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HOW TO MANAGE...

How we manage follicular lymphoma

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Major changes have taken place within the last few years in the management of follicular lymphoma (FL) leading to substantial improvement in prognosis and overall survival. For some patients with limited disease stages I and II, radiotherapy may be associated with durable responses; however, it is unclear whether patients are cured and new approaches such as the combination of irradiation with rituximab or even single-agent rituximab need to be explored. Whereas watch and wait is the current standard for stage III and IV disease with low tumour burden, better indices are warranted to potentially select patients for whom early intervention is preferred. For advanced stages with a high tumour burden, immunochemotherapy followed by 2 years of rituximab maintenance is widely accepted as standard therapy, although re-treatment at recurrence may be an alternative option. Highly attractive new therapeutic options have recently arisen from new antibodies, and from new agents targeting oncogenic pathways such as B-cell receptor signalling pathways or inhibition of bcl 2. Furthermore, immunomodulatory drugs may add to the therapeutic armamentarium and may lead to 'chemotherapy-free' therapies in the near future. Hence, the management of FLs has become a moving target and the hope is justified that the long-term perspectives of patients suffering from the disease will be further improved in the near future.

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INTRODUCTION

Follicular lymphoma (FL) is the second most frequent type of lymphoma subtype worldwide, with a rising incidence particularly in Western countries.[1,2] Biologically, tumour cells are malignant counterparts of normal germinal centre B-cells. Together with a heterogeneous group of cells, including macrophages, follicular dendritic cells, fibroblasts, endothelial cells and T lymphocytes, FL cells form a disease-specific microenvironment allowing a dynamic and bidirectional feedback process between cancer cells and the complex network of reactive cells.[3,4]

On the basis of the relative proportion of centrocytes to centroblasts, FL grades 1 to 3 are discriminated with a further separation of grade 3A and 3B.[5] Whereas FL grades 1 to 3A share common histologic and molecular features and have an indolent clinical course, FL grade 3B histologically resembles diffuse large B-cell lymphoma, reveals different molecular characteristics and is clinically more aggressive.

The genetic hallmark of FL, the translocation t(14;18)(q32;q21), results in the constitutive overexpression of the bcl 2 protein, which impairs the normal germinal centre apoptotic programme. Almost all cases of FL carry additional genetic alterations such as gains, losses or mutations of genes such as MLL2, EPHA7, TNFRSF14, BCL6, CREBBP, EZH2 and many others. However, the level of B-cell development at which these alterations occur, their sequence, their relation to the translocation t(14;18) and their impact on the pathogenesis of FL, remains unclear.[3,4] Weigert and Weinstock recently proposed a model for the molecular ontogeny of FL that considers different possibilities for the initial steps of malignant transformation within the hierarchy of lymphomagenesis.[6,7]

Clinically, FL is usually characterised by an indolent course, and many patients remain asymptomatic despite extended disease. In fact, the vast majority of patients are diagnosed at advanced stages III and IV. Although FL is still considered incurable, substantial progress has been achieved in the last decades, particularly through the introduction of monoclonal antibodies and of rituximab in particular into FL therapy and its combination with conventional chemotherapeutic regimens. In addition, diagnostic workup has been refined, including molecular markers, immunophenotyping and positron emission tomography (PET) imaging.

THERAPY OF FLs AT LIMITED STAGES I AND II

Approximately 15–25% of FL patients are diagnosed at early stages I and II. Because of the high radiosensitivity of FL and the potential for cure, national and international guidelines uniformly recommend radiotherapy for these patients.[8,9] In the past a series of studies have suggested that radiotherapy by way of involved or even extended field irradiation may achieve long-term disease-free survival and possibly cure.[10–15] However, these studies have been performed in the pre-rituximab era; most of them were retrospective and none of them compared the respective radiotherapeutic approach with other alternatives. Furthermore, the dose and field size of radiation are still not clearly defined, although a recent study suggests that 24 Gy may be sufficient.[16] Hence, the definition of radiotherapy as the standard treatment for localised stages of FL was not based on solid scientific evidence.

