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Recent landmark studies in follicular lymphoma

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ABSTRACT

Follicular lymphoma (FL) is the most common indolent lymphoma. Therapeutic advances in the past decade have improved its prognosis, but some questions remain open, particularly over adapting therapy to each individual patient’s disease risk. Several trials and large studies dealing with biological and therapeutic aspects of FL have been published in the past few months and may have immediate or near-future practice-changing implications. These studies include risk-assessment by gene expression profiling, the therapeutic strategy in localized FL, use of obinutuzumab or lenalidomide in the front-line setting, stem cell transplant in early treatment failure and phosphatidylinositol 3-kinase (PI3K) inhibition and chimeric antigen receptor (CAR) T-cells in multiply relapsed disease. This review aims to contextualize these studies, summarize their design and results, assess their impact, highlight related questions that remain unanswered and, finally, provide a personal view as to how they change our approach to non-transformed FL.

Keywords: follicular lymphoma, gene expression, CAR T-cell, localized, obinutuzumab, lenalidomide, copanlisib, duvelisib, stem cell transplantation.
1. Introduction

Follicular lymphoma (FL) is the second most common lymphoma and the most common indolent lymphoma in the western world [1]. In the last few years many developments leading to an improved understanding of the mechanisms of the disease [2,3], showing its biological [4] and prognostic heterogeneity [5,6] and increasing the therapeutic armamentarium [7–10] have taken place. However, despite the good prognosis of most patients suffering from FL [11–14] and the good tolerability of standard regimens, there is still uncertainty around essential questions. Two of the most crucial are how to pick out the minority of patients with suboptimal response to immunochemotherapy (ICT) before starting treatment, and how to improve their outcome [5,6]. In this setting, the concept of progression of disease at 24 months or early treatment failure (POD24 or ETF, respectively, defined as progression or relapse within 2 years of diagnosis or front-line treatment [5,15]) have come to define a population with a worse overall survival (OS) [5,15–17].

The last few months have seen the publication of studies attempting to resolve this, as well as, to a lesser extent, other open questions. The purpose of this narrative review is to contextualize these studies, summarize their design and results, assess their impact, highlight related questions that remain unanswered and, finally, provide a personal view as to how they change our approach to non-transformed FL.

2. Methods

We conducted a PubMed search with the PubMed MeSH term “Follicular lymphoma” for the period between November 2017 and November 2018. We selected publications that were either practice-changing or showed practice-changing potential for the near future. These included 1) studies finding prognostic factors leading to (or with a clear promise for) risk-stratification and risk-guided treatment, 2) studies leading to the approval of a new drug, 3) studies leading to a change in standard therapeutic approach for a subset of patients and 4) early phase trials showing exceptional survival results. We would have also selected studies leading to changes in standard staging or restaging procedures but none were found. Publications considered but ultimately not
selected can be found in the Supplementary Material. A subsequent publication from February 2019 was selected during the review period. Abstracts from the most recent American Society of Hematology (ASH) and International Conference on Malignant Lymphoma (ICML) were also searched for preliminary data but the publications selected for this review had to be peer-reviewed. An exhaustive PubMed search extending before November 2017, as well as one of ongoing trials in the clinicaltrials.gov webpage, was also conducted for further context.

3. Biology, diagnosis and staging

3.1. Gene-expression to determine prognosis [18]

3.1.1. Why was the study needed

Due in large part to technological advances (i.e., the advent of next generation sequencing), the understanding of the biology and mechanisms of FL has improved [2,3]. FL is now known to be driven not only by the translocation t(14;18) but also by mutations in genes with epigenetic functions [19]. Mutations in at least one of a handful of genes are present in the overwhelming majority of patients [20]. Yet, the practical implications of this knowledge are still scarce. A gene mutation-based prognostic score (m7-FLIPI) [20] that improved the accuracy of the follicular lymphoma international prognostic index (FLIPI) in picking out high-risk patients (table 1) remains far from clinical practice. Another large study confirmed that no single mutation or small group of them has a major prognostic role in most patients [4]. Indeed, this study demonstrated that the two major adverse prognostic groups of patients with FL, those with histological transformation [21,22] and those with ETF [5], have widely different clonal patterns [4].

Beyond the genetic mutations of the neoplastic cell, tumor microenvironment is well-known to play an essential role in FL [23]. A large study published in 2004 (with samples of patients treated without anti-CD20 therapy) showed that the analysis of gene expression of non-neoplastic cells in FL diagnostic samples defined major prognostic groups [24]. Importantly, these findings were never replicated and robust surrogate biomarkers (mainly immunohistochemistry or flow cytometry) were not found [25]. Gene expression remained unexamined in patients treated with combinations including anti-CD20 agents.
3.1.2. Study design (table 1)

A study by Huet et al [18] quantified RNA expression of a very large number of genes in fresh-frozen tumor samples from 134 patients from the PRIMA trial, including genes that might be relevant to B-cells as well as to the tumor microenvironment. Those that were independently associated with progression-free survival (PFS) and could technically be assessed in formalin-fixed paraffin-embedded tissue were retained for a final model, which was validated in three patient cohorts.

3.1.3. Results (table 1)

The final model included 23 genes, most of them related to tumor cells rather than microenvironment. Patients with high-risk disease in the training cohort had a PFS (5-yr probabilities of 26% [95%CI 16%-43%]), which was inferior to that of those with low-risk disease (73% [95% CI 64%-83%]). The pooled results from the three validation cohorts (n=460) revealed similar findings (median PFS of 3.1 years vs. 10.8 years in high-risk vs. low-risk disease). The positive predictive value (PPV) of a high-risk gene expression score for ETF was 38% and that of both a high-risk gene-expression score and high-risk FLIPI increased PPV for ETF to 50%.

3.1.4. What changes, what does not and what is next

This study offers major insights into the biology of the disease, such as the adverse prognostic impact of the ICA13 expression signature, one associated with germinal center dark zone centroblasts. However, a most remarkable finding is that it seems to indirectly signal that microenvironment is less relevant with ICT than with chemotherapy alone and that the prognostic relevance of some biological features is strongly dependent on the treatment administered. These results are in line with a large study indicating that a larger percentage of tumor-infiltrating macrophages had a favorable prognostic value in patients who received rituximab maintenance and those who received anthracycline-based treatment but was an adverse factor for those who received RCVP and no maintenance [26]. The different impact microenvironment has on survival based on the treatment administered suggests that results from the Huet study may not be applicable to patients treated with agents not used in the study, including bendamustine and lenalidomide.

Prognostic impact notwithstanding, the practical implications of gene-expression testing in the
short term are questionable. The technology required (and, specially, the possibility of testing samples routinely and in time to guide therapy) is still unavailable in most institutions. Furthermore, although the impact on PFS is unquestionable, the accuracy for ETF is suboptimal. Indeed, the PPV is similar to that of the international prognostic index (IPI) [27,28], albeit with higher sensitivity, and it is unclear that these values justify recommending entering clinical trials with experimental agents. Finally, as the authors themselves acknowledge, any genetic testing carried out from just one biopsy misses relevant information from disease clones that may be found only in other sites (spatial heterogeneity) [29] and it is still unknown to what extent testing multiple sites (or circulating tumor DNA [ctDNA]) may change risk categories.

One has to wonder whether the combination of the gene-expression score and the m7-FLIPI (which only share assessment of one gene, FOXO1) or other DNA-sequencing-based scores might be more accurate in the selection of high-risk patients than either one on its own. It is also likely that the addition of other data (e.g., copy number alterations, methylome analysis, microRNAs and transcriptomics more broadly etc [30–34]) is needed for an optimal model. An important question in this setting is that of the degree of redundancy between the different biological datapoints. In an interesting study, Mottok et al [35] recently reported that high FOXP1 expression by immunohistochemistry correlates with an adverse prognosis but also correlates with adverse clinical and analytical features, TP53 mutations, a lower frequency of GNA13, TNFRSF14, MEF2B and EZH2 mutations and an activated B-cell like gene expression signature. Unfortunately, multivariable analysis to assess what drives the adverse prognosis of these patients could not be performed and studies aiming to determine which of all these correlated variables retain independent prognostic value are still needed. Predictive factors should also be sought within biological subgroups [20, 33] given that their true impact may be diluted and underestimated in cohorts of unselected FL.

