

Current Immunochemotherapy Strategies in Follicular Lymphoma

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ABSTRACT

Nowadays, there is no consensus about the best treatment for patients with follicular lymphoma (FL) in differing situations. In frontline treatment, a watchful waiting policy remains a good option if the patient has no risk criteria; the role of rituximab is under investigation in this setting. In patients needing therapy, immunotherapy or immunochemotherapy are the best options; although it has not been established which chemotherapy, including cyclophosphamide, vincristine, and prednisone (CVP); cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP); fludarabine, or bendamustine combinations, is the best partner for rituximab. Following frontline treatment, recent and still unpublished data strongly suggest a role for maintenance with rituximab, instead of observation only. At relapse, immunochemotherapy is the standard induction approach. The role of maintenance after induction

is well established, although comparative studies with autologous stem-cell transplantation (ASCT) or other combinations are warranted. The role of ASCT in this setting is a matter of discussion. Other monoclonal antibodies, as well as vaccines and other immunotherapies, are currently under investigation. Finally, allogeneic transplantation should be reserved for a very select group of young high-risk patients in the setting of clinical trials.

Keywords: follicular lymphoma; immunochemotherapy strategies; rituximab

INTRODUCTION

Follicular lymphoma (FL) is the second-most common histological subtype of non-Hodgkin's lymphoma, with increasing incidence in recent decades in Western countries.¹ From the histological perspective, the disease is characterized by a follicular growth pattern, with a characteristic immunophenotype and the presence of translocation t(14,18)(q32;q21), which is typical but not pathognomonic of FL. From the clinical point of view, FL is diagnosed in adults with a median age of 60 years, usually in advanced stage at the time of diagnosis.

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The clinical course of FL is typically indolent, with multiple relapses that are separated by increasingly shorter intervals of time.² Whereas the median survival of patients with FL was previously about 8-10 years, the introduction of more effective treatments has substantially improved the outcome of these patients in recent years.^{3,4}

Among the aspects that should be taken into account to decide the treatment, the identification of histological grade 3b—which represents fewer than 5% of all cases—is important, because the behavior of these cases is closer to diffuse large B-cell lymphoma than to other FLs.⁵⁻⁷ The study of prognostic factors allows to predict the disease outcome, and in theory, to adapt treatment to the risk of each individual case. The Follicular Lymphoma International Prognostic Index (FLIPI), recently upgraded, is used in clinical practice.^{8,9} Moreover, the importance of microenvironment in the prognosis of patients with FL has been highlighted.¹⁰ However, this information is not yet applicable to clinical practice.

The list of therapeutic options in FL is long, and includes observation, radiotherapy, monotherapy with alkylating agents or other drugs, different polychemotherapies, and more intensive treatment such as, autologous or allogeneic stem-cell transplantation. For years, it has been impossible to establish the superiority of any of these approaches over the other, at least in terms of overall survival (OS). The introduction of immunochemotherapy, mainly in the form of the chimeric anti-CD20 monoclonal antibody rituximab, has substantially modified the treatment protocols in FL. Different studies have shown that immunochemotherapy increases the number, quality, and duration of response. The goal of this manuscript is to review the most recent data, on both induction and maintenance immunochemotherapy, in patients with FL.

FRONTLINE TREATMENT

The initial management of patients with FL is first conditioned by the extent of disease. Thus, patients in early stages, who represent fewer than 10% of all cases, can benefit from local radiotherapy-based management, resulting in high, prolonged remission rates and even curing of the disease in some cases. The role of systemic treatment, including immunochemotherapy, is not yet established in this setting.

In most patients, FL is diagnosed in advanced stages, and with current therapies, such cases are considered to be incurable. It has not been demonstrated that the immediate treatment, after diagnosis in patients with asymptomatic FL, was better in terms of OS or relapse pattern, than only observation.^{11,12} Therefore, in the absence of risk factors, to postpone treatment until disease progression, particularly in elderly patients or subjects with comorbidities, is considered a reasonable option.¹³ Nevertheless, the results of treating low-risk patients with rituximab are good (complete response [CR] rate around 40%-50% lasting for 4-5 years).^{14,15} For this reason, there are studies underway designed to evaluate whether or not the early treatment with rituximab could offer some benefit as compared with the classic watchful waiting policy.