A recent survey of the National LymphoCare Study consequently demonstrated that adherence to the standard is low.[17] Less than a third of 471 patients with stage I FL were actually treated with radiotherapy alone, whereas the rest were either only observed, received single-agent rituximab, or received a combination of rituximab plus chemotherapy with or without subsequent irradiation. In addition, only 206 patients were

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adequately staged by carrying out a mandatory bone marrow biopsy. Although this study was not designed to compare different therapeutic options in early-stage FL and the selection of treatment was not based on predefined entry criteria, it clearly illustrates that in clinical practice radiotherapy is not considered standard therapy in the majority of cases. Similar results also emerged from an analysis of guidance adherences in patients with malignant lymphomas from the Netherlands.[18] This obvious uncertainty about the most adequate therapy for early-stage FL may in part result from the observation that a watch-and-wait approach for these patients may not be inferior to radiation therapy.[19] Furthermore, the question remains whether clinically defined stages I and II really represent a localised disease or whether FL is primarily a disseminated disease even if no widespread clinical manifestations can be detected. On the other hand, the LymphoCare study reported that adequately staged patients had a better outcome compared with patients with insufficient staging at diagnosis. Remarkably, the different treatment modalities that were chosen all resulted in a comparably favourable outcome.

Which conclusion can be drawn from these data and how can we use them for the management of our FL patients with early stages of the disease today?

First, we have to admit that there is currently no generally accepted and scientifically validated standard therapy for patients with early-stage FL. Second, we have to re-emphasise the need for adequate staging at diagnosis to ensure the precise definition of the extent of the disease before taking a therapeutic decision. In this context, the role of ^{18}FDG PET needs to be better defined. Third, there is an urgent need to compare the different treatment options, such as rituximab followed by radiotherapy, immunochemotherapy followed by radiotherapy, or single-agent rituximab, in prospective randomized trials, some of which have already been initiated.[20,21] Fourth, new markers need to be developed to distinguish patients who need to be treated immediately from those who might be observed because of an indolent course of their disease.

Patients with early stages of FL should, therefore, preferentially be treated within prospective clinical studies. For patients outside clinical trials, an individual decision needs to be made that should consider the patient's age and general condition, symptoms of the disease such as B symptoms or bulky disease and other risk factors such as elevated lactate dehydrogenase or beta-2-microglobulin levels. On the basis of these criteria a combination of rituximab plus radiotherapy or even rituximab plus chemotherapy followed by irradiation may be adopted in younger and medically fit patients with a long life expectancy, whereas single-agent rituximab or even a watch-and-wait approach may be appropriate for older or medically unfit patients.

THERAPY OF FLs AT ADVANCED STAGES III AND IV

Patients without symptoms and low tumour burden

Because of the indolent course of FL and the lack of life-prolonging or even curative therapy, the strategy of withholding treatment in asymptomatic patients with a low tumour burden until the occurrence of disease-related symptoms was established in the 1990s. This 'watch-and-wait' approach was confirmed in a few prospective randomized studies demonstrating that the application of systemic cytostatic therapy could be safely delayed until treatment became necessary without any negative impact on patients' outcome.[22,23]

However, as for radiotherapy in limited stages I and II, these results were generated in the pre-rituximab era and need to be re-assessed on the basis of newer treatment modalities. In this respect, long periods of event-free survival were shown after single-agent rituximab therapy in patients with a low tumour burden.[24,25] Preliminary results of a prospective randomized trial were recently reported by Ardeshna *et al*.[26] Their study compared the three different strategies of watch-and-wait versus four weekly doses of rituximab versus four weekly doses of rituximab followed by 2 years of rituximab maintenance. Whereas the 4-week application of rituximab was stopped early, the analysis of the other two study arms revealed a significant prolongation of the time to initiation of chemo- or radiotherapy in favour of the early rituximab intervention. No relevant side effects were encountered in the rituximab-treated patients. However, follow-up is still relatively short and data on overall survival will not become available within the next few years. There was also an imbalance in design with one arm measuring time to first treatment and the other measuring time to second treatment, favouring the latter.

Longer follow-up is also required to evaluate whether early treatment with rituximab might impair the response to subsequent immunochemotherapy, which might become necessary at later disease progression.