Finally, even if accurate tests became available to risk-stratify patients, they would still need to show that outcomes can be improved with risk-adapted strategies. While likely, this remains unproven.

3.1.5. Personal view

Gene-expression analysis should not be performed and should not be used to guide treatment
outside a clinical trial.

4. Treatment

4.1. Localized follicular lymphoma. TROG 99.03 [36]

4.1.1. Why was the trial needed
Localized FL is an uncommon disease with an exceptionally good prognosis regardless of therapeutic strategy [37]. Guidelines favor treatment with radiotherapy (RT) alone [38] based on a lack of benefit with the addition of chemotherapy in studies conducted in the 1980s and the possibility of a cure in 40-50% of patients with this strategy [37]. However, most relapses occur outside the radiation field [37,39], suggesting that there must be disseminated disease at diagnosis. With the advent of more effective and less toxic regimens than those tested previously, it was necessary to conduct a randomized trial to determine whether the addition of systemic therapy brought any benefit to RT.

4.1.2. Study design (table 2)
The TROG (trans-Tasman radiation oncology group) 99.03 trial randomized patients with localized FL [36], staged by bone marrow biopsy and computed tomography (CT)-scan, to 30 Gy of involved-field RT vs. with the same treatment plus RCVP (although since recruitment started in 2000, rituximab was only added to the chemotherapy arm after 2006). Positron-emitting tomography (PET) was not mandatory. The primary efficacy endpoint was PFS.

4.1.3. Results (table 2)
Seventy-five patients were randomized to each arm and, with a median follow-up of almost 10 years, the addition of RCVP prolonged PFS (10-yr probabilities of 59% vs. 41%, p=0.033) but not OS (10-yr probabilities of 95% vs. 86%, p=0.4). Toxicity was greater in the combination arm but included predictable adverse events (AE). Patients staged with PET had a trend for longer PFS.

4.1.4. What changes, what does not and what is next
This trial is the first randomized one in decades for patients with localized FL [37]. As such, it shows what can be expected from two of the most reasonable (and now also evidence-based) therapeutic options. However, while we await updated guidelines to put forth their
recommendations, it is unclear that a single option is preferred in all patients. A longer PFS is consistent with the majority view that the longest possible response to front-line therapy is a worthwhile goal. And several studies, including a large prospective observational and a recent large retrospective trial [40,41], indicate that PFS with rituximab-containing strategies (regardless of the concomitant use of RT) is superior to that obtained with RT alone. Yet, PFS with RT alone is very long [36,37,39], some patients may be cured, regimens to treat relapsed disease effectively and with acceptable toxicity are available and very long-term AE, including secondary cancers and cardiovascular disease, may be lower.

It is uncertain to what extent PET-staging impacts survival in localized FL [39,40] but there is little doubt that it should be used to stage patients more accurately [37,42] because patients with already disseminated disease may be better managed as advanced-stage (and likely with watchful waiting). Most importantly, however, the TROG 99.03 trial will hopefully increase adherence to guidelines, which is a major problem with localized-stage FL [37,40,43].

It is unlikely that treatment strategies with a better efficacy/toxicity profile can be found for this subgroup of patients and most research will now have to focus on better patient selection [44]. Some patients staged with PET still eventually relapse [39] and more sensitive technology to detect advanced disease may be required. Although still at a very early stage, ctDNA is a promising technology for this purpose [45].

4.1.5. Personal view

RT should be part of the strategy of any localized FL. Patients should be informed of the pros and cons of adding ICT to RT. While we would suggest a combination of RT and ICT for those who place high value on a long PFS, we generally still recommend RT alone in patients with localized FL confirmed by PET/CT and bone marrow biopsy, except in patients with stage II disease involving non-contiguous nodal regions, disease that cannot be encompassed in a RT field or in the presence of bulky disease.

4.2. Symptomatic advanced stage FL. The GALLIUM trial [8]

4.2.1. Why was the trial needed

Rituximab has been the most relevant addition to the treatment of FL in the last two decades. But
obinutuzumab, a more potent anti-CD20 monoclonal antibody, has shown improved survival over rituximab in combination with the same alkylating agent in patients with CLL [46,47]. In FL, the combination of obinutuzumab and bendamustine has shown impressive results in rituximab-refractory patients [48].

4.2.2. Study design

The GALLIUM trial [8] was a randomized trial of chemotherapy with obinutuzumab (1g fixed dose on days 1, 8 and 15 of the first cycle and on day 1 of each cycle thereafter) vs. the same chemotherapy with rituximab for an induction phase and then a standard maintenance phase consisting of 12 doses of the monoclonal antibody over 2 years (table 3). The primary endpoint was PFS.

4.2.3. Results (table 3)

With 601 patients included in each arm (median age 58-60 years, about 40% with high-risk FLIPI), the obinutuzumab arm showed longer PFS (3-yr probabilities of 80% vs. 73%, p=0.001). The benefit was apparent in all chemotherapy subgroups but seemed greater for bendamustine, although the study was not designed to answer this question [49]. An increase in non-disease-related fatal events was seen with bendamustine (about 5% vs. <2% with CHOP and CVP) although bendamustine-treated patients were older and more comorbid. The increase in mortality seemed to be due to severe infections, particularly during maintenance, in patients ≥ 70 years [49].

4.2.4. What changes, what does not and what is next

Replacing rituximab for obinutuzumab (at the greater recommended dose of the latter) increases median PFS an estimated 3 years [50]. Its use over rituximab is consistent with the attempt to achieve the longest response with first-line for most patients, giving them the longest possible time off therapy and providing them with additional time during which more effective and/or less toxic regimens are developed. Furthermore, cumulative incidence of ETF decreased from 17% with rituximab to 10% with obinutuzumab [15], and post-ETF survival is similar with both agents [17]. However, there are arguments favoring the use rituximab. The first is a matter of cost and practicality. Rituximab is now notably less expensive and there are biosimilar drugs on the market [51]. Rituximab is currently available subcutaneously, which shortens administration time up to four times [52]. Secondly, there is no sign of a difference in OS between the rituximab and
obinutuzumab arms and one may be hard to prove given the good prognosis of FL generally [12–14]. Finally, physicians are now familiar with therapeutic alternatives for patients relapsing after rituximab combinations. Rituximab-refractory patients can now receive obinutuzumab-bendamustine with the expectation of a moderately long remission [9]. It is unknown how obinutuzumab-refractory patients can be rescued. An update of the European Society for Medical Oncology (ESMO) guidelines is awaited and may determine the role of obinutuzumab in the management of previously untreated FL. Although it is certain to become a clinical option in the front-line, it remains to be seen whether it will become the standard of care.

The GALLIUM trial has also brought back to the fore the question over the value of maintenance, considering the long remissions with standard ICT induction and the unexpected number of non-disease-related fatal events occurring during the maintenance phase in bendamustine-treated patients. Front-line rituximab maintenance still does not prolong OS, even with long follow-up [53,54] (despite an impressive median PFS difference of 4 vs. 10.5 years in the PRIMA trial [53]) and there is some evidence (albeit in a slightly different setting) that retreatment with rituximab offers similar effectiveness as maintenance rituximab [55]. Therefore, some authors have questioned the value of maintenance in some circumstances [56,57], and the latest ESMO guidelines merely suggest that physicians consider maintenance, based on its PFS benefit [38]. A recent retrospective study seems to indicate that omitting rituximab maintenance in patients in complete remission may not decrease PFS, at least in patients treated with rituximab-bendamustine [58], and two large trials (2016-004010-10 [EudraCT] and NCT02063685) are assessing the impact of omitting maintenance in the subgroup of patients with the best response to induction (PET-negative and PET and minimal residual disease [MRD]-negative patients, respectively).

