disclosure

The authors declared no conflict of interest.

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Phase II trial of galiximab (anti-CD80 monoclonal antibody) plus rituximab (CALGB 50402): Follicular Lymphoma International Prognostic Index (FLIPI) score is predictive of upfront immunotherapy responsiveness

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Background: This phase II CALGB trial evaluated the activity and safety of an extended induction schedule of galiximab (G) plus rituximab (R) in untreated follicular lymphoma (FL).

Patients and methods: Patients with previously untreated FL (grades 1, 2, 3a) received 4 weekly infusions of G + R, followed by an additional dose every 2 months four times. International Workshop Response Criteria were used to evaluate response.

Results: Sixty-one patients were treated and antibody infusions were well tolerated. The overall response rate (ORR) is 72.1% (95% confidence interval 59.2% to 82.9%): 47.6% complete response (CR)/unconfirmed complete response (CRu) and 24.6% partial response. At a median follow-up time of 4.3 years (range, 0.3–5.3 years) median progression-free survival (PFS) is 2.9 years. Notably, Follicular Lymphoma International Prognostic Index (FLIPI) correlated with ORR, CR rate, and PFS, and the low-risk FLIPI group (n = 12) achieved a 92% ORR, 75% CR/CRu rate, and 75% 3-year PFS.

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Conclusions: An extended induction schedule of G + R in previously untreated FL is well tolerated and appears particularly efficacious in those patients with low-risk FLIPI scores. In addition, this trial served as the initial platform for additional CALGB 'doublet' combination regimes of rituximab plus other novel targeted agents.

Key words: follicular lymphoma, Follicular Lymphoma International Prognostic Index (FLIPI), galiximab, immunotherapy, monoclonal antibodies, rituximab

introduction

Follicular lymphomas (FLs) are heterogeneous diseases with different histological grades (i.e. grades 1, 2, 3a, 3b), tumor- and patient-based prognostic indices [e.g. Follicular Lymphoma International Prognostic Index (FLIPI), tumor-associated macrophages, etc.] [1–3], and a variable therapeutic outcome. The majority of patients are initially treated with rituximab-based immunochemotherapy [4–10] with recent data suggesting benefit from rituximab maintenance (RM) therapy or a single infusion of Yttrium-90 ibritumomab tiuxetan [11]. However, based on the heterogeneity of FL, a single upfront treatment approach may not be appropriate for all FL patients. For example, a patient with non-bulky low-risk FLIPI disease may not require the same dose intensity as one with bulky symptomatic poor-risk disease. Rituximab monotherapy has been evaluated in the upfront treatment of FL and may be associated with prolonged progression-free survival (PFS) [12–15]. In fact, the randomized phase II SAKK 35/98 trial evaluated single-agent rituximab at two different schedules: standard therapy for four weekly doses, followed by randomization to observation or prolonged rituximab (i.e. 375 mg/m^2 every 2 months for four times) in those patients responding or with stable disease at week 12 [16]. Median event-free survival in chemotherapy-naive patients was significantly improved in patients receiving prolonged treatment ($n = 25$) versus observation ($n = 26$): 36 months versus 19 months, respectively. In an unplanned long-term analysis of patients participating on this trial, 45% of previously untreated patients receiving prolonged rituximab were without events at 8 years [17]. Some limitations of this long-term analysis include the following: the evaluation was retrospective, computed tomography (CT) scan tumor evaluations were required for only 5 years, FLIPI scores were not prospectively collected and unavailable retrospectively, and a relatively small number of patients were included in this dataset. Antibody combination regimens are also under development in an attempt to improve treatment outcomes, avoid non-specific toxicities typically associated with chemotherapeutic agents, and theoretically decrease the risk of developing rituximab resistance by targeting more than a single antigen [18–20]. Galiximab, a primatized (i.e. human-macaque chimeric) anti-CD80 monoclonal antibody (mAb) has been evaluated in phase I and II studies of indolent and FL. CD80 (B7.1) is a transmembrane glycoprotein which is involved in regulating the balance between immune activation and suppression. Published data suggest that CD80 is involved in activation/regulation of T-cells [21], transiently expressed on activated B cells and dendritic cells [22], plays a role in regulation and activation of normal and malignant B cells [23], and is constitutively expressed on malignant B cells [24]. Cross-linking surface CD80 on lymphoma cells with anti-CD80 antibodies is associated with inhibition of cellular proliferation, induction of antibody-dependent cellular cytotoxicity (ADCC), and upregulation of proapoptotic molecules [23, 25, 26]. In addition, galiximab may inhibit tumor progression by binding to non-malignant, CD80-positive cells in the tumor microenvironment (e.g. macrophages, dendritic cells, myeloid-derived suppressor cells) that may alter the cytokine profile and/or cellular composition to favor tumor inhibition. An initial phase I/II dose-escalation trial of galiximab monotherapy (i.e. 4 weekly doses) was found to be well tolerated with modest antitumor activity in patients with relapsed FL [5]. A phase I/II trial of galiximab plus rituximab in a relapsed/refractory FL population demonstrated a 66% overall response rate (ORR) [33% complete response (CR)/ unconfirmed complete response (Cru); 33% partial response (PR)] with a median PFS of 12.1 months [27]. Based on these promising results, the CALGB decided to test this promising biological 'doublet' in previously untreated FL patients.