On the basis of the currently available data, the question arises whether we should change the paradigm of watch-and-wait today. Given the many open questions on the unknown long-term outcome of early intervention, the most relevant justification for a change could be based on the assumed high level of anxiety that patients may encounter when they are faced with the fact that they suffer from a malignant disorder but remain untreated. Watch-and-wait has therefore frequently also been called 'watch-and-worry'. A recent evaluation of the study by Ardeshna *et al.*,[27] however, revealed that the proportion of patients suffering from high anxiety is surprisingly low and that patients assigned to watch-and-wait adjust to this approach in the vast majority of cases.

In addition, several other questions remain. When analysing the watch-and-wait arm of the study by Ardeshna in more detail it appears that 46% of patients did not require therapy within the first 3 years. Does that mean that almost half of the patients randomized for immediate intervention were treated too early and received an overtreatment? Is the benefit of delaying the onset of cytostatic therapy well balanced against a 2-year exposure to maintenance therapy? Is it really necessary to apply rituximab for 2 years to achieve this beneficial effect?

Results from the so-called RESORT study suggest that shorter courses of rituximab may lead to similar effects. In this study from the Eastern Cooperative Oncology Group, patients were initially treated with a 4-week course of rituximab after which one group of cases continued on rituximab maintenance until progression while the other group received no further therapy and was re-treated upon the recurrence of lymphoma manifestations.[28] After a median follow-up of almost 4 years, time to treatment failure was similar at 3.9 and 3.6 years, respectively. Five per cent of patients in the first group required subsequent chemotherapy, whereas this was necessary in 86% of patients in the second group. However, the first group received 15.8 applications of rituximab as compared with only 4.5 doses in the second group.

Further support for not changing the current watch-and-wait strategy is gained from the F2 study database that revealed no disadvantages in patients with a low tumour burden in whom immediate treatment was withheld.[29]

Hence, at present, watch-and-wait should still be the preferred choice for patients with asymptomatic, low tumour burden FL.[30] This recommendation is further supported by the perspective that the increasing insight into the biology of the disease will most certainly result in molecular markers that will allow the discrimination between patients with a rapidly progressive and those with a more indolent course of their disease. In addition, new and more specific anti-lymphoma therapies are rapidly emerging, which will most probably change the therapeutic approaches substantially.

Patients with symptoms or a high tumour burden—front-line therapy

For patients with a high tumour burden and/or with symptoms in need of therapy, the combination of rituximab plus chemotherapy (R-chemotherapy) has become the standard of care for frontline treatment. Four major prospective randomized studies uniformly demonstrated a significant increase in response rates, progression-free survival and particularly overall survival when comparing R-chemotherapy with chemotherapy alone.[31–35] Whether any of the different chemotherapeutic regimens has advantages over the alternatives remains currently unanswered. Indirect evidence from the PRIMA study and from a prospective randomized trial of the Italian FIL group indicates that R-CVP has a lower response rate as compared with R-CHOP or R-FM, whereas R-FM is substantially more toxic than R-CHOP.[36,37] Recently, Rummel *et al.*[38] reported the results of a prospective randomized trial comparing R-CHOP with R-bendamustine and described a significantly higher response rate and a longer progression-free survival in favour of R-bendamustine, which also had lower toxicity. However, no differences in overall survival were observed.[38] In contrast, a subsequently performed open label randomized comparison of R-bendamustine versus R-CHOP or R-CVP revealed no significant differences in response rates and time to progression and observed more side effects after R-bendamustine.[39] Still, R-bendamustine was not inferior to R-CHOP or R-CVP and therefore can be added to the currently available treatment options for initial therapy of patients with advanced-stage FL.

With modern R-chemotherapeutic regimens, overall response rates of more than 90% with complete remissions in the range of 20–60% can be expected with subsequent periods of median progression-free survival exceeding 4 to 5 years. Hence, the introduction of rituximab into frontline therapy of advanced FL represents an important step forward in the treatment of this disease (Figure 1).

Patients with symptoms or a high tumour burden—therapy in remission

Despite the high efficacy of initial anti-lymphoma therapy, the majority of patients with advanced-stage FL still suffer from a progression of their disease after a period of several years. Several attempts were made to prolong the time to progression, including consolidation with radio-immunotherapy or even autologous stem cell transplantation or prolonged rituximab maintenance.