4.2.5. Personal view

At present there is no evidence in support of any risk-guided strategy. However, we consider offering obinutuzumab rather than rituximab for patients with high-risk disease (high-risk FLIPI) because of the greater expected decrease in ETF. Although it seems likely that this decrease is at the expense of the patients who would have been rescued with second line obinutuzumab-bendamustine, this has not been shown [48]. Conversely, patients with low or intermediate risk
FLIPI scores are less likely to suffer ETF (and refractoriness [6,15]) and would be expected to obtain prolonged remissions and a life-expectancy similar to that of the general population with rituximab [13]. Regardless of FLIPI risk, young patients who place a high value on a longer PFS would likely also benefit from obinutuzumab instead of rituximab. More data to pick out patients who derive a benefit from obinutuzumab over rituximab is needed.

We still offer maintenance with rituximab to most patients because of the good safety profile and the substantial PFS benefit at a generally low toxicity but, based on the concerning safety data with the combination of obinutuzumab and bendamustine, we would be cautious with recommending maintenance therapy in older patients when this combination is chosen in the front-line setting.

The choice of chemotherapy is highly subject to personal experience and patient preference given that currently used regimens, including CHOP, bendamustine and CVP, have a good risk to benefit ratio and an acceptable safety profile. Guidelines do not suggest any one over the others [38]. However, absent particular patient considerations (including relevant comorbidities) or preferences, we generally favor CHOP over bendamustine based on the lower risk of opportunistic infections [8,49,59,60], the longer follow-up available with CHOP [12,61] and the greater experience with bendamustine than CHOP for relapsed disease [48,62].

4.3. Symptomatic advanced stage FL. The RELEVANCE trial [63]

4.3.1. Why was the trial needed

The biological differences between patients suffering ETF and patients with long remissions are still ill-defined [4]. However, tumor microenvironment is likely to play a significant role [23,24]. Lenalidomide is an immunomodulatory agent that could control the disease, at least in part, through immune system enhancement [64,65]. It has shown activity in early phase trials in the relapsed and front-line settings [66–68], particularly in combination with rituximab.

4.3.2. Study design

RELEVANCE was a phase 3 randomized trial [63] comparing rituximab-lenalidomide (see table 3 for the treatment schedule) vs. rituximab-chemotherapy (CHOP, bendamustine or CVP). The trial sought to establish the superiority of the experimental regimen over ICT in terms of PFS (and complete remission at 120 weeks of randomization).
4.3.3. Results (table 3)
The trial included 1030 patients (513 in the experimental arm), with a median age of 59, 49% of them with high-risk FLIPI. The primary endpoint was not met, as both arms resulted in the same PFS (3-yr probabilities of 77-78%). The dose of lenalidomide was reduced in 59% of patients and the treatment was discontinued in 11%. Although the toxicity profile was different in the two arms, there were no unexpected AE. The most common in the experimental arm were cytopenias and no grade ≥ 3 toxicity occurred in more than 5% of patients other than neutropenia and rash/cutaneous reactions. Secondary tumors were seen at similar frequencies in both arms.

4.3.4. What changes, what does not and what is next
Lenalidomide is currently not approved for previously untreated FL and, based on the results of the trial, it may not be, as the primary endpoint was not met. However, a most interesting question, based on the different antitumor mechanisms, is whether patients with ETF were biologically similar in the two arms. Clinically, the effectiveness of rituximab-lenalidomide seemed to be independent of FLIPI risk, unlike the rituximab-chemotherapy arm [63], so it is conceivable that lenalidomide is more active than the standard in at least a subset of patients with particular (adverse) biological features. We eagerly await the biological analysis of samples from patients who responded poorly to each strategy to determine whether this hypothesis has any merit. It should be noted that lenalidomide is, similar to obinutuzumab, notably more costly than ICT with rituximab, which may be a relevant consideration if lenalidomide was eventually approved for FL. Two large trials with lenalidomide in the relapsed setting are ongoing (NCT01996865, NCT01938001), one of them with very favorable results [69] and will probably lead to the approval of lenalidomide in this setting.

4.3.5. Personal view
Regardless of the approval or not by regulatory agencies, we would not suggest using lenalidomide-rituximab in patients with untreated FL, particularly in light of the GALLIUM study, which seems to indicate that obinutuzumab and chemotherapy is a more evidence-based strategy for potentially higher-risk patients.

4.4. Relapsed FL. Stem cell transplantation [70–72]
4.4.1. Why were these studies needed

With increasing attention to potential therapeutic alternatives for patients suffering ETF and multiple relapses, there has been renewed focus on stem cell transplant (SCT), both autologous and allogeneic. Although it is known that both are more toxic than standard ICT, this increased toxicity might be justified in a select group of high-risk patients in order to offer either the high doses of chemotherapy afforded by autologous SCT or the graft vs. lymphoma (GVL) effect afforded by allogeneic SCT. Prospective trials including SCT in the relapsed setting have historically been hard to conduct, and a recent one was stopped prematurely due to slow accrual [73]. This is likely due to the reluctance of patients and physicians to participate because of the high toxicity of the procedures (in a disorder that is usually quite indolent), and a lack of interest of pharmaceutical companies, which make it harder to obtain funding. Fortunately, large cohorts of patients can be analyzed from two SCT registries, the Center for International Blood and Marrow Transplant Research (CIBMTR) and the European Group for Blood and Marrow Transplantation (EBMT).

4.4.2. Study design (table 4)

In the front half of 2018, three different but complementary retrospective analyses including patients from these two registries were published. Casulo et al [70] compared outcomes from patients ≤ 70 years with ETF who did not receive SCT (from the National LymphoCare Study [NLCS]) and those who received autologous SCT (from the CIBMTR). Smith et al [72] compared allogeneic vs. autologous SCT in ETF patients from the CIBMTR. Sureda et al [71] analyzed the outcomes of all patients with FL undergoing matched-donor allogeneic SCT from the EBMT and CIBMTR.

4.4.3. Results (table 4)

Casulo et al [70] found no differences in ETF patients who received vs. those who did not receive autologous SCT generally (5-yr OS 67% vs. 60%, p=ns) but did report that patients receiving autologous SCT early after progression (i.e., ≤1 year) had a borderline higher OS (5-yr probabilities 73% vs. 60%, p=0.05). Two smaller trials in this past year have also lent support to the idea of autologous SCT being superior to standard-dose chemotherapy for patients with ETF [74,75]. Smith et al [72] found that autologous and allogeneic SCT from a matched sibling donor had
similar 5-yr OS probabilities (around 70%), substantially better than allogeneic SCT from a matched unrelated donor (5-yr OS probability of 49%) with predictable patterns in non-relapse mortality (greater in allogeneic, particularly unrelated donor, SCT) and relapse (greater in autologous SCT). Finally, Sureda et al [71] found a 5-yr OS probability of 61% in an impressive cohort of more than 1500 FL patients who received allogeneic SCT in a wide spectrum of clinical situations. Predictably, chemorefractoriness and a greater number of previous lines of treatment were correlated with lower OS.