patients and methods

study objectives

The primary objectives of the study were to determine the response rates (ORR and CR) and time to progression (TTP) of FL patients to G + R combination as initial therapy. Secondary objectives included: to evaluate the toxicity profile of this schedule, to determine the feasibility of this study design for future trials combining rituximab with other novel biologic agents, and to correlate Fc receptor polymorphism profile with treatment response.

eligibility criteria

Patients ≥18 years with previously untreated histologically confirmed FL, grades 1, 2, or 3a with stages III, IV, or bulky (i.e. single mass ≥7 cm in any unidimensional measurement) stage II disease were eligible for this study. Inclusion criteria also required: confirmation of CD20-positivity; Eastern Cooperative Oncology Group performance status of 0–2; measurable disease (e.g. tumor mass >1 cm), adequate hematological, renal, and hepatic function; no known central nervous system involvement, human immunodeficiency virus infection, or baseline human anti-chimeric antibody (HACA) positivity.

The study was conducted in accordance with the Declaration of Helsinki. Each participating clinical site obtained an Institutional Review Board-approved written informed consent from all study patients. As stated in the protocol, patients classified as poor-risk according to FLIPI were encouraged to be considered for participation on CALGB 50102/ SWOG 50016 [a phase III trial of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) plus rituximab × 6 versus CHOP × 6, followed by Iodine-131-labeled anti-B1

(CD20) mAb for treatment of newly diagnosed FL]. The study was registered at www.clinicaltrials.gov as #: NCT00117975.

study treatment

In this open-label multicenter, phase II study, patients received 'induction' rituximab (R) 375 mg/m^2 by IV infusion on day 1, month 1; then galiximab (G) (500 mg/m^2) over 60 min by IV infusion on day 3, month 1 because of expected longer infusion times typically associated with the first dose of rituximab. Both R + G (same doses) were given on days 8, 15, and 22 of month 1. 'Extended induction' therapy consisted of both R and G administered by IV infusion once in months 3, 5, 7, and 9. Overall, patients received a total of eight doses each of R and G over 9 months (see Figure 1).

study end points

efficacy

Disease assessments included CT scans or magnetic resonance imaging and physical examination at baseline, week 10, months 4, 6, 8, 10, and then every 4 months until disease progression or for a maximum of 10 years from study entry. Response to therapy was assessed using the IWG response criteria for non-Hodgkin's lymphoma (NHL) [28].

The primary efficacy end points were ORR and CR and PFS. ORR is defined as achievement of a CR or PR as the best observed response between trial entry and 12 months from enrollment on the trial. Secondary end points included correlation of Fc receptor polymorphism profile and FLIPI score with response to G + R therapy.

Follow-up evaluation included physical examinations, with vital sign measurements medical history/review of systems, adverse event (AE) documentation, complete blood counts, serum chemistry, serum immunoglobulin levels, HACA, and urinalysis.

statistical methods

The aim of this study was to evaluate the combination of galiximab plus rituximab in patients with previously untreated follicular NHL. If the data from this trial provided evidence of efficacy in this patient population, the treatment would be considered for further investigation. In evaluating response rate and PFS among FLIPI risk groups, the Cochran–Armitage test for trend and the log-rank test for differences in survival distributions were used, respectively.

