaluation employing sophisticated biomolecular techniques and PET could help in directing specific treatment strategies. As for more aggressive lymphomas, in which the mutation status of specific genes has been cleared to be useful for specific treatment strategies, this may become true also for indolent lymphomas in the next future. It is possible that new biologic agent combinations, the adoption of strategies aimed at augmenting the immune response against the disease or CAR-T cells could eventually lead to this goal.

**Key issues**

- The current prognostic options for FL are being innovated to better define groups of patients with different outcomes. The integration of molecular diagnostics (MRD, NGS mutational status and gene-expression panels) as well as PET, will help to identify patients who could benefit of different personalized therapeutic approaches.
- The use of conventional immune-chemotherapeutic regimens is still the gold-standard approach for FL patients. The definition of treatment initiation in early stages (I-II) and advanced stage (III-IV) low-tumor burden FL is still matter of discussion. The debate is between giving a treatment capable of prolonging the indolent state of the disease with low profiles of toxicities or maintain a “watch & wait” approach.
- The use of auto/allo stem cell transplantation is currently being delayed and, in some cases potentially avoided, thanks to the introduction of novel therapies.

- New agents are showing activity in patients with relapsed/refractory FL. These include MoAbs, kinase and check-point inhibitors and adoptive cell transfer therapies. However, a long-term follow-up will establish whether these agents will have an impact on OS and confirm their role in the clinical practice.

**Funding**

This paper was not funded.

**Declaration of interest**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

**Reviewer disclosure**

A reviewer on this manuscript has disclosed that they have served on advisory boards and received honoraria from Roche. Peer reviewers on this manuscript have no other relevant financial or other relationships to disclose.

**References**


1. Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. Ann Oncol.1998;9:717–20.
2. Weigert O, Weinstock DM. The evolving contribution of hematopoietic progenitor cells to lymphomagenesis. Blood 2012; 120: 2553–2561.
3. Zamò A, Pischimarov J, Schlesner M, et al. Differences between BCL2-break positive and negative follicular lymphoma unraveled by whole-exome sequencing. Leukemia. 2017 Aug 21. doi: 10.1038/leu.2017.270.
4. Kishimoto W, Nishikori M. Molecular pathogenesis of follicular lymphoma. J Clin Exp Hematop. 2014;54(1):23-30.
5. Roulland S, Kelly RS, Morgado E, et al. t(14;18) Translocation: A predictive blood biomarker for follicular lymphoma. J Clin Oncol. 2014 May 1;32(13):1347-55.
6. Dave SS, Wright G, Tan B, et al. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. N Engl J Med. 2004;351:2159–69.
7. Swerdlow SH, Campo E, Harris NL, et al. Geneva, Switzerland: WHO Press; 2008. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.
8. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68.
9. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood. 2004;104:1258–65.
10. Federico M, Bellei M, Marcheselli L, et al. 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;27:4555–62.

11. Pastore A, Jurinovic V, Kridel R et al. 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.
12. Huet S, Tesson B, Jais J, et al. A gene-expression profiling score for prediction of outcome in patients with follicular lymphoma: a retrospective training and validation analysis in three international cohorts. Lancet Oncol. 2018;S1470-2045(18)30102-5
13. Armitage JO, Weisenburger DD. New Approach to Classifying Non-Hodgkin's Lymphomas: Clinical Features of the Major Histologic Subtypes for the Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol. 1998;16(8):2780-95.
14. Filippi AR, Ciammella P, Ricardi U. Limited Stage Follicular Lymphoma: Current Role of Radiation Therapy. Mediterr J Hematol Infect Dis. 2016 Sep 1;8(1):e2016041.
15. Brice P, Bastion Y, Lepage E, et al. 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(3):1110–1117.
16. Friedberg J, Huang J, Dillon H, et al. Initial therapeutic strategy in follicular lymphoma: An analysis from the National LymphoCare Study. J Clin Oncol 2006;24:428s
17. 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.
18. Sungalee S, Mamessier E, Morgado E, et al. Germinal center reentries of BCL2-overexpressing B cells drive follicular lymphoma progression. J Clin Invest. 2014;124(12):5337–5351.
19. Klein U, Dalla-Favera R. Germinal centres: role in B-cell physiology and malignancy. Nat Rev Immunol. 2008;8(1):22–33.

