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Review

REVIEW

Recommendations for Clinical Trial Development in Follicular Lymphoma

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Abstract

Follicular lymphoma (FL) is the second most common lymphoid malignancy, representing 20% to 25% of all cases of non-Hodgkin's lymphoma (NHL), and the most common of the indolent NHLs. FL is considered incurable in the majority of patients with the current standard therapeutic approaches, although outcomes have improved in the last few decades with our current therapies, with a median overall survival that now exceeds 18 years. While the majority of patients with FL have improved outcomes with our current therapeutic approaches, there are patients with high-risk disease features that have inferior outcomes to these therapies. There is an urgent need to integrate novel therapeutic agents into the treatment regimens for these patients to improve outcomes with continued evaluation of biomarkers indicative of prognosis and effects of these regimens on quality of life.

Follicular lymphoma (FL) is the second most common lymphoid malignancy, representing 20% to 25% of all cases of non-Hodgkin's lymphoma (NHL), and the most common of the indolent NHLs (1). FL represents a heterogeneous disease, with some patients not requiring therapy for several years after diagnosis and achieving long remissions with treatment, while other patients require immediate therapy and relapse within a short time or are refractory to treatment, resulting in shortened survival. Additionally, approximately 30% of FL patients will transform to a more aggressive histology over the course of their disease, often leading to rapid progression and the need for intensive therapy (2).

There are several well-described clinical factors known to correlate with disease outcome in newly diagnosed FL including age, LDH (Lactose Dehydrogenase), β2-microglobulin, bulk, and extent of disease. These clinical factors have been used to develop prognostic tools such as the FLIPI (Follicular Lymphoma International Prognostic Index) (3), FLIPI2 (4), and guidelines to assist in making treatment decisions such as the GELF (Groupe d'Etude des Lymphomes Folliculaires) criteria (5). Additionally, newer clinical markers such as response by positron emission tomography/computerized tomography (PET-CT) and minimal residual disease (MRD) have been recognized to correlate with disease outcome. More recently, there has been an increased effort to identify different molecular and genetic factors that have prognostic significance in FL. Several promising biomarkers have been identified, including MLL2, EZH2, IRF4, CREPPB, and EPHA7, although these markers do not individually have clear correlation with disease outcomes. The newest risk prognostication developed in FL, the m7-FLIPI (6), has incorporated mutational analysis of seven genes along with the clinical risk factors of the FLIPI and Eastern Cooperative Oncology Group (ECOG) performance status to improve upon prognostication of FL patients receiving firstline chemoimmunotherapy.

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have markedly improved in the last few decades with the introduction of monoclonal anti-CD20 antibodies, rituximab in particular. While the median overall survival in the 1990s was 6.7 years, with only 34% of patients alive at 10 years (7), the most recent series from Stanford demonstrates a median overall survival that exceeds 18 years in the new era of therapy (8). The incorporation of newer monoclonal antibodies, radiolabeled anti-CD20 antibodies, immunomodulatory agents, and therapies targeting oncogenic pathways such as B-cell receptor signaling, continues to further improve outcomes and has brought into question the possibility of effective, "chemotherapy-free" treatment regimens for the future.

The current approach to frontline therapy for FL is most often based on stage and burden of disease. For patients with early-stage disease (stage I and II), one recommended approach to therapy has traditionally consisted of radiotherapy, given its potential for long-term disease-free survival. This is based on nonrandomized, retrospective studies in the prerituximab era, and despite the reported favorable outcomes, many of these patients are either observed or receive rituximab alone or in combination with chemotherapy (9). Lymphocare data support relatively comparable outcome with watch and wait, radiation, or single-agent rituximab.