Chemotherapy yielded similar results in terms of OS regardless of the regimen used (combinations of alkylating agents, anthracyclins, or purine analogs). CR rate and toxicity varied, with the most effective treatments generally also being the most toxic. This situation changed with the use of rituximab. Thus, although the results of rituximab monotherapy were modest in relapsed patients,¹⁶ the combination with chemotherapy (ie, cyclophosphamide, adriamycin, vincristine, and prednisone [CHOP]) showed high CR rates that persisted notoriously over time in patients previously treated or untreated, resulting in

a median of progression-free survival (PFS) of about 85 months.^{17,18} Subsequently, the advantage of immunochemotherapy over standard chemotherapy was demonstrated in relapsed patients in terms of CR rate and PFS, with no increase of toxicity.^{19,20}

Four randomized studies, evaluating with the highest level of evidence the efficacy of adding rituximab to different chemotherapy regimens for advanced FL in frontline treatment, are currently available (Table 1).²¹⁻²⁵ Again, immunochemotherapy showed clear superiority in all the studies in terms of CR rate, duration of response, time to progression, and need for new treatment. In addition, three of the four studies reported a significant increase in OS among the patients assigned to immunochemotherapy arms.^{21,22,24} In addition, immunochemotherapy did not result in any relevant increase in therapy-related toxicity.

Based on the above-mentioned studies, rituximab has emerged as a crucial drug in patients with FL, both in front-line and at relapse. In fact, nowadays the use of rituximab in FL is no longer discussed; rather, it is all about how

and when to combine it with chemotherapy. Among the many possible drug combinations, bendamustine should be mentioned. The combination rituximab-bendamustine (RB) has demonstrated extraordinary efficacy in a phase 2 trial for the treatment of indolent lymphomas (one-third of which corresponded to FL), showing CR rates, duration of response, and PFS similar to those afforded by rituximab-CHOP (R-CHOP).²⁶ Preliminary results of a randomized phase 3 study in indolent lymphomas (52% of which corresponded to FL), designed to evaluate the efficacy of RB versus R-CHOP in frontline treatment, showed significant advantages of RB in terms of response, PFS, and OS, with less toxicity.²⁷

POSTINDUCTION TREATMENTS

Given the natural history of FL characterized by multiple relapses, with increasingly shorter time intervals between them, attempts have been made for years to introduce additional treatments after induction, in order to prevent, or at least delay disease relapse.

Table 1. Phase 3 studies evaluating the addition of rituximab in the upfront treatment for advanced follicular lymphoma.

Upfront	Regimen	ORR (%)	CR (%)	Response duration (months)	OS (%)
Marcus et al. ^{23,24} (n=321)	CVPx8 vs. R-CVPx8	57 vs. 81	10 vs. 41	15 (TTP) vs. 34 (TTP)*	77 (4 yr) vs. 83 (4 yr)*
Hiddeman et al. ²² (n=428)†	CHOPx6 vs. R-CHOPx6	90 vs. 96	17 vs. 20	31 (PFS) vs. not reached (PFS)*	90 (2 yr) vs. 95 (2 yr)*
Herold et al. ²¹ (n=201)	MCPx8 + IFN vs. R-MCPx8 + IFN	75 vs. 92	25 vs. 50	28.8 (PFS) vs. not reached (PFS)*	74 (4 yr) vs. 87 (4 yr)*
Salles et al. ²⁵ (n=358)	CHVPx12 + IFN vs. R-CHVPx6 + IFN	72 vs. 81	50 vs. 67	35 (PFS) vs. not reached (PFS)*	79 (5 yr) vs. 84 (5 yr)

* $P \leq 0.05$.

†CHOP and R-CHOP was followed by IFN or autologous stem-cell treatment.

CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; CHVP=cyclophosphamide, adriamycin, etoposide, prednisolone; CR=complete response; CVP=cyclophosphamide, vincristine, prednisone; IFN=interferon; MCP=mitoxantrone, chlorambucil, prednisone; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; R=rituximab; TTP=time to progression.

Maintenance Treatment

The role of maintenance therapy after completing induction has been historically explored with the aim of improving the quality of response and particularly, the duration of response—thereby, prolonging the time to further progression and the need for new treatment. Before the rituximab era, chemotherapy with or without interferon, followed by maintenance with the same drug was one of the most effective frontline treatments in patients with FL.²⁸ While the addition of interferon did not increase the response rate, it did improve the duration of remission, and favored better long-term survival among the patients administered such treatment.²⁸ Nevertheless, the side effects of interferon limited its use in such situations.

The introduction of rituximab renewed the interest for maintenance therapy in FL, in view of the important efficacy of the drug and the relatively few adverse effects. Results are currently

available from several randomized trials that have explored maintenance treatment with rituximab at relapse and at frontline settings.^{20,29-33} In this context, two fundamental problems are raised when comparing different series. Firstly, in terms of treatment efficacy and possibly also in terms of toxicity, the maintenance results are strongly dependent upon the induction treatment used. Secondly, the term “maintenance treatment” refers in fact to very heterogeneous regimens in terms of dose, schedule, and duration. The most common schedules for maintenance with rituximab are detailed in Figure 1.^{20,29-31,34,35}

In the setting of relapse, several randomized studies have shown that maintenance with rituximab prolongs the duration of response and PFS of the patients (Table 2).^{20,29-31,33,34,36} In one trial, advantages in terms of OS, or at least a trend in this sense, has been described.^{20,33} It is important to note that the benefits of maintenance were demonstrated both in patients who were rituximab-naïve and in

Figure 1. Maintenance with rituximab in patients with follicular lymphoma: different schedules of administration.

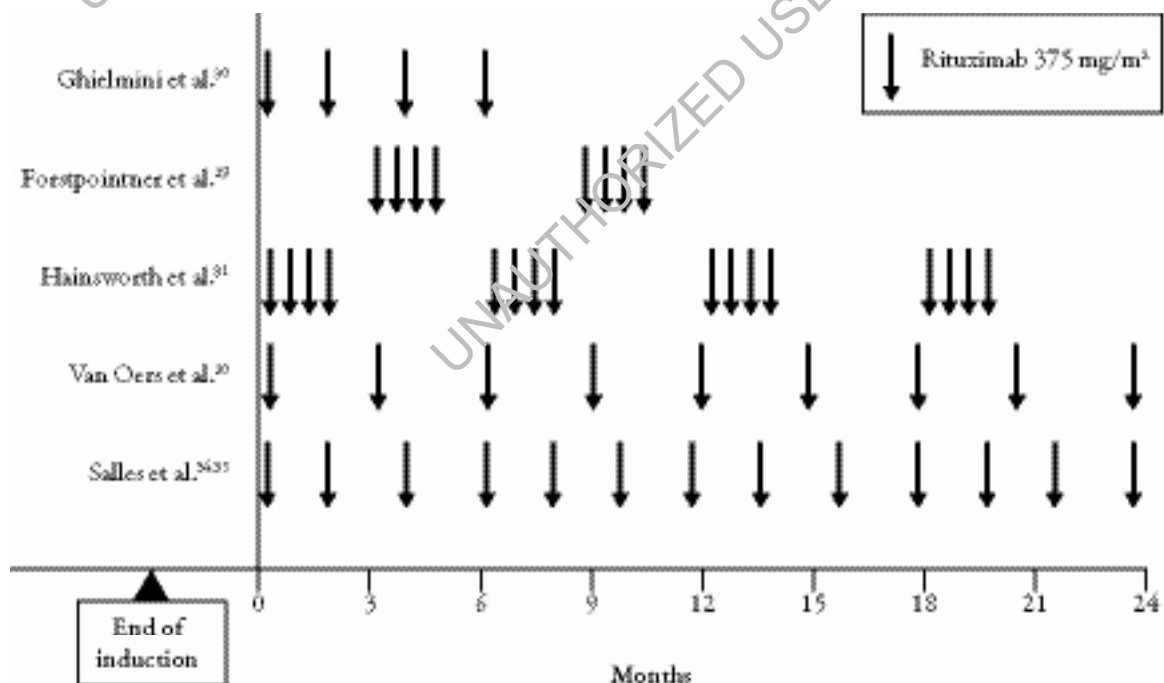


Table 2. Benefits of rituximab maintenance in patients with follicular lymphoma.