20. Kridel R, Sehn LH, Gascoyne RD. Pathogenesis of follicular lymphoma. J Clin Invest. 2012;122(10):3424–3431.
21. van Dongen JJM, Langerak AW, Brüggemann M, et al. Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: report of the BIOMED-2 Concerted Action BMH4-CT98-3936. Leukemia.
22. von Neuhoff N, Dreger P, Suttorp M, Marget M, Kell S, Schmitz N. Comparison of different strategies of molecular genetic monitoring following autologous stem cell transplantation in patients with follicular lymphoma. Bone Marrow Transplant. 1998;22(2):161–166.
23. Weinberg OK, Ai WZ, Mariappan MR, Shum C, Levy R, Arber DA. "Minor" BCL2 breakpoints in follicular lymphoma: frequency and correlation with grade and disease presentation in 236 cases. J Mol Diagn. 2007;9(4):530–537.
24. Cavalli M, De Novi LA, Della Starza I, et al. Comparative analysis between RQ-PCR and digital droplet PCR of BCL2/IGH gene rearrangement in the peripheral blood and bone marrow of early stage follicular lymphoma. Br J Haematol. 2017;177(4):588-596.
25. Drandi D, Kubiczkova-Besse L, Ferrero S, et al. Minimal Residual Disease Detection by Droplet Digital PCR in Multiple Myeloma, Mantle Cell Lymphoma, and Follicular Lymphoma: A Comparison with Real-Time PCR. J Mol Diagn. 2015;17(6):652-60.
26. Galimberti S, Luminari S, Ciabatti E, et al. Minimal residual disease after conventional treatment significantly impacts on progression-free survival of patients with follicular lymphoma: The FIL FOLL05 trial. Clin Cancer Res. 2014;20(24):6398-405.
27. Pulsoni A, Starza I Della, Frattarelli N, et al: Stage I/II follicular lymphoma: Spread of bcl-2/IgH+ cells in blood and bone marrow from primary site of disease and possibility of clearance after involved field radiotherapy. Br J Haematol. 2007;137(3):216–220.
28. Mamessier E, Broussais-Guillaumot F, Chetaille B, et al. Nature and importance of follicular lymphoma precursors. Haematologica. 2014;99(5):802–10.

29. Cheson BD, Fisher RI, Barrington SF et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma—the Lugano Classification. J Clin Oncol 2014; 32: 3059–3068.
30. Dreyling M., Ghielmini M., Rule S. et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Clinical Practice Guidelines. Annuals of Oncology, 27: v83-v90, 2016.
31. Wohrer S, Jaeger U, Kletter K et al. 18F-fluoro-deoxy-glucose positron emission tomography (18F-FDG-PET) visualizes follicular lymphoma irrespective of grading. Ann Oncol 2016; 17:780-84.
32. Luminari S, Biasoli I, Arcaini L et al. The use of FDG-PET in the initial staging of 142 patients with follicular lymphoma: a retrospective study from the FOLL 05 randomized trial of the Fondazione Italiana Linfomi. Ann Oncol 2013;24,2108-2112.
33. Le Dortz L, De Guibert S, Bayat S et al. Diagnostic and prognostic impact of 18F-FDG PET/CT in follicular lymphoma. Eur J Nucl Med Mol Imaging 2010;37:2307–2314.
34. Perry C, Lerman H, Joffè L et al. The value of PET/CT in detecting bone marrow involvement in patients with Follicular Lymphoma. Medicine 2016; 95(9) e2910.
35. Meignan M, Cottereau AS, Versari A et al. Baseline Metabolic Tumor Volume predicts outcome in high-tumor-burden follicular lymphoma: a pooled analysis of three multicentre studies. J Clin Oncol 2016. J Clin Oncol. 2016 Aug 22. pii: JCO669440. [Epub ahead of print]
36. Trotman J, Fournier M, Lamy T, et al. Positron emission tomography computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET-CT in a subset of PRIMA trial participants. J Clin Oncol. 2011; 29:3194–200.
37. Luminari S, Biasoli I, Versari A, et al. 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;25:442–7.

38. Dupuis J, Berriolo-Riedinger A, Julian A, et al. Impact of [18F] 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;30:4317–22.
39. Wilder RB, Jones D, Tucker SL, et al. Long-term results with radiotherapy for Stage I-II follicular lymphomas. Int J Radiat Oncol Biol Phys. 2001;51(5):1219–27.
40. Friedberg JW, Byrtek M, Link BK, et al. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. J Clin Oncol. 2012;30:3368–75.
41. Pugh TJ, Ballonoff A, Newman F, Rabinovitch R. Improved survival in patients with early stage low-grade follicular lymphoma treated with radiation: a Surveillance, Epidemiology, and End Results database analysis. Cancer. 2010;116(16):3843–3851.
42. 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):3725-32.
43. 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):4579–86.
44. Herold M, Dölken G, Fiedler F, et al. Randomized phase III study for the treatment of advanced indolent non-Hodgkin's lymphomas (NHL) and mantle cell lymphoma: chemotherapy versus chemotherapy plus rituximab. Ann Hematol. 2003;82(2):77–79.
45. Janikova A, Bortlicek Z, Campr V, et al. 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.