Patients with advanced-stage disease are treated based on extent of disease, given that patients with high tumor burden demonstrated a shorter median survival compared with patients with low tumor burden (9). Patients with low tumor burden FL are most often observed with a watch-and-wait approach (10,11) or treated with single-agent rituximab (12). Patients with high tumor burden FL are most often treated with combination chemoimmunotherapy (R-chemotherapy), with the possibility of rituximab maintenance. The most commonly used frontline regimens consist of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP), rituximab, cyclophosphamide, vincristine, prednisone (R-CVP), and rituximab, bendamustine (BR). Several major prospective randomized studies established this standard when they demonstrated an increase in overall response rates (ORRs), progression-free survival (PFS), and overall survival (OS) when comparing R-chemotherapy regimens with chemotherapy alone (13–17). A prospective multicenter study with 534 patients with stage II–IV FL randomly assigned patients to R-CVP, R-CHOP, or R-FM with a primary end point of time to treatment failure (TTF). While there were no statistically significant differences seen in ORR (88% with R-CVP, 95% CI = 82% to 93%; 93% for R-CHOP, 95% CI = 88% to 97%; and 91% for R-FM, 95% CI = 86% to 95%) or three-year OS (95% CI = 92% to 97%), three-year TTF (46% with RCVP, 57% with R-CHOP and 60% with R-FM) favored R-CHOP and R-FM but with R-FM having more hematologic toxicity and grade 3-4 neutropenia (18). Two recent phase III studies established the efficacy of BR in the frontline setting. The German indolent lymphoma study group (StiL) randomly assigned 549 patients with indolent NHL and mantle cell lymphoma to receive BR vs R-CHOP with a primary end point of PFS (19). The ORRs of the two regimens were similar (93% BR vs 91% R-CHOP), with a slightly higher CRR with BR (41% vs 30%) and a statistically significantly longer PFS in favor of BR (69.5 months vs 31.2 months, hazard ratio = 0.58, 95% CI = 0.44 to 0.74, two-sided $P < .0001$). There was no difference in OS between the two treatments, with median survival not reached in either group. BR was associated with less toxicity. The BRIGHT study compared BR vs R-CHOP or R-CVP in the same patient population (20) with a primary end point of CR rates. BR was shown to be noninferior to R-CHOP/R-CVP, with similar CRRs (31% BR vs 25% R-CHOP/R-CVP). The PRIMA study evaluated rituximab maintenance in patients achieving a response to initial chemoimmunotherapy, with patients receiving rituximab every eight weeks for two years. While maintenance rituximab improved three-year PFS to 75% from 58%, it did not improve OS and was associated with increased toxicity, leaving maintenance rituximab therapy controversial (21).

The National Cancer Institute's National Clinical Trials Network (NCTN) led one of the largest phase III trials in advanced-stage FL. The Southwest Oncology Group (SWOG) S0016 trial was a randomized phase III trial designed to compare the safety and efficacy of two chemoimmonotherapy regimens. The trial enrolled 554 patients who were randomly assigned to receive therapy with six cycles of R-CHOP vs six cycles of CHOP followed by consolidation with iodine-tositumomab radioimmunotherapy (RIT). While there was no statistically significant difference in PFS or OS between the two study arms, the outcomes were very promising overall with respect to PFS and OS (five-year PFS = 60% vs 66% and five-year OS = 92% vs 89% with R-CHOP and CHOP-RIT, respectively) (22). Further evaluation of these patients showed that despite the prognostic value of the FLIPI, FLIPI2, and LDH+β2M in predicting PFS and OS, the only factor potentially predictive of outcome by therapy was β2M, with patients having normal β2M showing a trend for improved PFS with CHOP-RIT, suggesting a potential benefit in lower-risk patients (23). This trial shows that while a large number of patients have favorable outcomes with our current accepted therapeutic approaches, there remains a high-risk group of patients with inferior outcomes. While we can identify these patients at high risk for shorter PFS and OS with standard chemoimmunotherapy approaches, we have not yet identified effective therapies for these high-risk patients or identified factors that lead to preferential response with individual therapies.

As most patients with FL will develop progressive disease requiring further therapy, there are a number of treatment options available to these patients, including immunotherapy alone, chemotherapy alone, combination chemoimmunotherapy, radioimmunotherapy, and consideration for consolidation with stem cell transplant (autologous or allogeneic) in selected patients. Many of the effective chemotherapeutic options have not been tested in rituximab-refractory patients, and while there has been a benefit shown in PFS and OS in studies evaluating the role of high-dose therapy followed by autologous stem cell transplantation (HDT/ASCT), these studies were conducted prior to the standard use of rituximab in frontline therapy (24–26). Nevertheless, both combination chemoimmunotherapy and HDT/ASCT are current strategies utilized in this setting, further highlighting the need to study effective therapies in these high-risk patients.