4.4.4. What changes, what does not and what is next Despite the retrospective design and the different patient populations, particularly in the Sureda study [71], which prevent comparisons between the studies and with other published series, it is hard not to be impressed by the results reported, considering the characteristics of the patients. Autologous SCT was already recommended as the preferred option for high-risk relapse by an expert panel [76] before the publication of the landmark NLCS report [5]. However, reports from the same NLCS group [70] as well as ours [6] have found that autologous SCT is rarely used in these high-risk patients. These 3 recent retrospective studies indirectly signal that either modality of SCT should be recommended in patients with ETF fit to be submitted to it who achieve remission with rescue therapy, especially absent a clinical trial. Since the earlier the allogeneic SCT is performed, the better the outcome [71,77], there probably is not a one-size-fits-all solution to the autologous vs. allogeneic SCT dilemma and many considerations should be kept in mind. One aspect under investigation is the type of remission achieved before SCT, where PET imagining may have an important role. Although more evidence is still needed, autologous SCT appears to offer better survival for patients in complete over partial remission [78] while allogeneic SCT may offer similar results for both [79]. Other considerations include the number lines of therapy needed to achieve remission as well as issues less directly related to the FL, including the presence of comorbidities, type of donor available, the experience of the medical team with allogeneic SCT in FL and patient preference. An exhaustive review of the current role of SCT is outside the scope of this manuscript but has recently been published [80]. Although reduced-intensity conditioning now seems preferable in most patients because the GVL effect is powerful in FL, non-relapse mortality is still quite high, particular in the first months after
the procedure. Similarly, graft-vs-host-disease (GVHD) is a relevant consideration because of its impact on the quality of life of these patients. Advances in anti-GVHD therapy, as well as in biomarkers that can reliably predict GVHD, have been slow in coming but they would provide essential data to decide what type of SCT would be preferable for each patient.

Finally, SCT is not an option for all patients with ETF because a large proportion of them are not candidates to receive the procedure or do not respond to standard rescue ICT. One of the most exciting ongoing trials in this setting (NCT03269669) randomizes patients with ETF to obinutuzumab-umbralisib (a phosphatidylinositol 3-kinase [PI3K]-delta inhibitor), obinutuzumab-lenalidomide or obinutuzumab-CHOP/Bendamustine (based on the front-line).

4.4.5. Personal view

In fit patients with ETF who achieve at least a partial remission after rescue treatment (based on a non-cross-resistant regimen and with obinutuzumab as the monoclonal antibody), we generally recommend autologous SCT, especially if clinical trials are unavailable. In patients who do not respond to second-line therapy (and require further lines of therapy to achieve any remission), we favor allogeneic SCT with reduced intensity conditioning. This largely aligns with a recent expert review [80] and with a 2015 report from the European Society for Blood and marrow transplantation, which considered autologous SCT the standard of practice in chemosensitive disease after a second line and allogeneic SCT as the standard after relapse post-autologous SCT [81]. In unfit patients, the GADOLIN trial showed that obinutuzumab-bendamustine followed by obinutuzumab maintenance offers a 26-month median PFS in patients not previously exposed to bendamustine in the previous 2 years, and this seems the best option that can be offered to these patients outside of a clinical trial [9,45].

4.5. Relapsed FL. PI3K inhibition (the CHRONOS-1 and DYNAMO trials) [10,82]

4.5.1. Why were these trials needed

Patients with refractory FL are likely not to respond to subsequent lines of therapy [6]. For those patients, targeted agents have offered a much needed alternative therapeutic strategy. Idelalisib, a PI3K delta inhibitor is already approved by the federal drug administration (FDA) for patients who have received at least two previous lines of therapy and the European Medicines Agency (EMA) for
patients refractory to two previous lines of therapy. With idelalisib, responses have been shown in a substantial proportion of patients who would not be expected to respond to standard treatment [7]. However, idelalisib increases the risk of opportunistic infections and can cause severe autoimmune toxicities [83].

4.5.2. Study design (table 5)

CHRONOS-1 and DYNAMO are single arm, phase 2 trials [10,82] testing copanlisib, a pan-PI3K (predominantly alpha and delta) inhibitor, and duvelisib, a PI3K gamma and delta inhibitor, in patients with previously treated indolent NHL. Table 5 shows the treatment schedule and the inclusion criteria regarding previous treatments in both trials.

4.5.3. Results (table 5)

The CHRONOS-1 included 142 patients (104 FL), with a median of 3 previous therapies, 60% refractory to the previous line of therapy while the DYNAMO study included 129 patients (83 FL), with a median of 3 previous therapies and 98% refractory to the previous line of therapy. Efficacy results for both compare favorably with the available therapeutic strategies for this population [84–86], and appear similar to those obtained with idelalisib [7] (table 5). The leading toxicities with copanlisib were hyperglycemia, hypertension (both infusion-related) and pneumonia, which occurred (grade ≥3) in 41%, 24% and 16%, respectively [10] and seem to include fewer and less severe autoimmune complications or opportunistic infections than idelalisib [87]. AEs with duvelisib appears more similar to idelalisib and caution is advised regarding opportunistic infections and autoimmune toxicity [88].

4.5.4. What changes, what does not and what is next

Copanlisib and Duvelisib are now FDA-approved for FL relapsed after at least two lines of therapy and more such targeted agents may be approved soon [89]. This is of particular relevance for patients with ETF, for which strategies available until recently were unsatisfactory. The availability of several agents offers the option of choosing the best one for each individual patient, according to their preferences and comorbidities.

However, even if longer than with other available strategies, responses to monotherapy with PI3K are still short-lived and are probably best used as a bridge to transplantation for those patients who can potentially benefit from it. Combinations including copanlisib in indolent NHL are being tested.
in the CHRONOS-3 (NCT02367040) and CHRONOS-4 (NCT02626455) trials (with rituximab and ICT, respectively). There are no ongoing trials with duvelisib in patients with FL.

The immunomodulatory drug lenalidomide will likely soon be approved for relapsed FL based on the results of the still unpublished AUGMENT (NCT01938001) trial [69]. The trial showed a PFS benefit (median PFS 39 vs 14 months) with rituximab-lenalidomide over rituximab alone in 358 patients with relapsed (median 1 previous therapy) indolent (84% FL) NHL. However, this trial excluded patients refractory to rituximab or rituximab combinations which makes its likely that it will be largely used in a different setting than PI3K inhibitors.

4.5.5. Personal view

Although they have not been directly compared in a trial, copanlisib and duvelisib seem to offer responses similar to idelalisib in a similar population and are approved for the same clinical situation. Given the larger experience with idelalisib [90], as well as the generally preferred oral administration route, we would recommend idelalisib (with the appropriate antiinfectious measures, including P.jirovecii prophylaxis and periodic quantitative cytomegalovirus testing) in most patients. However, due to their different toxicity profiles [87,90], copanlisib could be used in in patients in whom idelalisib might be best avoided (e.g. active hepatic disease) as well as patients for whom a once weekly intravenous treatment is preferred over a daily pill (such as where there are concerns over treatment compliance).

4.6. Relapsed FL. CAR T-cell therapy [91]

4.6.1. Why was the trial needed

Chimeric antigen receptor T-cells (CAR T-cells) are T-cells that have been engineered to express an antigen relevant for the neoplastic cell to lead the patient’s immune system against it. This relatively new type of cellular therapy has been successfully used in, and is already approved for, relapsed lymphoblastic leukemia (by the FDA and EMA) and DLBCL (by the FDA) [92–94]. Given these promising results, this is a very appealing option for patients with FL in need of alternative therapeutic strategies.

4.6.2. Study design

The CTL019 is the CAR T-cell construct initially designed by the University of Pennsylvania. It is
already approved for the treatment of relapsed acute lymphoblastic leukemia [93]. It was among the first of the second generation CAR T-cells and is, therefore, among the ones with the most experience and longest follow-up. Schuster et al [91] recently reported on the extended follow-up of 14 patients with FL treated with CLT019.

4.6.3. Results

With a median follow-up of 28 months, 70% of patients (who had received a median of 5 previous lines of treatment) remained free from progression. 89% of patients who initially responded were in continued remission. Toxicity largely consisted of what has been widely reported, i.e., cytokine release syndrome, which has become more manageable with growing experience, and neurotoxicity, which is most often mild and reversible.