46. Mondello P, Steiner N, Wasle I, Pitini V, Mian M. Radiotherapy for stage I/II follicular lymphoma (FL): is it time for a re-appraisal? Anticancer Res. 2014;34(11):6701–4.
47. Dreyling M, Ghielmini M, Rule S, Salles G, Vitolo U, Ladetto M. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v83–v90.
48. Reynders K, Illidge T, Siva S, Chang JY, De Ruysscher D. The abscopal effect of local radiotherapy: using immunotherapy to make a rare event clinically relevant. Cancer Treat Rev. 2015;41(6):503–510.
49. Lowry L, Smith P, Qian W, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. Radiother Oncol. 2011;100(1):86–92.
50. Cencini E, Puccini B, Rigacci L, et al. Radiotherapy plus rituximab as first-line regimen for localized follicular lymphoma. Leuk Lymphoma. 2017 Oct 10:1-7.
51. Ruella M, Filippi AR, Bruna R, et al. 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(4):783–791.
52. Pulsoni A, Della Starza ID, Cappelli LV, et al. Early Stage Follicular Lymphoma. Predictive Role of Minimal Residual Disease (MRD) and Impact of MRD-Driven Treatment with Radiotherapy and Rituximab on Clinical Outcome; Blood 2016 128:2959.
53. Paryani SB, Hoppe RT, Cox RSet al. Analysis of non-Hodgkin's lymphomas with nodular and favorable histologies, stages I and II. Cancer 1983;52(12):2300-7.
54. Gospodarowicz MK, Bush RS, Brown TC, et al. Prognostic factors in nodular lymphomas: A multivariate analysis based on the Princess Margaret Hospital experience. Int J Radiat Oncol Biol Phys 1984;10:489-497.
55. Vaughan Hudson B, Vaughan Hudson G, MacLennan KA et al. Clinical stage 1 non-Hodgkin' s lymphoma: long-term follow-up of patients treated by the British National Lymphoma Investigation with radiotherapy alone as initial therapy. Br J Canc 1996;69:1088-93.

56. Mac Manus 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(4):1282-90.
57. Stuschke M, Hoederath A, Sack H, et al. Extended field and total central lymphatic radiotherapy in the treatment of early stage lymph node centroblastic-centrocytic lymphomas: Results of a prospective multicenter study. Cancer 1997;80: 2273-2284.
58. Neumann H, Blanck H, Koch R, Fiedler S, Lesche A, Herrmann T. Follicle centre lymphoma: treatment results for stage I and II. Strahlenther Onkol. 2003;179(12):840-6.
59. Petersen PM, Gospodarowicz MK, Tsang R et al. Long-term outcome in stage I and II follicular lymphoma following treatment with involved field radiation therapy alone. J Clin Oncol 2004;22(14s):652.
60. Horning SJ, Rosenberg SA: The natural history of initially untreated low-grade non-Hodgkin's lymphomas. N Engl J Med 311:1471-1475, 198424
61. Ardeshna KM, Smith P, Norton A, Hancock BW, Hoskin PJ, 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 362:516-522, 2003
62. Colombat P, Salles G, Brousse N, et al.: Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. Blood 2001;97:101-106,
63. Colombat P, Brousse N, Salles G, et al.: Rituximab induction immunotherapy for first-line low-tumor burden follicular lymphoma: survival analyses with 7-year follow-up. Ann Oncol 2012;23:2380-2385.
64. 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;30:3848-3853.

65. 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;15:424–435.
66. Federico M, Caballero D, Marcheselli L, et al. The risk of transformation of follicular lymphoma "transformed" by rituximab: the ARISTOTLE study promoted by the European Lymphoma Institute. Hematological Oncology, 2017;35(S2):115–116.
67. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantlyimproves 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;106:3725–3732.
68. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005;105:1417–1423.
69. Herold M, Haas A, Srock S, et al. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. J Clin Oncol 2007;25:1986–1992.
70. Salles G, Mounier N, de Guibert S, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. Blood 2008;112:4824–4831.
71. 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):1506-13.
72. 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;1;36(7):689-696.