Continued biologic exploration of tumor tissue in both low-risk and high-risk FL patients to better characterize the natural history and biologic behavior of this disease and identify molecular and genetic markers that impact the pathogenesis of FL will be essential for advancing both our understanding and treatment of this disease. New therapeutic strategies targeting the high-risk population and those with shortened survival should be directed at more effective therapies that produce prolonged remission durations with less toxicity.

Current Landscape of Clinical Trials in Follicular Lymphoma

There are several recently completed and ongoing studies in frontline FL, including several through the NCTN groups. The

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Table 1. Current and recent trials in follicular lymphoma*

Study name	Treatment regimen
The Asymptomatic Follicular Lymphoma (AFL) Trial: A phase III study of single-agent rituximab immunotherapy versus zevalin radioimmunotherapy for patients with new, untreated follicular lymphoma who are candidates for observation	Rituximab +/- yttrium Y-90 ibritumomab tiuxetan
CALGB 50803 – A phase II trial of lenalidomide plus rituximab in previously untreated follicular lymphoma with bulky stage II, stage III–IV and FLIPI $\leq$ 2	Lenalidomde + rituximab
A051103 – A phase I study of rituximab, lenalidomide and ibrutinib in previously untreated bulky stage II, stage III–IV follicular lymphoma of any FLIPI to determine recommended phase II dosing of the combination	Rituximab, lenalidomide, and ibrutinib
CALGB 50904 – A randomized phase II trial of ofatumumab and bendamustine with ofatumumab maintenance vs ofatumumab, bortezomib and bendamustine with ofatumumab and bortezomib maintenance in previously untreated bulky stage II, III–IV follicular lymphoma	Ofatumumab, bendamustine, +/- bortezomib followed by ofatumumab +/- bortezomib
E2408-bendamustine hydrochloride and rituximab with or without bortezomib followed by rituximab with or without lenalidomide in treating patients with high-risk stage II, stage III, or stage IV follicular lymphoma	Bendamustine, rituximab, +/- bortezomib, followed by rituximab, +/- lenalidomide
"Relevance" Trial: A phase 3 open label randomized study to compare the efficacy and safety of rituximab plus lenalidomide (CC-5013) versus rituximab plus chemotherapy followed by rituximab in subjects with previously untreated follicular lymphoma	Rituximab + lenalidomide vs rituximab + chemotherapy (CHOP, CVP and bendamustine)

*A051103 = Alliance for Clinical Trials in Oncology; CALGB = Cancer and Leukemia Group B; E2408 = Eastern Cooperative Oncology Group.

ongoing goal of improving the treatment of FL has recently focused on including the use of newer anti-CD20 monoclonal antibodies; nonchemotherapeutic combinations utilizing the incorporation of novel targeted oral agents alone, in combination with each other or in combination with immunotherapy both in the frontline setting (27) and in the relapsed setting; and different approaches to maintenance strategies. While there are number of ongoing studies in FL, we have highlighted some of the larger trials in Table 1, which includes a majority of NCTN trials.

Clinical Trials Questions

What Should the Overarching Goals of Research in Follicular Lymphoma Be?

We believe it is time to initiate a transition in the goals of FL treatment and research to that of developing a precision approach to therapy. As detailed above, current evidence suggests that the majority of patients with follicular lymphoma will have a prolonged overall survival. There does exist a subset of patients that includes those with high-risk disease and younger patients, who may tolerate prolonged exposure to more intensive treatments and could benefit from improved therapeutic regimens with the potential to cure patients of this disease. At the same time, given the overall favorable outcomes of FL in general, in low-risk patients and many elderly patients whose diagnosis may not affect their overall survival, we should try to limit overexposure to therapies with major toxicities, prolonged treatment schedules, and high expense when they do not improve the quality of life. Rather than continuing to regard this disease with a standard approach by early or advanced stage, we will need to focus on identifying those at highest risk and incorporate the most effective agents into novel combinations with the goal of achieving durable complete remissions in these patients.

We believe that the focus in FL should be to design trials that focus on both identifying patients who will benefit from promising and potentially curable therapies in the frontline and relapsed setting and prioritizing efficient evaluation of these novel agents in such patients. While there are several ways to identify high-risk patients, our recommended strategy is to first focus on the high-risk population of patients who have a suboptimal response to initial therapy. Prioritizing this high-risk population will assure that when new active agents are discovered, those who need help most urgently will be the first to realize benefit and will help to determine what therapies are worthy of further study in the frontline setting for all patients. The treatment strategy that is effective in this population of patients should then be compared with current frontline treatment approaches for newly diagnosed follicular lymphoma patients with high-risk features.