4.6.4. What changes, what does not and what is next

CAR T-cells offer the upside of allogeneic SCT without its greatest downside, i.e., GVHD. This has made them a bona fide revolution in malignant hematology. Probably because of the availability of many other effective therapies and clinical trials, the experience in FL is still very scarce and follow-up is insufficient given the kinetics of relapse of indolent lymphomas. Yet, the remissions observed in this trial are notably longer than would be expected in such heavily pretreated patients [84,86] or reported with targeted agents in a less pretreated population [7,10,95]. It is important to recognize that CAR T-cells are only produced (and will most likely only be produced) in a minority of institutions and are extremely costly (although in the long-term they may actually be cost-effective, particularly when compared with targeted agents, which are given until progression). This raises questions about actual availability, even when they eventually become approved for FL. More patients and further follow-up is needed to determine what CAR T-cells offer to patients with FL and what is their place in the treatment algorithms of FL. Several ongoing trials with different CAR T-cell constructs (e.g., NCT03105336, NCT03568461, NCT02721407, NCT03277729, NCT03676504) will help better understand what can be expected from CAR T-cell therapy in FL, particularly whether there are biomarkers that can reliably predict sustained clinical responses and CAR T-cell persistence.

4.6.5. Personal view

CAR T-cells are still not approved for FL but they appear to be an excellent option for multiply-
relapsed patients who can receive them within a clinical trial. They are likely to become a relevant therapeutic strategy in FL for the minority of patients with disease refractory to conventional strategies. Data from ongoing phase 2 trials will set the foundations for randomized trials in this population.

5. Summary and future considerations

Clinical and translational research in FL is very active. Table 6 shows a selection of ongoing trials. Relevant studies are published almost monthly and new drugs have been approved yearly in the past few years. In large part thanks to this, as well as improvements in supportive care, long-term outcomes are currently excellent for most patients [12,13]. And new developments follow at a fast pace. Some of these, however, may pose new dilemmas for practicing physicians because their benefit over the standard may be somewhat limited or its cost-effectiveness may be questionable. Similarly, different alternatives might be available for any one patient in a specific clinical situation. Guidelines often (wisely) leave decisions open to each specific patient because few developments are so groundbreaking that should be applied to everyone and in all cases. We have raised what we believe are the dilemmas that may arise from the major studies published in the last few months and offered our take on what they mean for FL research and how they should impact clinical practice (Figure 1). Briefly, there are no changes in staging and a PET/CT scan and bone marrow biopsy, aside from the diagnostic nodal biopsy, are the recommended tests. FLIPI and FLIPI2 remain the prognostic indices of choice to risk-stratify patients but have no formal therapeutic implications. A simplified score, which includes only beta2-microglobulin and bone marrow involvement, was recently published [96]. On the other hand, a somewhat more accurate model derived from the patients enrolled in the GALLIUM study and which includes 11 variables was also proposed in the most recent ASH meeting [97]. PET/CT is now the test of choice to both stage and restage the disease after therapy, although there are valid concerns over a lack of correlation with very long-term outcomes, false positives, and clinical overreliance on its results, particularly in FL where the mere presence of metabolically-detectable disease does not translate a need for therapy (as in high-grade lymphomas) [98]. Newer molecular or imaging-based tests
(such as m7-FLIPI, circulating tumor DNA, total metabolic tumor volume [20,45,99,100]) remain experimental, are generally not available and there is no evidence that any risk-guided strategy improves outcomes. Selection of high-risk patients by molecular analysis needs further validation and is still too complex (and not standardized) for widespread use, although this is the goal of much ongoing research and may change in the next few years. Regarding treatment, watchful waiting remains the standard for low tumor burden disease [38,101]. Long-term results of a phase III trial randomizing rituximab monotherapy vs. placebo [102] in this setting are awaited. The addition of ICT to RT in localized-stage FL has become an evidence-based alternative that improves PFS over RT alone [36]. For advanced-stage FL, a single regimen is not standard and depending on the clinical situation and patient preferences, one of two anti-CD20 antibodies (rituximab and obinutuzumab) in combination with one of three chemotherapy backbones (CHOP, CVP and bendamustine) is preferable. Obinutuzumab offers longer PFS than rituximab when added to chemotherapy for previously untreated FL [8]. Its role in the management of FL as a whole remains to be determined. The use of rituximab maintenance offers a PFS but no OS benefit. For relapsed non-refractory FL, a wide spectrum of strategies and regimens (watchful waiting, anti-CD20 monotherapy, ICT) are available, and are chosen based on disease and patient-related factors. Lenalidomide-rituximab may soon be approved and become an additional therapeutic option in this setting [69]. For patients with ETF, obinutuzumab with CHOP or bendamustine (based on the front-line) is the standard. For those who achieve remission with second-line therapy, autologous SCT should be considered, particularly where a clinical trial is unavailable. For subsequent remissions or one requiring more than two lines of therapy, allogeneic SCT may be preferred. Three PI3K inhibitors [7,10,82] are now available for patients relapsed after two previous lines of therapy. Despite the limited duration of response, the response rate is promising in a highly refractory population, and may currently be the only alternative for some patients. Finally, CAR T-cell therapy and other agents still in development may soon be available for those patients as well. Further research and upcoming trials are sure to continue to improve on the present knowledge and available strategies with the ultimate aim of offering a personalized and risk-adapted treatment to each patient.
6. Practice points

6.1. Gene-expression of a reduced panel of 23 genes offers prognostic information independent of classical clinical and analytical variables in FL but its applicability remains limited and the practical value still needs to be determined.

6.2. RCVP added to RT offers a PFS, but so far no OS, benefit over RT alone in localized FL. The best regimen for each patient likely depends on many considerations, particularly patient preference.

6.3. ICT with obinutuzumab offers a PFS, but so far no OS, benefit over ICT with rituximab. The best regimen for each patient likely depends on many considerations, particularly disease risk.

6.4. Rituximab and lenalidomide is not more effective than ICT with rituximab.

6.5. Autologous or allogeneic SCT are the therapeutic options of choice for patients with ETF, particularly in the absence of a clinical trial.

6.6. Copanlisib and duvelisib are newly approved PI3K inhibitors that offer objective, although relatively short-lasting, responses in patients with heavily pre-treated FL.

6.7. Although experience is limited, CAR T-cell therapy is a very promising approach for patients with FL and no standard therapeutic alternatives.

6.8. Ongoing trials will help better delineate therapeutic strategies in different clinical settings and new trials will lead to novel therapeutic agents and combinations offering greater efficacy and decreased toxicity for high-risk patients.

7. Research agenda

7.1. Large studies integrating multiple level biological testing including, but not limited to, gene sequencing, copy number alterations, gene-expression, microRNA and methylome analysis.

7.2. Further biological study of patients with ETF (already a major ongoing effort)

7.3. More sensitive staging in localized FL, perhaps with ctDNA.

7.4. When more accurate risk stratification is available, trials with risk-adapted approaches
including combinations of targeted agents and monoclonal antibodies with or without chemotherapy for patients with high-risk disease and standard or lower-intensity immunotherapy or immunochemotherapy for those with low-risk disease.

7.5. Response adapted maintenance or consolidation therapy (already under study).

7.6. Optimal combinations for patients with ETF, i.e., anti-CD20 plus PI3K inhibitor, lenalidomide or chemotherapy (already under study).

7.7. Prospective (and comparative) data with SCT (autologous and allogeneic) in patients with ETF.


7.9. Better understanding of the mechanisms behind CAR T-cell persistence in FL and predictors of long-term disease-free survival in CAR T-cell recipients.