Considering the high radiosensitivity of FL and the possibility of directing a radioactive tracer specifically to lymphoma cells, radio-immunotherapy is a highly attractive option for consolidation of first remission. In fact, promising data were reported by several phase II studies.[40–43] A randomized phase III study reported by Morschhauser *et al.*[44] compared 90Yi-ibritumomab treatment versus observation in patients in CR or PR after initial therapy and found a significantly longer progression-free survival in favour of radio-immunotherapy. However, only a minority of patients received rituximab during induction, thus limiting the significance of these findings. In a most recent study by Press *et al.*[45] patients with untreated FL were randomized for initial therapy with R-CHOP versus CHOP followed by ^{131}iodine-tositumomab . After a median follow-up of 4.9 years no differences in progression-free or overall survival were observed with high estimated 2-year progression-free survival rates of 76% for R-CHOP and 80% for CHOP-RIT. Although a longer follow-up is needed to judge the long-term effects of the different approaches of this study, it will not answer the question whether and how radio-immunotherapy could further improve the outcome of patients with advanced-stage FL. Hence, radio-immunotherapy remains investigational at this time in this setting.

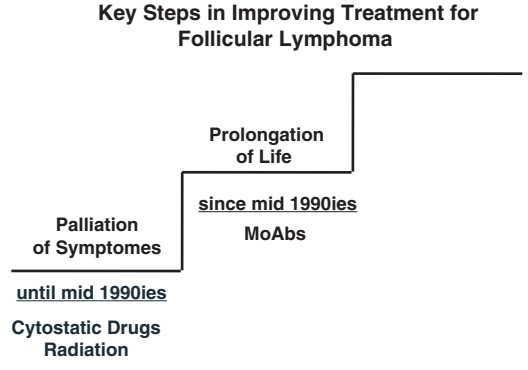

Figure 1. Key steps in the treatment of follicular lymphomas.

The high radiosensitivity of FL was at least in part also one of the arguments using myeloablative (radio)-chemotherapy followed by autologous stem cell transplantation (ASCT) for consolidation of first remission in patients with advanced-stage FL. In three of the four published major randomized trials a significant improvement in progression-free survival was reported but in all studies overall survival was not prolonged.[46–50] Although it may still be possible that a certain proportion of patients are cured by ASCT as consolidation therapy, ASCT has lost its relevance as first-line therapy for advanced-stage FL as similar results are nowadays achieved by less toxic and more easily applicable R-chemotherapeutic regimens.[51] ASCT, however, retains its role as a therapeutic option in the relapse setting where long-lasting remissions can be achieved.[52–56] Whether and when ASCT should be applied, that is, at first, second or third relapse, is not defined and must currently remain an individual's decision, which may be based on the patient's age and general condition, type and intensity of prior therapy and actual lymphoma manifestations including risk factors such as bulky disease, extranodal involvement, lactate dehydrogenase and beta-2-microglobulin levels.

After several prospective randomized studies had suggested a beneficial effect of rituximab maintenance in patients with untreated and relapsed FL,[57–61] the PRIMA study established rituximab maintenance as a new standard of care for first-line therapy of patients achieving first remission after initial therapy with either R-CHOP, R-CVP or R-FCM.[62] The data were recently updated at a median follow-up of 73 months and showed that rituximab maintenance resulted in a highly significant prolongation of progression-free survival at 6 years of 59.2% as compared with 42.7% of patients without maintenance ($P < 0.0001$).[63] The beneficial effect of R-maintenance was seen across all ages and the Follicular Lymphoma International Prognostic Index (FLIPI) risk groups and leads further to an increase in the rate of complete remissions at the end of the 2-year maintenance.

Although no data are yet available on the impact of rituximab maintenance on overall survival, 2 years of rituximab maintenance following successful initial R-chemotherapy is broadly considered a new standard for first-line therapy of patients with advanced-stage FL (Figure 2).

However, maintenance is associated with increased expense and toxicity. In addition, major questions remain or even arise: is continuous maintenance really necessary or is re-treatment at progression equally effective and possibly more cost-efficient[64] as also suggested by the results of the RESORT study?[28] Is 2 years of rituximab maintenance adequate, too short or too long? What can actually be achieved by maintenance—lymphoma control or even eradication? Can maintenance be adjusted to pretherapeutic risk factors such as the FLIPI or the quality of remission that is achieved by initial R-chemotherapy? Can maintenance be adjusted to minimal residual disease (MRD) in remission? Is the efficacy of rituximab maintenance dependent on the type of initial chemotherapy as suggested by Vitolo *et al.*?[65] These and other questions must be addressed in subsequent studies.