These precision approaches should focus on integrating standard and novel agents into an induction without committing patients to indefinite therapy or prolonged maintenance treatment. We recommend that a defined treatment period leading to complete remission (and potentially cure) should be the goal rather than indefinite or prolonged therapy.

What Population(s) of Follicular Lymphoma Patients Should Be a Priority for Future Research?

In order to improve outcomes of patients with FL, it is critical to first identify those patients who have inferior survival with standard therapeutic approaches and who would benefit most from novel treatment approaches, from which we would be able to extrapolate outcomes to a more generalized setting. It is also important to gain a better understanding of the disease and to characterize the biology resulting in earlier disease progression than in patients who have durable remissions.

We have therefore identified two populations of patients who are thought to be the highest priority for further study. The first population of patients we recommend as a priority for further study are those patients whom we consider to have high-risk disease. While we recognize that there are several ways to define high-risk patients, we have defined the high-risk population as those patients who do not achieve a complete response (CR) by PET-CT with initial chemoimmunotherapy (28–31), those

who require retreatment within two years (32,33), or those patients who do not maintain a CR at 30 months after initial chemoimmunotherapy (FLASH project). We recommend limiting inclusion to those patients whose initial therapy included combination chemoimmunotherapy, given that this is the population of patients identified to have a poor prognosis in established studies (28–31). We would recommend that patients receive R-CHOP or R-bendamustine and not R-CVP, as the latter appears inferior to the other two regimens (21) and the role, timing, and rate of PET positivity in those patients receiving novel therapies has not been established. This high-risk population is one for which no standard therapy exists. If we were to identify an effective combination therapy in this high-risk population of relapsed patients, this treatment would be worthy of further study in patients considered high risk prior to treatment as identified by the different prognostic scores.

While therapeutic intervention trials should be prioritized for high-risk patient populations as described above, biologic exploration should proceed in other follicular lymphoma patients. The second population of follicular lymphoma patients recommended for study is the "watch and wait" group, or those considered low risk. Of particular interest are the patients who are observed and whose disease remains stable without progression. In addition to the high-risk population defined above to be studied in therapeutic trials, we recognize that to gain a better understanding of the natural history and biology of follicular lymphoma it will also be important to study the characteristics of the patients with a less aggressive presentation. We would recommend newly diagnosed patients with follicular lymphoma who are not receiving any therapy but are instead being observed without indication for immediate treatment be enrolled in clinical trials in order to collect initial specimens (peripheral blood, bone marrow, lymph node). Specimens from patients subsequently progressing and requiring therapy should also be collected for further study of biological characteristics in association with disease behavior in those patients who progress rapidly and those who have indolent disease for several years. In order to assure that these patients are similar at diagnosis, we would recommend the use of the GELF criteria to identify low-risk patients who are appropriate for observation.

What Should the Structure of Follicular Lymphoma Trials Be?

We do not believe that a randomized phase III trial in follicular lymphoma is possible at the present time. Currently, insufficient data exist to provide a rationale for comparing two treatment strategies in this fashion. We feel the best approach to a trial in this high-risk population of patients would be a randomized phase II trial with multiple treatment arms (3,4). Currently, there is no standard therapy for patients who rapidly progress or fail to achieve a CR after chemoimmunotherapy for follicular lymphoma. Treatment combinations that result in CRs or remissions that last more than two years would be regarded as having substantial efficacy in this high-risk group. In order to identify such a regimen, it is best to define one control arm to be used as a comparator against multiple regimens, as it is most statistically efficient to evaluate one control arm against two to three experimental arms as opposed to comparing two or more new regimens in a "pick the winner" fashion. We recommend defining a control that could be included in trials for the next two to three years as a comparator with new therapeutic regimens and believe this control arm is best defined collaboratively by the NCTN groups with the individual experimental arms to be decided by individual groups. We would recommend that the control arm be a combination R-chemotherapy regimen. Therefore, we recommend a single national study comparing the best standard treatment combination (control arm, preferably R-chemotherapy) with multiple experimental arms. While we would encourage the use of novel combination therapies and those that minimize or exclude chemotherapy, we would leave the specifics of the combinations to the individual NCTN groups in designing what they consider to be the most effective experimental therapeutic strategy as we recognize there will be patients who benefit from chemotherapy regimens, thus retaining a potential role for chemotherapeutic agents. With the goal of curing follicular lymphoma patients, we would, however, recommend that therapy be given for a finite period of time as opposed to prolonged or continued therapy regimens. Although it is recognized that some of the noncytotoxic agents can take longer to effectively induce responses, therefore making extended induction and/or short "maintenance" (not indefinite) courses necessary, we discourage the use of prolonged or indefinite therapy. If extended induction or short maintenance is considered to be necessary because of the timing of the effectiveness of the proposed agents, we would discourage the continuation of multiple agents in a prolonged treatment regimen. Finally, we encourage evaluating the benefit of further consolidation with autologous stem cell transplant in selected high-risk patients who respond to therapy.