**Conflict of interest disclosure**

Dr. Sancho reports honoraria from Roche, Janssen, Celgene, Kern-Pharma, Gilead, Sanofi, Servier, Mundipharma and advisory board from Roche, Janssen, Kern-Pharma, Gilead, Celltrion and Bristol-Myers. Dr Sorigue reports no conflict of interest.
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Legend

**Figure 1.** Overview of evidence-based staging, prognostic tools and strategies and treatment of follicular lymphoma (FL).
Standard of practice elements in each of these 3 areas (staging, prognosis and treatment) are encased in squares with solid lines while those that are still in development or undergoing validation are encased in squares in dashed lines.
Table 1. Design and results of the landmark gene-sequencing and gene-expression studies in follicular lymphoma (FL)

<table>
<thead>
<tr>
<th></th>
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</tr>
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<tbody>
<tr>
<td><strong>DESIGN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Previously untreated high tumor burden G1-3A FL treated with ICT</td>
<td></td>
</tr>
<tr>
<td>Training cohort</td>
<td>134 patients with fresh-frozen biopsy available, 53 also with FFPE treated in the PRIMA trial</td>
<td>151 patients treated with RCHOP from the GLSG2000 trial</td>
</tr>
<tr>
<td>Validation cohort</td>
<td>460 patients from the PRIMA trial (n=172), the mayo clinic (n=186) and the Hospital Clinic de Barcelona (n=102) with available FFPE diagnostic tissue</td>
<td>107 patients treated with RCVP in the British Columbia Cancer Agency</td>
</tr>
<tr>
<td>Technical aspects</td>
<td>Gene-expression* tested by means of Affymetrix U133 in fresh-frozen tissue. Genes correlated with PFS selected. Further selected genes (technical and biological considerations) tested by nanostring in FFPE. Genes with the best correlation in expression by both methods chosen for the final model</td>
<td>Exome of 74 genes was sequenced* from FFPE tissue. Non-silent mutations with VAF ≥ 10% analyzed</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>36% &gt; 60 years old, 49% female, 36% high-risk FLIPI, 81% RCHOPa</td>
<td>45% &gt;60 years old, 47% female, 50% high-risk FLIPIa</td>
</tr>
<tr>
<td><strong>RESULTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final model</td>
<td>Gene expression of 23 genes</td>
<td>Mutational status of 7 genes (weighted) + ECOG PS + FLIPI</td>
</tr>
<tr>
<td>C-statistic</td>
<td>0.63-0.71 (validation and training cohorts)</td>
<td>0.79-0.8 (validation and training cohorts)</td>
</tr>
<tr>
<td>PFS in the high-risk group</td>
<td>26% at 5 years (training cohort). Median 3.1 years (validation cohort)</td>
<td>HR 3.68 (training cohort), 2.3 (validation cohort)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38% at 5 years (training cohort). 25% at 5 years (validation cohort)bc</td>
</tr>
<tr>
<td>PFS in the low-risk group</td>
<td>73% at 5 years (training cohort). Median 10.8 years (validation cohort)</td>
<td></td>
</tr>
<tr>
<td>ETF</td>
<td>19% among low-risk vs. 38% among high-risk patients (Se 0.43, Sp 0.79, PPV 0.38, NPV 0.82)</td>
<td>Se 0.43-0.61, Sp 0.79-0.86, PPV 0.38-0.48, NPV 0.84-0.91 (training and validation cohorts)</td>
</tr>
<tr>
<td>OS</td>
<td>No association</td>
<td>42-65% at 5-years in the high-risk vs. 84-90% in the low-risk group</td>
</tr>
<tr>
<td>Other findings</td>
<td>TP53 mutations independently correlated with a worse OS (HR 6.3)</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>The activated macrophage/dendritic cell signature correlated with a favorable</td>
<td>Patients with EZH2 mutations showed a distinct gene expression pattern and longer</td>
<td></td>
</tr>
<tr>
<td>prognosis, unlike in a large prerituximab study [22]. The T-cell signature also</td>
<td>failure-free survival</td>
<td></td>
</tr>
<tr>
<td>correlated with more favorable outcomes, as in the older study. Of several</td>
<td></td>
<td></td>
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<tr>
<td>gene expression signatures, the authors underscore the ICA13 signature, similar</td>
<td></td>
<td></td>
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<tr>
<td>to that of dark zone centroblasts and Burkitt lymphoma cells, and which</td>
<td></td>
<td></td>
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<tr>
<td>correlated with an inferior PFS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICT: Immunochemotherapy; FFPE: Formalin-fixed, paraffin-embedded tissue, RCHOP: rituximab, cyclophosphamide, Adriamycin, vincristine, prednisone; RCVP: rituximab, cyclophosphamide, vincristine, prednisone; PFS: Progression-free survival; VAF: variant allele frequency; FLIPI: follicular lymphoma international prognostic index; ECOG PS: eastern cooperative oncology group performance status; HR: hazard ratio; ETF: early treatment failure (progression/relapse within 2 years of diagnosis); se, sp, PPV, NPV: sensitivity, specificity, positive predictive value and negative predictive value; OS: overall survival.

aData for pooled training and validation cohorts.

bFailure-free survival.

The training cohort received RCHOP and the validation cohort received RCVP.

* Unlike DNA sequencing (which analyzes the genetic sequence), gene expression profiling analyzes the quantity of each RNA molecule that is transcripted from the DNA sequence. This provides information about the activity of the cell.
Table 2. Design and efficacy results of the landmark TROG 99.03 trial, of stage I patients from the National LymphoCare study (NLCS) and of a very large analysis of RT-alone in PET-staged patients

<table>
<thead>
<tr>
<th></th>
<th>TROG 99.03 [36]</th>
<th>NLCS [40]</th>
<th>Brady et al [39]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DESIGN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Localized disease staged by CT and BMB. PET optional</td>
<td>Stage I based on BMB and imaging testing (CT or PET)</td>
<td>PET-staged localized disease treated with RT-alone (≥24 Gy)</td>
</tr>
<tr>
<td><strong>Patients and treatment groups</strong></td>
<td>N=150</td>
<td>N=206&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>N=512</td>
</tr>
<tr>
<td>75 RT alone (30 Gy)</td>
<td>35 WW</td>
<td>56 RT alone</td>
<td></td>
</tr>
<tr>
<td>75 CM (RT 30 Gy + CVP/RCVP)</td>
<td>82 I/ICT</td>
<td>26 CM</td>
<td></td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Median 57 years old, 48% female, 75% stage I, 15% bulky disease (&gt; 5 cm)</td>
<td>53% &gt; 60 years old, all stage I, treatment groups not comparable</td>
<td>Median 58 years old, 50% female, 80% stage I</td>
</tr>
<tr>
<td><strong>RESULTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median follow-up</td>
<td>9.6 years (range 3.1 to 15.8)</td>
<td>4.75 years</td>
<td>4.3 years</td>
</tr>
<tr>
<td>PFS</td>
<td>59% at 10-years for CM vs. 41% for RT alone (HR 0.57). Stage not associated with PFS</td>
<td>Median of 72 months for RT alone, not reached for other groups. ICT and CM longer than RT (HR 0.36 [95% CI 0.16-0.82] and 0.11 [0.01-0.83], respectively)</td>
<td>69% at 5 years&lt;sup&gt;c&lt;/sup&gt;. Lower for patients with stage II disease (74% in stage I vs. 49% in stage II)</td>
</tr>
<tr>
<td>OS</td>
<td>95% at 10-years for CM vs. 86% for RT alone (HR 0.62, p=NS)</td>
<td>No differences between groups (probabilities not reported)</td>
<td>96% at 5 years</td>
</tr>
</tbody>
</table>

TROG: trans-Tasman radiation oncology group; CT: computed tomography; BMB: bone marrow biopsy; PET: positron-emitting tomography; RT: radiotherapy; CM: combined modality (i.e., RT and systemic treatment); CVP/RCVP: cyclophosphamide, vincristine, prednisone with or without rituximab; WW: watchful waiting; I/ICT: immune or immunochemotherapy; PFS: Progression-free survival; HR: hazard ratio; 95% CI: 95% confidence interval; HT: histological transformation; p=NS: p value not significant; ; NR: not reported; OS: overall survival.