73. 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;381:1203–1210.

74. 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-

75. Mondello P, Steiner N, Willenbacher W, Wasle I, Zaja F, Zambello R, Visentin A, Mauro E, Ferrero S, Ghione P, Pitini V, Cuzzocrea S, Mian M. Bendamustine plus rituximab versus R-CHOP as first-line treatment for patients with indolent non-Hodgkin's lymphoma: evidence from a multicenter, retrospective study. Ann Hematol. 2016 Jun;95(7):1107-14.

76. Salles G, Seymour JF, Offner F, Lopez-Guillermo A, Belada D, Xerri L et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet 2011;377:42–51.

77. Salles G, Seymour JF, Feugier P, Offner F, Lopez-Guillermo A et al. Updated 6 year follow-up of the PRIMA study confirms the benefit of 2-year rituximab maintenance in follicular lymphoma patients responding to frontline immuno-chemotherapy. Blood 2013;223: a50

78. Kahl BS, Burke JM, van der Jagt R, et al. Assessment of Maintenance Rituximab after First-Line Bendamustine-Rituximab in Patients with Follicular Lymphoma: An Analysis from the BRIGHT Trial. Blood 2017 130:484.

79. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med. 2017 Oct 5;377(14):1331-1344.

80. Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a Multicenter Study. Cancer. 2010 Jan 1;116(1):106-14.

81. Czuczman MS, Fayad L, Delwail V, et al. Ofatumumab monotherapy in rituximab-refractory follicular lymphoma: results from a multicenter study. Blood. 2012 Apr 19;119(16):3698-704.
82. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014 Mar 13;370(11):1008-18.
83. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol. 2016 Aug;17(8):1081-1093.
84. 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 Mar 27
85. Gyan E, Foussard C, Bertrand P, et al. High-dosetherapy followed by autologous purged stem cell transplantation and doxorubicin-based chemotherapy in patient with advanced follicular lymphoma: A randomized multicenter study by the GOELAMS with final results after a median follow-up of 9 years. Blood 113:995-1001, 2009
86. Lenz G, Dreyling M , Schiegnitz E, et al: Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: Results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group. Blood 104:2667-2674, 2004
87. Sebban C, Mounier N, Brousse N, et al: Standard chemotherapy with interferon compared with CHOP followed by high-dose therapy with autologous stem cell transplantation in untreated patients with advanced follicular lymphoma: The GELF94 randomized study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA). Blood 108:2540-2544, 2006

88. Ladetto M, De Marco F, Benedetti F, et al: Prospective, multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: The superior disease control of R-HDS does not translate into an overall survival advantage. Blood 111:4004-4013, 2008
89. 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 33:2516-2522, 2015
90. van Besien K, Loberiza FR Jr, Bajorunaite R, et al: Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood 102:3521-3529, 2003
91. Robinson SP, Canals C,Luang JJ, et al: The outcome of reduced intensity allogeneic stem cell transplantation and autologous stem cell transplantation when performed as a first transplant strategy in relapsed follicular lymphoma: An analysis from the Lymphoma Working Party of the EBMT. Bone Marrow Transplant 48:1409-1414, 2013
92. Klyuchnikov E, Bacher U, Kroger NM, et al: Reduced-intensity allografting as first transplantation approach in relapsed/refractorygrades one and twofollicular lymphoma provides improved outcomes in long-term survivors. Biol Blood Marrow Transplant 21: 2091-2099, 2015
93. Robinson SP, Boumendil A, Finel H, et al: Reduced intensity allogeneic stem cell transplantation for follicular lymphoma relapsing after an autologous transplant achieves durable long term disease control. An analysis from the Lymphoma Working Party Of the EBMT. Ann Oncol 27:1088-1094, 2016
94. Fowler NH, Davis RE, Rawal S et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. Lancet Oncol 2014; 15: 1311–1318.

95. Martin P, S-H Jung, B Pitcher et al. A phase II trial of lenalidomide plus rituximab in previously untreated follicular non-Hodgkin's lymphoma (NHL): CALGB 50803 (Alliance). Annals of Oncology 2017; 28: 2806-2812.

96. Tuscano JM, Dutia M, Chee K et al. Lenalidomide plus rituximab can produce durable clinical responses in patients with relapsed or refractory, indolent non-Hodgkin lymphoma. Br J Haematol 2014; 165: 375–381.