As prolonged remission duration while maintaining quality of life in follicular lymphoma patients is the ultimate goal, we do not believe that trials need to incorporate rituximab maintenance. Furthermore, although rituximab is reasonable to consider as part of any initial novel combination therapy, it is not essential for a potentially successful combination of novel agents. We discussed the idea of maintenance or prolonged induction and decided that it would be dependent on the chosen novel regimen. Although prolonged induction and/or maintenance have an appropriate place based on the agent or agents chosen for induction, we discourage the use of additional agents as a maintenance approach.

Clinical Trial End Points

Similar to the criteria to define the high-risk follicular lymphoma patients for inclusion into studies, we recommend that the primary end points for trials in follicular lymphoma be 1) PET-negative CR after induction therapy and/or 2) continuous CR at 30 months. We have purposefully not defined PET negativity after induction therapy as this is an evolving field and may differ when novel agents are used. Accordingly, we have not defined a specific Deauville score but recommend that PET negative be defined in the study. We recommend that the PET-negative time point occurs at the end of induction therapy but the time course of induction not be defined. Timing may depend on the induction regimen chosen, and whether treatment is a chemoimmunotherapy regimen vs a regimen that includes a nonchemotherapeutic approach (targeted therapies, immunomodulating agents, immunotherapies). We would recommend that a bone marrow biopsy be performed to confirm CR if a PET-negative end point is reached.

While the importance of being conscientious of the cost of these regimens is recognized, as is the expense associated with some of the newer therapies, we would not at this time recommend the exclusion of any potential regimen solely based on financial considerations. However, we do recommend that these

trials include a cost-effectiveness analysis (CEA) for all of the regimens being studied in the randomized phase II trials. These analyses take into consideration the cost of the current therapy but also, if the regimen is potentially curative, the cost savings from eliminating the need for future therapy or prolonged therapy. As a precision approach to the treatment of FL with prolonged remission duration while maintaining quality of life in follicular lymphoma patients is the ultimate goal, we would be willing to tolerate greater expense in the frontline setting that would probably lead to overall cost savings by preventing multiple relapses. Well-validated CEA measures have been studied and can form a basis for those planned for these trials.

We also recognize the importance of and emphasis on quality of life with the varying treatment regimens, both during therapy and in association with long-term toxicities. Several assessments have been validated in respect to global/overall health and quality of life, in addition to assessments in individual areas regarding mentality, physicality, emotion, social activity, and spirituality. Such assessments should be included in the recommended phase II trial prior to initiation of treatment, at designated time points throughout therapy, and during follow-up appointments after completion of therapy in order to compare both short-term and long-term quality of life assessments between the different treatment arms. Not only should the focus be to better recognize the importance of and assessment of quality of life, but we need to prioritize improving our abilities to make these assessments and the tools that are used to do so. Many of our novel therapies are oral targeted therapies, which present new challenges in considering effects on quality of life, including different toxicities, cost, and management. It is critical that we identify improved methods to evaluate these challenges and association to quality of life so that we are best able to improve upon these treatments.

Biomarkers

At a minimum, all patients enrolled in clinical trials should have their histologic diagnoses confirmed by central Pathology review. For FL, the grade and histologic pattern (follicular, mixed, or diffuse) should be noted (34–37), and immunophenotyping performed for BCL2 protein and fluorescent in situ hybridization (FISH) for BCL2 translocation (38,39). For cases with otherwise typical morphology but lacking BCL2 abnormalities, FISH should be performed for BCL6 and IRF4 gene abnormalities (40). A tissue microarray should be constructed from cases with sufficient material to permit subsequent correlative studies. Biopsies should also be taken at relapse to determine if the histologic grade of the tumor has changed or if there has been transformation to a large cell lymphoma.