<sup>a</sup>Although there were 471 patients included, most of the data refers to the 206 patients staged with BMB and CT or PET.

<sup>b</sup>7 patients categorized as receiving "other" strategies and not accounted for.

<sup>c</sup>Freedom from progression defined as time from completion of RT to progression of disease (deaths were censored).
Table 3. Design and efficacy results of the landmark GALLIUM and RELEVANCE trials

<table>
<thead>
<tr>
<th></th>
<th>GALLIUM [8]</th>
<th>RELEVANCE [63]</th>
</tr>
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<tbody>
<tr>
<td><strong>DESIGN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Randomized trial including high tumor burden FL grade 1-3a from 2011 until 2014</td>
<td>Induction: lenalidomide 20 mg po days 2-22 of 6 28-day cycles. If CR move onto maintenance. If PR 3-6 additional cycles and then maintenance. Rituximab 375 mg /m² days 1,8,15,22 of cycle 1 and day 1 of each 28-day cycle thereafter</td>
</tr>
<tr>
<td>Experimental arm</td>
<td>Induction: standard CT with Obinutuzumab 1g days 1,8,15 of cycle 1 and day 1 of each 21 or 28-day cycle thereafter</td>
<td>Maintenance: Lenalidomide 10 mg po per day up to a total of 18 cycles (including induction). Rituximab 375 mg /m² day 1 of each of 12 2-month cycles</td>
</tr>
<tr>
<td></td>
<td>Maintenance: Obinutuzumab 1g day 1 of each of 12 2-month cycles</td>
<td></td>
</tr>
<tr>
<td>Patients and treatment groups</td>
<td>N=1202 601 CT with obinutuzumab 601 CT with rituximab CT was bendamustine in 57%, CHOP in 33% and CVP in 10%</td>
<td>N=1030 513 lenalidomide-rituximab 517 CT with rituximab CT was CHOP in 72%, bendamustine in 23% and CVP in 5%</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Median 58-60 years old, 53% female, 41-42% high-risk FLIPI</td>
<td>Median 59 years old, 51% female, 49% high-risk FLIPI</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>PFS</td>
<td>PFS and CR at 120 weeks</td>
</tr>
<tr>
<td><strong>RESULTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median follow-up</td>
<td>2.8 years</td>
<td>3.2 years</td>
</tr>
<tr>
<td>3-yr PFS (95%CI)</td>
<td>80% (76-84%) with obinutuzumab-CT vs. 73% (69%-78%) with rituximab-CT (HR 0.66 [0.51 to 0.85])</td>
<td>77% (72%-80%) with lenalidomide-rituximab and 78% (74%-82%) with rituximab-CT (HR 1.10 [0.85 to 1.43])</td>
</tr>
<tr>
<td>3-yr OS (95%CI)</td>
<td>94% (92-96%) with obinutuzumab-CT vs. 92% (90%-94%) with rituximab-CT (HR 0.75 [0.49 to 1.17])</td>
<td>94% in both arms</td>
</tr>
</tbody>
</table>

FL: follicular lymphoma; CT: chemotherapy; CR: complete remission; PR: partial remission; CHOP: rituximab, cyclophosphamide, Adriamycin, vincristine, prednisone; CVP: cyclophosphamide, vincristine, prednisone; FLIPI: follicular lymphoma international prognostic index; PFS: Progression-free survival; HR: hazard ratio; 95%CI: 95% confidence interval; OS: overall survival.
Table 4. Patient characteristics and main outcomes from 3 large studies assessing the value of SCT in FL published in 2018

<table>
<thead>
<tr>
<th>Registry</th>
<th>NLCS</th>
<th>CIBMTR</th>
<th>CIBMTR</th>
<th>CIBMTR+EMBT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATIENT CHARACTERISTICS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response-based inclusion criteria</td>
<td>Early treatment failure</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type/Source of SCT</td>
<td>NA</td>
<td>Autologous</td>
<td>Autologous</td>
<td>Matched sibling</td>
</tr>
<tr>
<td>Number of patients</td>
<td>174</td>
<td>175</td>
<td>240</td>
<td>105</td>
</tr>
<tr>
<td>Median age at SCT</td>
<td>NA</td>
<td>55</td>
<td>56</td>
<td>52</td>
</tr>
<tr>
<td>Number of previous therapies</td>
<td>NA</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Disease status at SCT</td>
<td>NA</td>
<td>40% CR 39% PR 17% PD</td>
<td>36% CR 38% PR 23% PD</td>
<td>24% CR 30% PR 44% PD</td>
</tr>
<tr>
<td>RIC</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>66%</td>
</tr>
<tr>
<td><strong>OUTCOMES</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3-yr TRM/NRM</td>
<td>NA</td>
<td>NR</td>
<td>4%</td>
<td>15%</td>
</tr>
<tr>
<td>3-yr PFS</td>
<td>NR</td>
<td>NR</td>
<td>45%</td>
<td>59%</td>
</tr>
<tr>
<td>OS</td>
<td>76% at 2 yearsc</td>
<td>82% at 2 yearsc</td>
<td>79% at 3 years</td>
<td>75% at 3 years</td>
</tr>
<tr>
<td>G2-4 aGVHD at 100 days</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>35%</td>
</tr>
<tr>
<td>G2-4 cGVHD</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>54% at 2 years</td>
</tr>
</tbody>
</table>

NLCS: National lymphoCare Study; CIBMTR: Center for International Blood and Marrow Transplant Research; EBMT: European Society for Blood and Marrow Transplantation; SCT: stem cell transplant; NA: Not applicable; CR: complete remission; PR: partial remission; PD: progressive disease; TRM/NRM: transplant-related mortality/non-relapse mortality; PFS: progression-free survival; OS: overall survival; GVHD: graft-vs-host-disease

aHigher for older and more heavily pretreated patients, with chemoresistant disease, lower performance status and myeloablative conditioning.
bBoth PFS and OS were lower for older and more heavily pretreated patients, with chemoresistant disease, lower performance status, myeloablative conditioning and grade 3 FL.
cAutologous SCT showed an increased OS for patients who received it ≤ 1 year after treatment failure.
Table 5. Design and results of the pivotal trials for copanlisib and idelalisib for indolent NHL

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>DESIGN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial design</td>
<td>Single arm phase II</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>Patients with relapsed/refractory indolent NHL after at least two lines of therapy</td>
<td>Patients with indolent NHL refractory to rituximab and chemotherapy or RIT</td>
<td>Patients with indolent NHL refractory to rituximab and alkylators</td>
</tr>
<tr>
<td>Treatment regimen*</td>
<td>Copanlisib 60 mg iv days 1, 8 and 15 of each 28-day cycle</td>
<td>Duvelisib 25 mg po every 12 hours</td>
<td>Idelalisib 150 mg po every 12 hours</td>
</tr>
<tr>
<td><strong>Patient characteristics</strong></td>
<td>Median 63 years old, 50% female, 3 (median) prior regimens. -73% (104/142) FL</td>
<td>Median 65 years old, 32% female, 3 (median) prior regimens -64% (83/129) FL</td>
<td>Median 64 years old, 36% female, 4 (median) prior regimens -58% (72/125) FL</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Overall response rate (ORR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RESULTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median follow-up</td>
<td>6 months</td>
<td>32 months</td>
<td>9.7 months</td>
</tr>
<tr>
<td>ORR</td>
<td>59% (14% CR)*</td>
<td>42% (1%)*</td>
<td>57% (6% CR), 54%*</td>
</tr>
<tr>
<td>DOR</td>
<td>12 months*</td>
<td>10 months</td>
<td>12.5 months</td>
</tr>
<tr>
<td>Time to response</td>
<td>2 months</td>
<td>2 months</td>
<td>2 months</td>
</tr>
<tr>
<td>PFS</td>
<td>11 months</td>
<td>9.5 months</td>
<td>11 months</td>
</tr>
<tr>
<td>Grade ≥ 3 AE in at least 10% of patients</td>
<td>Hyperglycemia (41%), hypertension (24%), neutropenia (24%), pneumonia (16%)</td>
<td>Neutropenia (25%), diarrhea (15%), anemia (15%), thrombocytopenia (12%)</td>
<td>Neutropenia (27%), diarrhea (13%), ALT elevation (13%)</td>
</tr>
<tr>
<td>Discontinuation due to AE (%)</td>
<td>25%</td>
<td>31%</td>
<td>20%</td>
</tr>
</tbody>
</table>