97. J-P Leonard, S-H Jung, J Johnson et al. Lenalidomide plus Rituximab in patients with recurrent Follicular Lymphoma: CALGB 50401 (Alliance). J Clin Oncol 33:3635-3640.

98. Morschhauser F, Le Gouill S, Feugier P et al. A phase II LYSA study of obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma. Hematol Oncol 2017; 35: 52–53.

99. R-H Advani, J-J Buggy, J-P Sharman et al. Bruton tyrosine kinase inhibitor (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol 2012; 31:88-94.

100. N-L Bartlett, B-A Costello, B-R LaPlant et al. Single-agent ibrutinib in relapsed or refractory follicular lymphoma: a phase 2 CONSORTIUM trial. Blood 2018; 131(2):182-190.

101. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014;370:1008-18.

102. Gopal AK, Kahl BS, Flowers CR, et al. Idelalisib is effective in patients with high-risk follicular lymphoma and early relapse after initial chemoimmunotherapy. Blood 2017; Vol. 129, n. 22.

103. Smith SM, Pitcher B, Jung S, et al. Unexpected and serious toxicity observed with combined idelalisib, lenalidomide and rituximab in relapsed/refractory B cell lymphomas: Alliance A051201 and A051202. Blood. 2014;124:3091.

104. Scott WJ, Hentemann MF, Rowley RB, et al: Discovery and SAR of novel 2,3-dihydroimidazo[1,2- c]quinazoline PI3K inhibitors: Identification of copanlisib (BAY 80-6946). ChemMedChem 2016;11: 1517-1530.

105. Dreyling M, Santoro A, Mollica L et al. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. J Clin Oncol 2017; 35(35):3898-3905.

106. Zinzani, P, Wagner-Johnston N, Miller C, et al. DYNAMO: a phase 2 study demonstrating the clinical activity of duvelisib in patients with double-refractory indolent non-Hodgkin lymphoma. Hematological Oncology, 35(S2):69–70.

107. Wang C, Thudium KB, Han M et al. In vitro characterization of the anti-PD1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates. Cancer Immunol Res. 2014, 2 (9): 846.56.

108. Zijun Y. Xu-Monette, Jianfeng Zhou and Ken H. Young. PD-1 expression and clinical PD-1 blockade in B-cell lymphomas. Blood 2018, Vol. 131, n.1.

109. Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: Preliminary results of a phase Ib study. J Clin Oncol. 2016;34(23):2698-2704.

110. Nastoupil LJ, Westin JR, Fowler NH, et al. Response rates with pembrolizumab in combination with rituximab in patients with relapsed follicular lymphoma: Interim results of an on open-label, phase II study. J Clin Oncol. 2017;35(15). Abstract 7519.

111. Roberts AW, Davids MS, Pagel JM, et al: Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med 374:311-322, 2016.

112. Davids MS, Roberts AW, Seymour JF, et al. Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma. J Clin Oncol. 2017 Mar 10;35(8):826-833.

113. Schuster JS, Svoboda J, Chong EA et al: Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. New Engl J Med 2017;377(26):2545-2554

114. Subramanian J, Cavenagh J, Desai B, and Jacobs I. Rituximab in the treatment of follicular lymphoma: the future of biosimilars in the evolving therapeutic landscape. Cancer Manag Res. 2017; 9: 131–140.

115. Kim WS, Buske C, Ogura M, et al. Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 compared with rituximab in patients with previously untreated advanced-stage follicular lymphoma: a randomised, double-blind, parallel-group, non-inferiority phase 3 trial. Lancet Haematol. 2017;4(8):e362-e373.

116. Jurczak W, Ilidia M, Govindbabu KS, et al. A phase III efficacy and safety study of the proposed rituximab biosimilar GP2013 versus rituximab in patients with previously untreated advanced follic Treatment of limited stage follicular lymphoma with Rituximab immunotherapy and involved field radiotherapy in a prospective multicenter Phase II trial-MIR trial

**Table 1. Role of post-induction PET in follicular lymphoma.**

| | **LYSA trial PRIMA**[36] | **FIL FOLL05**[37] | **GOELAM trial**[38] |
|---|---|---|---|
| **Patients (n)** | 122 | 202 | 121 |
| **Treatment** | R-CHOP *vs* R-CVP +/- R- maintenance | R-CHOP *vs* R-CVP *vs* R-FM | R-CHOP |
| **PET+ after induction therapy** | 26% | 24% | 22% |
| **PFS PET+ *vs* PET-** | **32,9% *vs* 70,7%** at 42 months *(HR 3,3; p<0.001)* | **35% *vs* 66%** at 36 months *(HR 2,59; p<0.001)* | **51% *vs* 87%** at 23 months *(HR 6,6 ; p<0.0001)* |
| **OS PET+ *vs* PET-** | **78,5% *vs* 96,5%** at 42 months *(p=0.001)* | _ | **88% *vs* 100%** at 24 months *(p=0.0128)* |