There are several standard markers that are known to correlate with disease and outcome. These parameters are predominantly clinical factors and include LDH, β2-microglobulin, FLIPI, and MRD (minimal residual disease). There are also several promising biomarkers that have been identified, but they do not yet have clear correlation with disease outcomes (eg, MLL2, EZH2, IRF4, t(14;18)) (41). The newest prognostic index, the m7-FLIPI, is the closest we have come to a prognostic marker that integrates genetic factors with clinical risk factors to identify low-risk and high-risk FL patients. The focus should be on both validating this in the setting of novel therapy and using it as a baseline to develop a more robust prognostic index. Given ongoing evaluation of multiple biomarkers using several different techniques (immunohistochemistry, gene expression profiling, sequencing, nanostring), the best approach is a post hoc biomarker analysis as opposed to random assignment, risk stratification, response assessment, or monitoring based on these biomarkers at this time. Both germline DNA and tumor samples (peripheral blood, bone marrow, lymph node) should be collected at baseline, at completion of treatment in both PET-negative and PET-positive patients, and at relapse in those patients who achieve PET negativity. These samples could be used to assess MRD using sensitive molecular methods and correlated with post-treatment imaging studies at these key time points. The other biomarkers would be analyzed after completion of the trial with the eventual goal of their inclusion in adaptive designs in future clinical trials. These investigations should include the study of surrogate markers for CR and prognosis in follicular lymphoma.

These laboratory and imaging recommendations are summarized in Table 2, with an indication of their status as standard of care, integral, or integrated. Standard of care indicates the minimal testing expected from any hospital or institution. Integral indicates that the test is necessary to enroll a patient in a trial. Integrated markers may not be validated sufficiently to guide a clinical trial decision but could be performed centrally and may help in risk stratification or future trial design. Integrated and integral designations are not mutually exclusive and are dependent on the circumstances of the trial. Validated relates to biomarkers for which there are multiple published studies with consistent results. For genetic testing, validation is achieved using an orthogonal method or at least another technological platform. Exploratory indicates biomarkers that are not yet considered to be validated.

Promising Novel Agents to Be Included in Follicular Lymphoma Trials

We have recommended the consideration of "chemotherapy-free" regimens, acknowledging this is difficult to define, but in general we would define chemotherapy as DNA-damaging agents and "chemotherapy-free" as encompassing other therapies that include pathway-targeted agents, biologics, and immunomodulatory agents. At present it is unclear that "chemo-free" regimens have the ability to produce a cure; however, to date we have not been able to identify a chemotherapy-based curative regimen. We would therefore highly encourage targeted agents and "chemotherapy-free" combinations for further study in future clinical trials.

There are several novel agents of particular interest at this time. Newer monoclonal antibodies, both novel anti-CD20 antibodies (ofatumumab, obinutuzumab, veltuzumab) and those targeting other B-cell-associated antigens (CD19, CD22, CD37) expressed on mature B cells, should be considered for use in combination therapy. Several newer antibody drug conjugates are being developed (CD22 ADC, CD37 ADC, CD79b ADC) and represent a promising therapeutic approach. Immunomodulatory agents have recognized activity in the relapsed FL setting and are being incorporated earlier in therapy, representing attractive options for combination nonchemotherapeutic-based approaches.

Several novel agents targeting pathways critical to cell cycle progression, proliferation, survival, transcriptions factors, and signal transduction have emerged as potential effective therapies. Perhaps the most exciting thus far has been the small molecule kinase inhibitors that target pathways critical to the survival of B-cell malignancies including the PI3 kinase/AKT inhibitors and B-cell receptor-modulating (BCR) agents. Idelalisib, an oral PI3K delta inhibitor, received FDA approval in July 2014 for relapsed FL after a phase II study showed single-agent