The associations between each of ORR, CR, PFS, and FcR status (homozygous Val 158; homozygous Phe 158; heterozygous) were also evaluated in an exploratory fashion. In addition, FLIPI score versus ORR, CR rate, and PFS was also evaluated in an exploratory fashion.

A sample size of 51 patients was determined on the basis of the null hypothesis of an ORR of ≤0.65 tested against the alternative that the ORR is ≥0.80. An ORR of 0.80 would be considered worthy of further investigation. If ≥38 patients responded out of the total 51, then the study
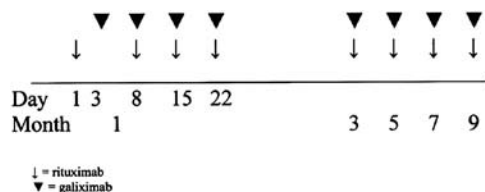

Figure 1. Treatment schema. Patients received a total of eight intravenous infusions of 375 mg/m^2 of rituximab and eight infusions of 500 mg/m^2 of galiximab over a period of 9 months.

regimen would be considered for further investigation. The exact test had a one-sided α = 0.10 and 87% power.

All patients were to be followed until progression or a minimum of 10 years. TTP was measured from study entry until documented progression of disease or death due to NHL. All events were progressions or death due to NHL. Assuming a median TTP of 36 months and a period of 3 months to complete data entry, these analyses were scheduled to be analyzed at ~40 and 55 months after study activation, respectively.

results

patient characteristics

Although 51 patients were originally planned to be enrolled on this trial, 61 assessable patients were actually enrolled between 3 August 2005 and 30 June 2006 at 21 CALGB institutions as the closure notice was sent on 15 June 2006 when accrual was at 52. In the last 2 weeks of accrual, 10 additional patients were registered, 8 within the last 2 days.

One patient never began treatment and was dropped from the analysis.

Baseline characteristics of all 61 treated patients are summarized in Table 1. Of note: 93% of patients had stage III/IV disease; 48% of patients were >60 years of age; 24% of patients had bulky (i.e. >7 cm) disease; and 37% of patients were classified as poor-risk by FLIPI stratification.

Eighty-two percent of patients completed all planned therapy. Reasons for not completing planned therapy are as follows: death (on day 5 due to NHL, n = 1); withdrawal from study (n = 2); non-protocol treatment given (n = 1); missed last treatment (n = 1); no response (n = 1); progression of disease (n = 5). Sixty-one patients were evaluable for safety and efficacy. Median follow-up is 4.3 years (range 0.3–5.3 years) as of 4 April 2011.

clinical AEs

Overall, G + R doublet biological therapy was well tolerated with only 13% of patients experiencing AEs. No patient

Table 1. Summary of baseline patient characteristics (n = 61)

Histology: FL, grades 1/2/3a	44%/46%/10%
Male : female	61% : 39%
Median age (years)	57 (range: 22–85)
Age > 60 years	48%
ECOG performance status 0/1/2	75%/22%/3%
Stage III/IV	38%/55%
Bone marrow involvement	46%
Elevated LDH	23%
>4 nodal sites	58%
Bulky disease (>7 cm)	24%
FLIPI score	
0–1	20.3%
2	42.4%
3–5	37.3%

FL, follicular lymphoma; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; FLIPI, Follicular Lymphoma International Prognostic Index.
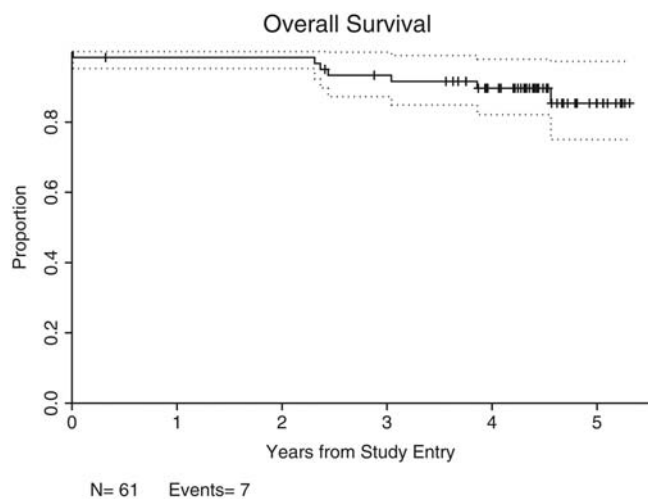
Figure 2. Overall survival of 61 assessable patients over a median follow-up time of 4.3 years (7 patients died of post-progression).