Induction treatment	Reference(s)	Progression-free survival	Overall survival
Relapsed disease			
Rituximab alone	30	↑	=
Chemotherapy alone	20, 33	↑	↑
Rituximab + chemotherapy	19, 20, 33	↑	↑ =
Initial disease			
Rituximab alone	30	↑	=
Chemotherapy alone	32	↑	↑*
Rituximab + chemotherapy	34, 36	↑	?

* $P=0.08$.

↑=increase; (=)=no significant increase; ?=no data.

MCP=mitoxantrone, chlorambucil, prednisone; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; R=rituximab; TTP=time to progression.

patients in whom rituximab was part of the salvage regimen.^{20,33} Recently, a meta-analysis summarizing the results of these randomized trials has been published, including 945 patients with FL.³⁷ The analysis concluded that maintenance resulted in benefits in terms of disease control and OS, although maintenance was related to a larger number of adverse effects, including infections. Another approach to assess the usefulness of maintenance with rituximab, is to compare maintenance after response versus retreatment with rituximab at next progression. The only study designed in this sense was unable to demonstrate differences in the outcome, though a longer time to progression was observed in the patients who received the maintenance.³¹ Thus, there is strong evidence that maintenance with rituximab in relapsing FL prolongs the duration of response, PFS and, most likely, OS and for this reason, it is considered the standard of care by many authors. It remains to be established which of the different maintenance schedules is the most effective in terms of disease control, cost-efficacy, and toxicity. Moreover, whether or not maintenance is better than other options, such as, intensification with stem-

cell transplantation or radioimmunotherapy (RIT), should be addressed in future clinical trials. Finally, despite some concerns about the prolonged immunosuppression induced by rituximab that could facilitate the appearance of serious infections,³⁶ including hepatitis B reactivation, *Pneumocystis jiroveci* pneumonia, or even multifocal leukoencephalopathy, after years of widespread use of this drug, within and outside of clinical trials, rituximab is demonstrated to be very safe. Nevertheless, a careful evaluation of patients is advisable when making treatment decisions.

Regarding maintenance after frontline therapy, the study published by Ghielmini et al. indicated that duration of response was prolonged in patients previously treated with rituximab alone, although OS was not modified.³⁰ The study of the American Eastern Cooperative Oncology Group (ECOG) group demonstrated advantages, both in terms of PFS and OS, in those patients receiving maintenance after an initial response to cyclophosphamide, vincristine, and prednisone (CVP) induction therapy.³² However, it should be noted that these patients were rituximab-naïve. The final study to establish

the exact role of maintenance with rituximab after frontline induction in patients with FL will be the Primary Rituximab and Maintenance (PRIMA) trial, the preliminary results of which have just been communicated.^{34,35} This study included over 1200 patients with FL, treated with one of three possible conventional induction regimens (R-CVP, R-CHOP, or rituximab, fludarabine, cyclophosphamide, and mitoxantrone [R-FCM]). Responders (CR or partial response) were randomized to either rituximab (375 mg/m² as a single dose every 8 weeks for 2 years) or to observation. The preliminary data, after a median follow-up of 24 months after the randomization, showed a significant advantage of the maintenance in terms of PFS, which was the primary end-point: 2-year PFS 66% versus 82% (hazard ratio [HR] 0.50; 95% confidence interval [CI]: 0.39, 0.64; $P < 0.0001$) for the observation and maintenance arms, respectively. The benefit was seen in all the risk groups. On the other hand, the maintenance treatment was well tolerated and no unexpected toxicity was observed. This study opens the door to incorporate maintenance with rituximab after induction immunochemotherapy as standard of care for patients with FL needing therapy.