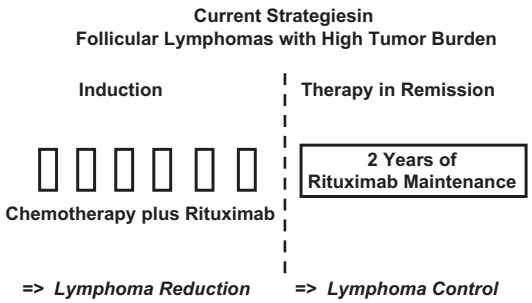

Figure 2. The current strategy of therapy in follicular lymphomas with a high tumour burden comprises initial immunochemotherapy for achieving a complete or partial remission, followed by 2 years of rituximab maintenance.

FUTURE PERSPECTIVES IN THE TREATMENT OF FLs—NEW AGENTS

The aforementioned discussion about the most appropriate chemotherapy to be combined with rituximab will most certainly soon be replaced by the more relevant question of which of the new agents that are currently under development should be incorporated into first-line therapy and how should these new drugs be combined with each other.

Actually, a real plethora of new agents is currently explored, some of which have entered clinical phase III evaluation already.[66,67]

New CD20 antibodies

CD20 remains an attractive target in FL and several second- and third-generation monoclonal antibodies have been developed to target that antigen. One of these is ofatumumab, which demonstrated a high single-agent activity in relapsed FL but failed to induce a significant response rate in rituximab refractory patients.[68,69] Obinutuzumab or GA 101, on the other hand, proved effective in relapsed, rituximab refractory FL as well, both in a single-agent setting[70,71] and when combined with chemotherapy.[72] Obinutuzumab is currently randomly compared with rituximab in combination with chemotherapy for first-line therapy within the so-called international GALLIUM study.

Other B-lineage antigen-directed antibodies

Although targeting CD22 and CD23 by antibodies such as epratuzumab or lumiliximab was less successful when applied as single agents, the combination of epratuzumab with rituximab induced considerable response rates both in relapse and front-line therapy.[73,74] A similar activity was found when the CD22 antibody inotuzumab was conjugated with ozogamicin and its combination with rituximab.[75,76] Promising data were also achieved by combining the anti-CD 80 antibody galiximab with rituximab in patients with untreated FL.[77] A further highly attractive approach is the application of the bi-specific T-cell engaging antibody blinatumomab targeting CD19 and CD3. Although the development of this bi-specific T-cell engager antibody is currently focussed on B-precursor acute lymphoblastic leukaemia, promising early results were also obtained in B-cell lymphomas, although considerable neurotoxicity with encephalopathy was observed.[78,79]

Drugs targeting oncogeneic pathways

Crucial pathways in the pathogenesis of malignant lymphomas comprise the PI3K/Akt/mTOR pathway as well as B-cell receptor signalling. mTOR inhibitors such as temsirolimus and everolimus revealed a significant single-agent activity predominantly in mantle cell lymphoma but also in FL and are currently explored in combination with different chemotherapeutic regimens.[80–82] Promising data were also achieved by targeting PI3K with drugs such as idelalisib, which showed a high single-agent activity in refractory FL.[83,84] Most interesting are recent data on the impairment of B-cell receptor signalling pathways through drugs such as fostamatinib or Brutońs tyrosine kinase inhibitors such as ibrutinib.[85,86]

Bcl 2 inhibitors

Interesting data also emerged from agents interfering with the bcl 2 family of proteins. Hence, promising response rates were initially reported from phase I studies with ABT-263 (navitoclax), which is, however, associated with thrombocytopenia. A better efficacy-toxicity profile is revealed by the BH3 mimetic ABT-199 (GDC-0199),[87,88] which is currently being actively developed.

Immunomodulatory drugs

One of the most promising new agents in the treatment of FL is lenalidomide. Its mechanism of action is not fully understood but probably includes a modulation of the lymphoma microenvironment and an enhanced anti-lymphoma immune response.[89] After promising single-agent activity was seen particularly in patients with refractoriness to prior therapies,[90] lenalidomide was combined with rituximab and achieved high response rates in first-line therapy.[91,92] An international prospective randomized phase III trial (RELEVANCE) currently compares the so-called R^2 combination of lenalidomide and rituximab against conventional R-chemotherapies, both arms being followed by a respective maintenance in remission.