experienced dose-limiting toxicity and none withdrew from the study due to toxicity. A total of 48% grade 2 and 13% grade 3 reversible AEs were reported. The following hematologic AEs were noted: 7% grade 2: leukopenia, $n = 1$; lymphopenia, $n = 3$; neutropenia, $n = 1$; and 2% grade 3: lymphopenia, $n = 1$. The following non-hematologic AEs were recorded: 44% grade 2 and 11% grade 3 and included fatigue, pain at tumor sites, cytokine release, allergy/rash, transient hypotension, and chills. Only three cases of grade 2 infections were reported.

efficacy

An ORR of 72.1% [44 of 61 patients; 95% confidence interval (CI): 59.2% to 82.9%; $P = 0.1504$] was achieved, with CR/CRu of 41%/6.6% (25/4 = 29 of 61 patients; 95% CI = 34.6% to 60.7%). Twenty-five percent of patients ($n = 15$) achieved PRs. The majority of the 44 responders achieved an initial 'response' at 2–3 months after initiating therapy; 7 patients had 'delayed' initial response ranging from 8 to 14 months after starting treatment; 12 patients converted from stable disease or PR to CR/CRu after ≥9 months on therapy. The median follow-up time is 4.3 years (0.3–5.3 years) in the 25 patients who have not progressed (Figure 2). Seven deaths secondary to progressive disease have occurred in this time period (no deaths due to other causes) and the overall median PFS is 2.9 years (Figure 3).

An analysis of outcome by FLIPI prognostic score was carried out and demonstrated a statistically significant association between FLIPI score and ORR ($P = 0.004$) and CR rate ($P = 0.008$), and PFS ($P = 0.003$); see Table 2 and Figure 4.

Fc gamma receptor IIIA-VV [29] and receptor IIA-HH [30] genotypes have been associated with an improved response rate in FL patients treated with rituximab monotherapy. In the present study, no correlation was identified between Fc gamma RIIIA or RIIA polymorphisms with ORR, CR rate, or PFS.

discussion

Over the past decade, the initial therapy of FL has been evolving. Although many novel agents and treatment

approaches have been tested, no single regimen or approach has been shown to be optimal for all patients [31–37]. Single-agent rituximab or rituximab-containing immunochemotherapy (e.g. R-CVP, R-CHOP) have been the most common induction therapy for FL patients in the United States in the past decade [33]. Two recent studies already appear to be changing the induction treatment paradigm for FL. Bendamustine plus rituximab has been reported to be superior to R-CHOP as the initial treatment of patients with symptomatic grades 1 and 2, and FL [10]. Second, the Primary Rituximab Maintenance (PRIMA) study demonstrated that use of q 2 month RM therapy following induction R-chemotherapy (R-CHOP, R-CVP, or R-FCM) demonstrated a 14% improvement in 2-year PFS compared with those patients in an observation arm [38]. Nevertheless, these treatment approaches would be considered excessive for most patients with low-risk FL. Galiximab, a primatized anti-CD80 mAb, is a costimulatory molecule that is constitutively expressed on neoplastic B cells, is capable of mediating ADCC against NHL cells following its binding to surface CD80, and is also found on non-malignant CD80-expressing immunoeffector cells present in the tumor microenvironment (which may contribute to its antitumor activity). Galiximab is also well tolerated as a 1-h infusion in prior clinical trials [5, 21] and has an excellent toxicity profile.