Autologous Stem-Cell Transplantation

Before the era of monoclonal antibodies, autologous stem-cell transplantation (ASCT) was considered in different studies as an alternative to conventional chemotherapy. At the relapse setting, a number of phase 2 trials showed that ASCT could prolong PFS, but there was only one randomized study with a small number of patients.³⁸⁻⁴¹ In addition, three randomized studies in the pre-rituximab era showed discrepant results in frontline therapy, probably due to the different inclusion criteria.⁴²⁻⁴⁵ The extent to which the potential benefits of ASCT may be

strongly conditioned by the use of rituximab in the immunotherapy era is not clear. The Gruppo Italiano Trapianto di Midollo Osseo, Intergruppo Italiano Linfomi (GITMO/IIL) randomized study, including rituximab in the two treatment arms, did not record improved OS among the patients subjected to consolidation therapy with ASCT.⁴⁶ The same issue is being examined in the ongoing RiCHOP trial, where after initial treatment with R-CHOP the patients are randomized to either ASCT followed by maintenance rituximab, or to maintenance rituximab only.

The only strategy offering healing potential in advanced stage FL is allogeneic transplantation. However, despite the advantage of fewer relapses, this treatment option continues to involve important morbidity and mortality, even in reduced-intensity conditioning modalities.⁴⁷ As a result, although some promising new data suggest that this could be a curative option for selected patients, its indication should still to be regarded as experimental in FL.

Radioimmunotherapy (RIT)

The inherent radiosensitivity of FL has led to the development of different RIT protocols for this disease. Fundamentally, two compounds have been developed: yttrium-90 bound to lritumomab tiuxetan, and iodine-131 bound to tositumomab. Both compounds consist of murine anti-CD20 antibodies associated to radioisotopes, which thus selectively reach the different locations of disseminated FL. The role of RIT in the management of FL has been mainly explored within the context of consolidation therapy. Different phase 2 studies have demonstrated the viability of this approach, and in fact RIT in consolidation therapy after first-line treatment for FL has resulted in an increase in the number and quality of responses obtained, regardless of the type of induction used. In

addition, a significant increase in PFS has been reported among patients with both partial and CR in a phase 3 trial.⁴⁸ The main weakness of this study is that the immense majority of the patients had not received rituximab in frontline treatment. RIT has also been explored in FL at myeloablative doses followed by stem-cell rescue and in combination with chemotherapy in ASCT conditioning.

Other Immune Therapies

Lastly, within the generic field of immunotherapy, vaccines must be mentioned, which seek to induce a highly specific humoral and/or cellular response against the lymphoma antigens. Phase 2 studies have demonstrated the safety and immunogenicity of anti-idiotypic vaccines for these patients and suggest a prolongation of treatment response among the vaccinated subjects. The results of three randomized studies have recently shown that overall, approximately half of all patients develop antibodies against the tumor.⁴⁹⁻⁵¹ Those patients showing an immune response have improved PFS. However, in two of the mentioned studies, there were no differences in either PFS or OS between the vaccination arm and the placebo arm.^{49,50} In the third study, which has not yet been formally published, differences have been found in favor of the vaccine in a selected cohort of responding individuals showing a persistence of response for more than 6 months.⁵¹

NEW TREATMENTS IN FL

Much progress has been made during the last few decades in the treatment of FL. Monoclonal antibodies represent a major advance towards a targeted therapy that can dramatically improve the anti-tumor effect, ideally with a substantial reduction of toxicity derived from therapy.

There are many new antibodies in use in clinical trials, including the new anti-CD20s (GA-101, ofatumomab) and anti-CD22 (unconjugated or calicheamicin-conjugated). Finally, the identification of new targets and development of novel targeted therapies is crucial to exploit the biology of FL, in order to prevent relapse and prolong survival. Ultimately, one of the goals of many researchers in FL is to find an active and “free-of-chemotherapy” regimen that can be the gold standard for the next decades.