Overall, a large number of promising new agents are currently being explored for the treatment of patients with FL. On the basis of available data the expectation seems to be highly justified that further improvements in the outcome of patients with FL can be achieved in the near future.

FUTURE PERSPECTIVES IN THE TREATMENT OF FLs—BETTER USE OF CURRENTLY AVAILABLE THERAPIES

While waiting for the exploration of new agents we may make better use of currently available therapies—for example, by adjusting them to prognostic factors or distinct response parameters.

The FLIPI is mainly based on age and clinical characteristics, including lactate dehydrogenase, and classifies patients into three major prognostic subgroups with 10-year overall survival rates of 71, 51 and 36%, respectively.[93] Although the FLIPI was developed in the pre-rituximab era its relevance could also be demonstrated for rituximab-based therapies.[94] The FLIPI as well as the subsequently reported modified FLIPI2[95] is a valuable tool for patient stratification in clinical trials and for evaluating treatment effects in the respective prognostic subgroups. However, owing to the marked variation in outcome within each subgroup, FLIPI does not allow for an adjustment of individual treatment decisions.

Modern cell biologic and genetic techniques including gene sequencing provide deeper insights into the pathobiology of FL and may allow the discrimination of distinct biologic subgroups. Indeed, associations between certain gene signatures or compositions of the microenvironment and clinical outcome have been described.[96–99] Data are inconsistent, however, and cannot be applied for guidance of treatment today.

In contrast, early assessment of treatment response by PET appears to be closely associated with patient outcome. Whereas the prognostic relevance of PET is already well established in Hodgkin's disease and diffuse large B-cell lymphoma, its role in FL remained undetermined. Several recent reports, however, describe a highly significant correlation between the results of PET imaging after R-chemotherapy for advanced-stage FL and

progression-free and even overall survival.[100–102] In these studies PET negativity or positivity, respectively, proved superior to conventional definitions of complete or partial response and therefore support the incorporation of PET into routine response assessment as already suggested in 2007 by the revised response criteria for malignant lymphoma.[103]

Individualised adaptation of therapy seems also possible by molecular monitoring of treatment response using PCR for the detection and quantification of the BLC2-IGH rearrangement that results from the translocation t(14;18).[104] PCR monitoring of MRD after successful cytoreductive therapy proved highly predictive for response duration[104–107] and was even used for pre-emptive therapy in patients with persistent MRD after ASCT.[108–111] Hence, monitoring of MRD may allow optimisation of the currently available treatment options by their adaptation to the MRD status in individual patients. This means that rituximab maintenance, for example, may be stopped when MRD negativity is achieved and restarted upon re-occurrence of the MRD signal.

Early assessment of treatment response by PET and molecular monitoring of MRD therefore provide the perspectives to further improve the management of patients with FL by adapting currently available therapeutic options to the status of the disease in individual patients.

CONCLUSIONS

After decades of stagnation until the mid 1990s the perspectives of patients with FL have changed substantially. The introduction of rituximab into FL therapy has led to significant improvement in long-term outcome and has challenged prior therapeutic paradigms such as radiotherapy for limited stages of the disease or the watch-and-wait approach for asymptomatic patients with low tumour burden. Hence, we are faced with the challenge to re-evaluate our therapeutic directives and to also take advantage of the large number of new agents that are currently entering clinical phase I to III studies. These developments are highly encouraging and justify the expectation that the management of patients with FL will further improve within the coming years. In this context we are also faced with the challenge to re-define our therapeutic goals. Are we aiming at cure and final disease eradication or are we aiming at making FL a chronic disease that we can control and re-treat with as little therapy as necessary upon potential re-occurrences to allow patients to live with their disease but experience ideally a normal life expectancy?

Considering that the majority of patients are at higher age, the latter approach may be most appropriate. Hence, therapy for FL remains a moving target and a challenge for basic researchers and clinicians.

CONFLICT OF INTEREST

WH serves as a member of the International Advisory Board of Roche AG and receives research grants from Roche for the support of clinical trials.

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