The current CALGB trial evaluated the efficacy and safety of G + R in a unique schedule: G + R for four consecutive weeks, followed by extended dosing with G + R (every 2 months for four times) in previously untreated FL, grades 1, 2, and 3a. The stratification of various FL-risk groups in current clinical trials will ultimately help guide the choice of therapy for individual patients and avoid under-treating poorer risk patients, but at the same time avoiding over-treating lower risk patients. Furthermore, trials that utilize mAbs having different mechanisms-of-action that target unique CD20 epitopes or other unique surface antigens or that limit the total amount of rituximab exposure (e.g. unnecessary use of prolonged maintenance rituximab schedules) to minimize the
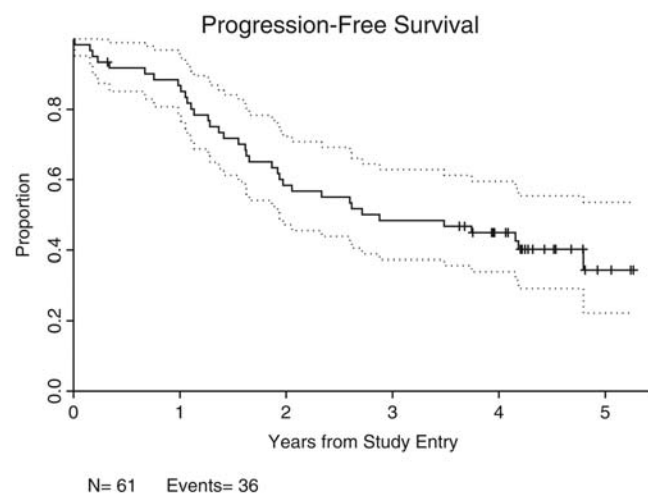

Figure 3. Overall progression-free survival curve. Kaplan–Meier analysis of overall progression-free survival, carried out in 61 assessable patients.
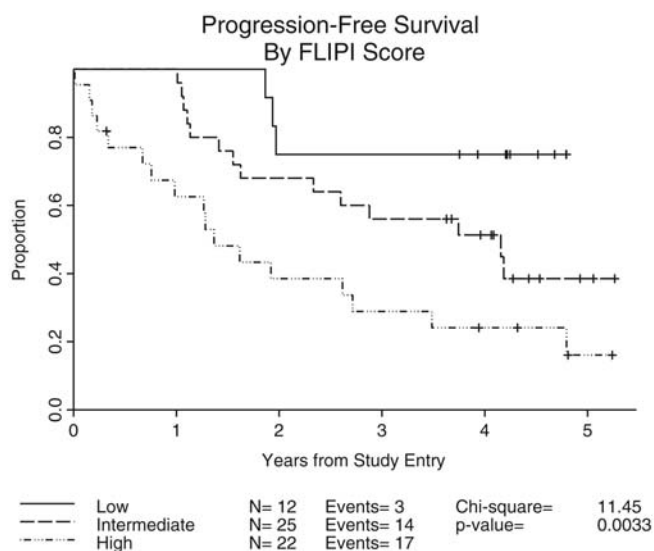
Figure 4. Progression-free survival by FLIPI score. Log-rank test analysis of progression-free survival versus FLIPI subgroup, carried out in 61 assessable patients. FLIPI, Follicular Lymphoma International Prognostic Index.

development of rituximab resistance are needed in order to continue to advance the field of lymphoma therapeutics and to optimize upfront and subsequent therapy in different risk-stratified subgroups.

Of interest in this study is the correlation between FLIPI and ORR, CR rate, and PFS with this biological doublet. FLIPI has been shown to be predictive in patients treated with immunochemotherapy [39], predicts transformation [40], and can be applied in first relapse [41]. In our database, we have demonstrated the validity of the prognostic significance of the FLIPI when combination immunotherapy (i.e. G + R) is utilized in the upfront setting.

Early phase I/II trials of four weekly infusions of galiximab alone [5] or in combination with rituximab [27] were evaluated in patients with relapsed or refractory FL. G monotherapy demonstrated modest (i.e. 11% ORR) clinical activity; however, G + R produced a 66% ORR (33% CR/CRu) with a median PFS of 12.1 months. Results with an eight infusion rituximab monotherapy dosing schedule (i.e. patients received 375 mg/m^2 weekly four times and if responding or with stable disease were randomized to receive an additional 375 mg/m^2 every 2 months for an additional four times or observation) published by Ghielmini et al. [16] demonstrated