**Table 2. Trials reporting the results of IF-RT alone for stage I-II follicular lymphoma.**

| Authors | Pts (n) | Total RT dose (Gy) | RT Volume | Follow-up (yrs) | PFS (%) | OS (%) |
|---|---|---|---|---|---|---|
| Paryani et al, 1983[53] | 26 | 35-50 | IF, EF, TNI | 5,5 | 5-yr: 62<br>10-yr: 54<br>15-yr: 42 | 5-yr: 84<br>10-yr: 68<br>15-yr: 40 |
| Gospodarowicz et al, 1984[54] | 248 | 20-50 (86%: <35) | IF | 12 | 5-yr: 56<br>10-yr: 53 | 5-yr 73<br>10-yr 58 |
| Vaughan Hudson et al, 1996[55] | 208 | 35 | NS | 10 | 10-yr: 47 | 10-yr CSS: 71-84 |
| MacManus et al, 1996[56] | 177 | 35-44 | IF, EF, TNI | 7,7 | 5-yr: 55<br>10-yr: 44<br>15-yr: 40 | 5-yr: 82<br>10-yr: 64<br>15-yr: 44 |
| Stuschke et al, 1997[57] | 117 | 26 + 10 | EF, TNI | 5,7 | 5-yr: 71<br>10-yr: 59 | 5-yr: 86<br>10-yr: 86 |
| Neumann et al, 2003[58] | 116 | 20-50 | IF, EF, TNI | 4 | 5-yr: 62<br>10-yr: 48 | 5-yr: 76<br>10-yr: 51 |
| Petersen et al, 2004[59] | 460 | 16-47.5 | IF | 12,5 | 5-yr: 56<br>10-yr: 41 | 5-yr: 79<br>10-yr: 62 |

Abbreviations: IF (involved field); EF (extended field); TNI (total nodal irradiation); NS (not specified); CSS (cancer specific survival). Adapted by Filippi AR et al[14]

**Table 3. Trials reporting R as single agent or in addition to standard IF-RT for stage I-II follicular lymphoma.**

| Authors | Pts (n) | Treatment | R Dose | Follow-up (yrs) | PFS |
|---|---|---|---|---|---|
| Janikova et al, 2015[45] | 93 | IF-RT *vs* IF-RT + R *vs* R alone | 375 mg/m$^2$ weekly x 4-8 doses | 3.4 | IF-RT: 3.3 yrs (median)<br>R: 4,9 yrs (median)<br>IF-RT+R: not reached |
| Cencini et al, 2017[50] | 41 | IF-RT *vs* IF-RT + R | 375 mg/m$^2$ weekly x 4 doses | 3.8 | 5-yr: 90 % |
| Mondello et al, 2014[46] | 108 | IF-RT *vs* IF-RT + R *vs* R alone | 375 mg/m$^2$ weekly x 4-8 doses | 1 | IF-RT: 2.3 yrs (median)<br>R: 5 yrs (median)<br>IF-RT+R: 6 yrs (median) |
| Ruella et al, 2016[51] | 94 | IF-RT *vs* IF-RT + R | 375 mg/m$^2$ weekly x 4 doses | 10.9 | 10-yr (IF-RT): 50.7% 10-yr (IF-RT+R): 64.6% |

**Table 4. GELF criteria for high tumor burden disease definition (adapted from (15) with permission)**

| |
|---|
| High tumor burden defined by at least one of the following:<br>- Involvement of three distinct nodal sites, each with a diameter of 3 cm<br>- Any nodal or extranodal (except spleen) tumor mass with a diameter of 7 cm<br>- Symptomatic splenomegaly (enlarged spleen)<br>- Cytopenias (leukocytes < 1.0 x 10/l and/or platelets <100 x 10/l<br>- Leukemia (>5.0 x 10/l malignant cells)<br>- Pleural effusions or peritoneal ascites |
| B symptoms |
| Elevated LDH or beta2-microglobulin (>3g/dl) |
| ECOG PS (>1) |