Table 2. Biomarkers in follicular lymphoma*

Recommendations	Standard of care	Integral	Integrated	Exploratory	Validated	Identifies high-/low-risk groups	Identifies therapeutic target
Histopathology							
Morphology: follicular vs diffuse, Grade: 1-2 vs 3a vs 3b	Yes	Yes	No	No	Yes	Yes	No
T follicular helper cell quantitation by PD1 IHC	No	No	Yes	Yes	Yes	Yes	No
Genetics							
FISH for BCL2 abnormalities	Yes	Yes	Yes	No	Yes	No	No
FISH for BCL6 rand/or IRF4 rearrangements if IGH/BCL2-negative	No	No	Yes	No	Yes	No	No
Molecular							
Immune response signature	No	No	Yes	Yes	No	Yes	No
Targeted resequencing: eg, EZH2, MLL2, CD79b	No	No	Yes	Yes	No	No	Yes
Imaging							
Response profile in high tumor burden FL: MRD evaluation in combination with quantitative FDG PET/CT during therapy for early risk stratification	No	No	Yes	Yes	No	Yes	No

*BCL2 = B-cell lymphoma 2; EZH2 = enhancer of zeste homolog 2; FDG PET/CT = fluoro deoxy glucose positron emission tomography/computerized tomography; FISH = fluorescent in situ hybridization; IHC = immunohistochemistry; IRF4 = interferon regulatory factor 4; MLL2 = mixed-lineage leukemia protein 2; MRD = minimal residual disease; PD1 = programmed death 1.

response rates of 57% (95% CI = 48% to 66%), with a median PFS of 11 months (range = .03 to 16.6) in relapsed/refractory FL (42). Ibrutinib, an oral BTK inhibitor, had a promising 55% ORR in relapsed/refractory FL in a phase I study (43), and a phase II single-agent study has recently completed enrollment (NCT01849263) with a 30% ORR, 65% of patients having reduction in tumor burden, with a median PFS of 9.9 months (44). A number of other PI3K inhibitors (copanlisib, duvelisib, BKM-120, TGR-1202) and BTK inhibitors (ACP196) have been developed and evaluated in recent and ongoing clinical trials. Copanlisib, an oral PI3K delta and alpha inhibitor (45), duvelisib, an oral PI3K delta and gamma inhibitor (46), and TGR-1202, an oral once-daily delta inhibitor (47), have all shown preliminary efficacy in relapsed/refractory FL, with TGR-1202 having an improved reported safety profile with respect to hepatotoxicity and colitis. Histone deacetylase (HDAC) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, immune checkpoint inhibitors, BCL-2 antagonists, and Syk inhibitors all represent promising classes of novel therapies that should be considered for further study alone in or combination.

Although these novel agents represent promising new therapies alone and in combination, their toxicities make it critical to study these combinations in the setting of clinical trials. Recent data from a safety analysis of three ongoing phase III idelalisib combination clinical trials showed increased risk of death and serious adverse events among patients treated with combination therapy in the frontline (BR ± idelalisib in CLL) and relapsed settings (BR ± idelalisib and rituximab ± idelalisib in indolent B-cell NHL), leading to the discontinuation of these trials (48). Deaths were largely attributable to an increase in opportunistic infections, including pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV) reactivation, which has led to recommendations for PJP prophylaxis and evaluation for CMV prior to initiation of therapy and monitoring while on treatment. The potential for increased toxicities of these agents when they are utilized as therapy earlier in the course of the disease and in combination with other agents highlights the need for rigorous and thoughtful design and conduct of clinical trials incorporating these agents into the therapy landscape for FL.

Summary and Conclusions

Although outcomes with FL have markedly improved in the modern era of therapies, there are patients who will experience unacceptable morbidity from their disease and/or treatment, ultimately succumbing to their disease. The final recommendation of the NCI Lymphoma Clinical Trials Planning Meeting Follicular Subcommittee is that a single national study for these high-risk relapsed or refractory follicular lymphoma patients be developed. High-risk patients will be defined as patients who fail to achieve a CR or rapidly relapse after frontline therapy. The study should compare the best standard treatment combination (selected as the control arm, which should be an R-chemotherapy regimen) to multiple (two to three) experimental arms, preferably combination novel therapeutics without prolonged therapy durations. The primary end points of the study should be achievement of a PET-negative CR at the end of therapy and/or continuous CR at 30 months, with secondary end points of cost analysis and quality of life. The study should include biomarkers (particularly at study entry, response, and progression), but the biomarkers would be analyzed after completion of the trial rather than used to guide treatments. We should continue to validate and improve upon our abilities to access prognostic markers and quality of life so as to improve therapeutic approaches in all FL patients.

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