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REFERENCES

1. Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. *J Natl Cancer Inst.* 2010;92:1240-1251.
2. Johnson PW, Rohatiner AZ, Whelan JS, et al. Patterns of survival in patients with recurrent follicular lymphoma: a 20-year study from a single center. *J Clin Oncol.* 1995;13:140-147.
3. Fisher RI, LeBlanc M, Press OW, Maloney DG, Unger JM, Miller TP. New treatment options have changed the survival of patients with follicular lymphoma. *J Clin Oncol.* 2005;23:8447-8452.
4. Liu Q, Fayad L, Cabanillas F, et al. Improvement of overall and failure-free survival in stage IV follicular lymphoma: 25 years of treatment experience at The University of Texas M.D. Anderson Cancer Center. *J Clin Oncol.* 2006;24:1582-1589.
5. Hans CP, Weisenburger DD, Vose JM, et al. A significant diffuse component predicts for inferior survival in grade 3 follicular lymphoma, but cytologic subtypes do not predict survival. *Blood.* 2003;101:2363-2367.
6. Hiddemann W, Buske C, Dreyling M, Weigert O, Lenz G, Unterhalt M. Current management of follicular lymphomas. *Br J Haematol.* 2007;136:191-202.

7. Ott G, Katzenberger T, Lohr A, et al. Cytomorphologic, immunohistochemical, and cytogenetic profiles of follicular lymphoma: 2 types of follicular lymphoma grade 3. *Blood*. 2002;99:3806-3812.
8. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood*. 2004;104:1258-1265.
9. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. *J Clin Oncol*. 2009;27:4555-4562.
10. Dave SS, Wright G, Tan B, et al. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *N Engl J Med*. 2004;351:2159-2169.
11. Ardeschna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. *Lancet*. 2003;362:516-522.
12. Horning SJ, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. *N Engl J Med*. 1984;311:1471-1475.
13. Solal-Celigny P, Lepage E, Brousse N, et al. Doxorubicin containing regimen with or without interferon alfa-2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaires 86 Trial. *J Clin Oncol*. 1998;16:2332-2338.
14. Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. *Blood*. 2001;97:101-106.
15. Colombat P, Brousse N, Morschhauser F, et al. Single treatment with rituximab monotherapy for low-tumor burden follicular lymphoma (FL): survival analyses with extended follow-up (F/Up) of 7 years. *Blood*. 2006;108:486. Abstract.
16. McLaughlin P, Grillo-López AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol*. 1998;16:2825-2833.
17. Czuczman MS, Grillo-López AJ, White CA, et al. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. *J Clin Oncol*. 1999;17:268-276.
18. Czuczman MS, Weaver R, Alkuzweny B, et al. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. *J Clin Oncol*. 2004;22:4711-4716.
19. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*. 2004;104:3064-3071.
20. van Oers MH, Klasa R, Marcus RE, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. *Blood*. 2006;108:3295-3301.
21. Herold M, Haas A, Srock S, et al. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. *J Clin Oncol*. 2007;25:1986-1992.
22. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*. 2005;106:3725-3732.
23. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood*. 2005;105:1417-1423.
24. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol*. 2008;26:4579-4586.
25. Salles G, Mounier N, de GS, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. *Blood*. 2008;112:4824-4831.