*All PI3K given until progression or unacceptable toxicity

*In follicular lymphoma
Table 6. Selected ongoing clinical trials in FL*. Further details from the trials can be found in the www.clinicaltrial.gov website

<table>
<thead>
<tr>
<th>Trial identifier</th>
<th>Technology/Experimental drug/Therapeutic approach</th>
<th>Study population</th>
<th>Design and brief description</th>
<th>N</th>
<th>Primary completion date (actual or expected)**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03190928</td>
<td>Multi-level biological testing</td>
<td>Untreated FL</td>
<td>Prospective observation and tissue sampling and outcome correlation</td>
<td>88</td>
<td>July 2022</td>
</tr>
<tr>
<td>NCT03436602</td>
<td>Multi-level biological testing</td>
<td>Untreated FL</td>
<td>Retrospective biological testing (immunohistochemistry, sequencing, gene expression) and outcome correlation</td>
<td>650</td>
<td>March 2021</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FRONT LINE: LOW TUMOR BURDEN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00112931*</td>
<td>Rituximab</td>
<td>Low tumor burden FL</td>
<td>Phase 3. Randomization: rituximab vs. WW</td>
<td>600</td>
<td>March 2014</td>
</tr>
<tr>
<td>NCT02320292</td>
<td>RIT (Y-90 ibritumomab tiuxetan)</td>
<td>Low tumor burden FL</td>
<td>Phase 3. Randomization: rituximab with vs. without RIT</td>
<td>128</td>
<td>January 2026</td>
</tr>
<tr>
<td><strong>FRONT LINE: INDUCTION</strong></td>
<td></td>
<td></td>
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<tr>
<td>NCT02947347*</td>
<td>Ibrutinib</td>
<td>High tumor burden FL</td>
<td>Phase 3. Randomization: rituximab with vs. without ibritinib</td>
<td>440</td>
<td>January 2022</td>
</tr>
<tr>
<td><strong>FRONT LINE: MAINTENANCE AND RESPONSE-ADAPTED POST-INDUCTION TREATMENT</strong></td>
<td></td>
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<tr>
<td>NCT00877214</td>
<td>Prolonged rituximab maintenance</td>
<td>FL in remission after induction</td>
<td>Phase 3. Induction with RB and randomization if remission: 2 vs. 4 years of rituximab maintenance</td>
<td>1272</td>
<td>April 2022</td>
</tr>
<tr>
<td>NCT02063685</td>
<td>Response-adapted intensification/maintenance</td>
<td>Untreated FL</td>
<td>Phase 3. Induction with RCHOP or RB and randomization: standard maintenance vs. response-adapted</td>
<td>807</td>
<td>December 2018</td>
</tr>
<tr>
<td>EudraCT number: 2016-004010-10\textsuperscript{d}</td>
<td>Response-adapted intensification/maintenance</td>
<td>FL in remission after induction</td>
<td>Phase 3. Randomization if remission after induction. PET-negative randomization: standard rituximab maintenance vs. no maintenance PET-positive (partial remission) randomization: standard rituximab maintenance vs. lenalidomide maintenance</td>
<td>840</td>
<td>November 2025</td>
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</table>

**RELAPSED/REFRACTORY DISEASE: EARLY TREATMENT FAILURE**

<table>
<thead>
<tr>
<th>NCT03269669</th>
<th>Therapeutic approach to ETF</th>
<th>ETF FL</th>
<th>Phase 2. Randomization: O-umbralisib vs. O-lenalidomide vs. O-CHOP/O-B (depending on front-line)</th>
<th>150</th>
<th>December 2022</th>
</tr>
</thead>
</table>

**RELAPSED/REFRACTORY DISEASE: TARGETED AGENTS AND IMMUNOMODULATORY DRUGS**

<table>
<thead>
<tr>
<th>NCT01897571</th>
<th>Tazemetostat</th>
<th>DLBCL or FL</th>
<th>Phase 2, single arm. Monotherapy</th>
<th>420*</th>
<th>November 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02187861</td>
<td>Venetoclax</td>
<td>R/R FL</td>
<td>Phase 2. Randomization: RB with vs. without venetoclax</td>
<td>164</td>
<td>September 2016</td>
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<tr>
<td>NCT02417285</td>
<td>Avadomide</td>
<td>R/R NHL</td>
<td>Phase 2, single arm. Avadomide with obinutuzumab</td>
<td>79</td>
<td>April 2019</td>
</tr>
<tr>
<td>NCT02793583</td>
<td>Umbralisib</td>
<td>R/R NHL</td>
<td>Phase 2 and 3. Randomization: Umbralisib with or without</td>
<td>500</td>
<td>May 2019</td>
</tr>
<tr>
<td>NCT Identifier</td>
<td>Anti-CD20 ublituximab and with or without bendamustine (3 arms)</td>
<td>Relapsed/Refractory Disease: CAR T-Cell Therapy</td>
<td></td>
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<tr>
<td>NCT02953509</td>
<td>Anti-CD47 (Hu5F9-G4)</td>
<td>R/R B-NHL Phase 1b/2 72 March 2020</td>
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<tr>
<td>NCT03105336</td>
<td>Anti-CD19 CAR (Axicabtagene ciloleucel)</td>
<td>R/R iNHL Phase 2, single arm 80 March 2020</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03568461</td>
<td>Anti-CD19 CAR (Tisagenlecleucel)</td>
<td>R/R FL Phase 2, single arm 113 February 2021</td>
<td></td>
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</tr>
<tr>
<td>NCT02631044</td>
<td>Anti-CD19 CAR (lisocabtagene maraleucel)</td>
<td>NHL Phase 1, single arm 274 December 2020</td>
<td></td>
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</tbody>
</table>

*A more detailed description of some of the ongoing trials as well as potential trials can be found in the supplementary data.**

*Long-term results. With 3-yr follow up no OS difference between R and WW [102]*

*The phase 2 clinical trial NCT02451111 is also comparing an induction (4 weekly doses) and standard maintenance with rituximab vs the same regimen with ibrutinib.*

*Patients in the ibrutinib-rituximab arm are randomized a second time after induction and standard maintenance to further ibrutinib vs. placebo.*

*No NCT identifier listed.*

*Including the dose-finding phase 1 and the phase 2 G:**

FL: follicular lymphoma; WW: watch and wait; RIT: radioimmunotherapy; RCHOP: rituximab, cyclophosphamide, adriamycin, vincristine, prednisone; RB: rituximab, bendamustine; CR: complete remission; MRD: minimal residual disease; PET: positron-emitting tomography; ETF: early treatment failure; O: obinutuzumab; iNHL: indolent NHL; NHL: non-Hodgkin lymphoma; DLBCL: diffuse large B cell lymphoma; R/R: relapsed/refractory; CAR: chimeric antigen receptor.
Figure 1