prolonged PFS rates in the chemotherapy-naive subset of patients and served as the basis for the choice of schedule for our G + R trial. Unfortunately, a formal comparison between the potential benefit of adding an additional biological (i.e. galiximab) to rituximab in this extended induction schedule is not carried out since specific patient characteristics (i.e. FLIPI) of the 25 previously untreated patients receiving 'prolonged' rituximab in the Ghielmini et al. [16] trial were not prospectively collected and not currently obtainable [17]. In addition, significant differences in the required monitoring of study patients on these two studies exist (e.g. the G + R study required a more extensive and frequent evaluation of disease assessment). In the present study, no correlation between Fc gamma RIIIA or RIIA polymorphisms and ORR, CR rate, TTP, or PFS was demonstrated in patients treated with galiximab plus rituximab. This finding suggests that the mechanism(s) of antitumor activity seen with G + R differs and may be unique from that associated with rituximab monotherapy alone.

G + R achieved an ORR of 72.1% (95% CI 59.2% to 82.9%) in the entire group and did not achieve our pretreatment estimation that an ORR ≥ 80% would be considered worthy of further investigation. However, clinical characteristics/ prognostic factors (e.g. FLIPI) strongly influenced the therapeutic response. For example, although they were not formally excluded, eligibility criteria clearly stated that patients classified as poor-risk FLIPI should be considered for participation in CALGB 50102/SWOG 50016. Nonetheless, 37.3% of patients participating on our trial had poor-risk FLIPI which ultimately influenced the therapeutic outcomes. Indeed, if the 22 high-risk FLIPI patients were excluded from our database, the resultant ORR would be 86.5% and the CR rate 60%. The excellent results achieved in low-risk FLIPI patients treated with G + R suggests that this combination is highly effective with an excellent toxicity profile and has the advantage of delaying and perhaps avoiding myelotoxic chemotherapy and limiting the amount of rituximab exposure associated with prolonged RM schedules which adds expense, potential risk for the development of rituximab resistance, and does not appear to add benefit to good-risk patient populations. Of interest are data presented by Ardeshna et al. [42] at the 2010 annual ASH meeting from a UK intergroup randomized trial comparing rituximab with watchful waiting in asymptomatic non-bulky FL (grades 1, 2, and 3a) patients. Arm C (rituximab weekly four times, then q 2 months for 12 times) resulted in a 49% CR/CRu rate and the median time to initiation of new therapy (i.e. chemotherapy or radiotherapy)

Table 2. Association of FLIPI with ORR, CR rate, and DFS

	ORR[a] ($P = 0.004$)[b]	CR/CRu rate ($P = 0.008$)[b]	PFS ($P = 0.007$), 1 year	PFS ($P = 0.007$), 2 years	PFS ($P = 0.007$), 3 years
Entire group	72.1%	47.5%	0.87	0.58	0.48
FLIPI 1 (good-risk)	11/12 (92%)	9/12 (75%)	1.0	0.75	0.75
FLIPI 2 (intermediate-risk)	21/25 (84%)	13/25 (52%)	1.0	0.68	0.56
FLIPI 3–5 (poor-risk)	12/22 (55%)	7/22 (32%)	0.63	0.39	0.29

[a]ORR was not associated with stage, gender, marrow involvement, age > 60 years, or Fc gamma receptor polymorphism status.
[b]One-sided P-value for trend with respect to differences in FLIPI scores.
FLIPI, Follicular Lymphoma International Prognostic Index; ORR, overall response rate; CR, complete response; DFS, disease-free survival.

not reached at 4 years. Our CR/CRu rate of 48% and overall 3-year PFS of 48% in the entire group (but 75% in the good-risk FLIPI subgroup) are promising and achieved with only using a total of 8 rituximab infusions (in combination with galiximab) compared with a total of 16 rituximab infusions in the UK intergroup study. G + R is the first of several rituximab-based doublets which are being evaluated sequentially by the CALGB in an attempt to determine an optimal upfront non-chemotherapy-based therapeutic approach for the treatment of FL and will serve as the benchmark for future comparisons.

In conclusion, G + R combination immunotherapy is a novel, active, and well-tolerated upfront treatment strategy for FL patients, especially those with 'low-risk' FLIPI and warrants comparison with other front-line regimens in this population.

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Menstrual and reproductive factors, and hormonal contraception use: associations with non-Hodgkin lymphoma in a pooled analysis of InterLymph case–control studies

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