26. Rummel MJ, Al Batran SE, Kim SZ, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. *J Clin Oncol.* 2005;23:3383-3389.
27. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: final results of a randomized phase iii study of the StiL (Study Group Indolent Lymphomas, Germany). *Blood.* 2009;114:405. Abstract.
28. Rohatiner AZ, Gregory WM, Peterson B, et al. Meta-analysis to evaluate the role of interferon in follicular lymphoma. *J Clin Oncol.* 2005;23:2215-2223.
29. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). *Blood.* 2006;108:4003-4008.
30. Ghielmini M, Schmitz SF, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. *Blood.* 2004;103:4416-4423.
31. Hainsworth JD, Litchy S, Shaffer DW, Lackey VL, Grimaldi M, Greco FA. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma – a randomized phase II trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol.* 2005;23:1088-1095.
32. Hochster H, Weller E, Gascoyne R, et al. Maintenance rituximab after CVP results in superior clinical outcome in advanced follicular lymphoma (FL): results of the E1496 Phase III Trial from the Eastern Cooperative Oncology Group and the Cancer and Leukemia Group B. *Blood.* 2009;27:1607-1614.
33. van Oers MH, van Glabbeke M, Giurgea M, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. *J Clin Oncol.* 2010;28:2853-2858.
34. Salles GA, Seymour JF, Feugier P, et al. Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma alter response to immunochemotherapy. *J Clin Oncol.* 2010;28:15s. Abstract 8004.
35. Salles GA, Catalano J, Feugier P, et al. Rituximab maintenance for 2 years significantly improves the outcome of patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy: results of the PRIMA study. *Haematologica.* 2010;95(suppl. 2):229.
36. Gea-Banacloche JC. Rituximab-associated infections. *Semin Hematol.* 2010;47:187-198.
37. Vidal L, Gafter-Gvili A, Leibovici L, et al. Rituximab maintenance for the treatment of patients with follicular lymphoma: systematic review and meta-analysis of randomized trials. *J Natl Cancer Inst.* 2009;101:248-255.
38. Apostolidis J, Gupta RK, Grenzelijs D, et al. High-dose therapy with autologous bone marrow support as consolidation of remission in follicular lymphoma: long-term clinical and molecular follow-up. *J Clin Oncol.* 2000;18:527-536.
39. Bierman PJ, Vose JM, Anderson JR, Bishop MR, Kessinger A, Armitage JO. High-dose therapy with autologous hematopoietic rescue for follicular low-grade non-Hodgkin's lymphoma. *J Clin Oncol.* 1997;15:445-450.
40. Freedman AS, Neuberg D, Mauch P, et al. Long-term follow-up of autologous bone marrow transplantation in patients with relapsed follicular lymphoma. *Blood.* 1999;94:3325-3333.
41. Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. *J Clin Oncol.* 2003;21:3918-3927.
42. Deconinck E, Foussard C, Milpied N, et al. High-dose therapy followed by autologous purged stem-cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by GOELAMS. *Blood.* 2005;105:3817-3823.
43. Gyan E, Foussard C, Bertrand P, et al. High-dose therapy followed by autologous purged stem cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by the GOELAMS with final results after a median follow-up of 9 years. *Blood.* 2009;113:995-1001.

44. Lenz G, Dreyling M, Schiegnitz E, et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group. *Blood*. 2004;104:2667-2674.
45. Sebban C, Mounier N, Brousse N, et al. Standard chemotherapy with interferon compared with CHOP followed by high-dose therapy with autologous stem cell transplantation in untreated patients with advanced follicular lymphoma: the GELF-94 randomized study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA). *Blood*. 2006;108:2540-2544.
46. Ladetto M, De MF, Benedetti F, et al. Prospective, multicenter randomized GITMO/III trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: the superior disease control of R-HDS does not translate into an overall survival advantage. *Blood*. 2008;111:4004-4013.
47. van Besien BK, Loberiza FR Jr, Bajorunaite R, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. *Blood*. 2003;102:3521-3529.
48. Morschhauser F, Radford J, Van HA, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. *J Clin Oncol*. 2008;26:5156-5164.
49. Ai WZ, Tibshirani R, Taidi B, et al. Anti-idiotypic antibody response after vaccination correlates with better overall survival in follicular lymphoma. *Blood*. 2009;113:5743-5746.
50. Freedman A, Neelapu SS, Nichols C, et al. Placebo-controlled phase III trial of patient-specific immunotherapy with mitumprotimut-T and granulocyte-macrophage colony-stimulating factor after rituximab in patients with follicular lymphoma. *J Clin Oncol*. 2009;27:3036-3043.
51. Schuster SJ, Neelapu SS, Gause BL, et al. Idiotypic vaccine therapy (BiovaxID) in follicular lymphoma in first complete remission: phase III clinical trial results. *J Clin Oncol*. 2009;27:13