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Recombinant interferon- α 2b added to oral cyclophosphamide either as induction or maintenance in treatment-naïve follicular lymphoma: Final Analysis of CALGB 8691

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Abstract

Recombinant interferon alpha-2b (IFN- α 2) has direct and indirect antiproliferative effects in lymphoma, and may augment cytotoxicity when combined with chemotherapy. CALGB 8691 is a randomized study of daily oral cyclophosphamide (CPA) at 100 mg/m² with or without IFN- α 2 at 2×10^6 IU/m² three times per week, followed by a second randomization between IFN- α 2 maintenance (2×10^6 IU/m² three times weekly) versus observation in treatment-naïve patients with follicular lymphoma. 581 patients were randomized to either CPA (n=293) or CPA plus IFN- α 2 (n=288). 105 responding patients were randomized to observation and 99 to maintenance IFN- α 2. With a median follow-up of 11.5 years, the median event-free and overall survival for CPA induction alone was 2.5 years (95% CI 2.2, 3.0) and 9 years (95% CI 7.7, 10.2), compared to 2.4 years (95% CI 2.1, 3.1) and 8.4 years (95% CI 7.5, 11.1) for the combination arm (p=NS). Patients with a PR and randomized to observation had the worst outcome (EFS 1.8 years versus 3.9 years; p=0.002). Patients with a PR randomized to IFN- α 2 had a similar EFS to CR patients, but this did not translate into a survival advantage. Myelosuppression was increased in IFN- α 2-containing

arms. Despite the small benefit in event-free survival in PR patients randomized to IFN- α 2 maintenance, we conclude that the addition of low dose IFN- α 2 did not significantly improve the response rate, duration of response, event-free or overall survival obtained with single-agent daily oral CPA in patients with previously untreated follicular lymphoma.

Keywords

follicular lymphoma; interferon; maintenance; cyclophosphamide

Introduction

Follicular lymphoma is the second most common non-Hodgkin lymphoma and the most common of the indolent lymphomas. Although intensive front-line chemotherapy regimens such as CVP or CHOP are effective in inducing remissions, no regimen at the time of this study clearly prolonged survival and cures were not achievable, and the optimal initial management remains unknown. Daily oral cyclophosphamide is an approach widely used in the past, with an acceptable toxicity profile and efficacy. The CALGB had performed a randomized phase III study demonstrating equivalency between daily oral cyclophosphamide 100 mg/m² to much more intensive five-drug regimens in relapsed follicular lymphomas.¹ Since the addition of intensive agents did not improve efficacy over cyclophosphamide alone, there was a need for an agent with a complementary mechanism of action to chemotherapy. At the time of the design of this study, however, few non-cytotoxic non-chemotherapeutic options were available to assess in combination with chemotherapy.

Recombinant interferon alpha-2b (IFN- α 2) was one of the handful of biologic agents available for testing, and it had already demonstrated promising single agent activity in indolent non-Hodgkin lymphomas (NHL).² IFN- α 2 is a type I interferon, and has both direct and indirect anti-tumor effects, with a distinct mechanism of action compared to cytotoxic chemotherapy. The most relevant IFN effects for cancer control include a direct antiproliferative effect on lymphocytes, the induction and repression of gene expression (IFN-inducible genes), priming of cells to antibody-dependent cellular cytotoxicity (ADCC), induction of pro-apoptotic proteins, and antiangiogenic effects, among others.³⁻⁵ Similar to other IFN family members, IFN- α 2 uses both surface receptors and JAK-STAT signal transduction to mediate its cellular effects, although this was not yet known at the time of the current study design. In addition, IFN family members have been used as adjuvants to tumor vaccines following the discovery that interferons enhance both tumor-associated surface antigen and MHC I expression.³

CALGB 8553, a phase II study, indicated that the combination of IFN- α 2 plus cyclophosphamide (CPA) was both feasible and efficacious.⁶ One hundred five advanced stage III or IV patients with pathologically diagnosed International Working Formulation B or C histology (follicular lymphoma, grade 1-2) were treated with IFN- α 2 at a dose of 2×10^6 IU three times weekly plus CPA 100 mg/m² daily. Both treatment-naïve and relapsed patients were eligible. The authors found an overall response rate of 86% (58% complete response) for previously untreated patients, and an overall response rate of 62% (25%

complete response) in relapsed patients based on subgroup analysis. The 5-year overall survival was 63% for those without prior chemotherapy and 39% for previously treated patients. Toxicity was also less in the treatment-naïve group. Based on these promising results, CALGB 8691⁷ was designed as a prospective phase III randomized trial to test the hypothesis that the addition of IFN- α 2 could augment the therapeutic effects of oral cyclophosphamide given on a low-dose, daily schedule to patients with previously untreated follicular lymphoma, and forms the basis of this report.

PATIENTS AND METHODS

Study Design

CALGB 8691 (EST7486) was an open-label, randomized, multicenter phase III efficacy and toxicity study of daily oral cyclophosphamide (CPA) versus daily oral cyclophosphamide plus recombinant interferon alpha-2b (IFN- α 2), and was open to accrual between November 1986 and May 1991. In 1989, the protocol was amended to include a second randomization testing the efficacy of maintenance IFN- α 2 versus observation in responding patients. The study was approved by Institutional Review Boards at participating institutions and all patients signed a written informed consent form. Twenty-seven institutions from CALGB and ECOG participated. Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson. Statistical analyses were performed by CALGB statisticians. As part of the quality assurance program of the CALGB, members of the Audit Committee visit all participating CALGB institutions at least once every three years to review source documents. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in a sample of protocols at each institution.

Patient Selection

Eligible patients included previously untreated patients with stage III or IV nodular, poorly differentiated lymphocytic (International Working Formulation B, IWF-B) and nodular mixed lymphocytic-histiocytic lymphoma (IWF-C), corresponding to World Health Organization (WHO) follicular lymphoma grades 1-2. If more than 100 days had elapsed since the time of initial diagnosis, a second biopsy was performed to exclude a change in histology. Other eligibility criteria included: performance status ≥ 2 and normal renal, hepatic, and bone marrow function. Eligible patients were stratified by age greater than or less than 60 years, histopathologic subtype (follicular lymphoma, grade 1 versus grade 2) as determined at the institution where the patient was treated, stage III or IV, time since diagnosis (greater than or less than 100 days) and whether the patient was symptomatic versus asymptomatic. Patients were considered “asymptomatic” if they did not have B symptoms, bulky tumor with associated symptoms or physiologic threat, pleural effusion or ascites, rapid enlargement of lymph nodes, hemoglobin less than 9 gm/dl, leukopenia, thrombocytopenia or significant abnormalities of hepatic function. All patients registered to this study, including those designated “asymptomatic”, were started on treatment immediately upon randomization.

Treatment Plan

For the induction phase, patients were randomized to receive continuous daily oral cyclophosphamide at 100 mg/m² with or without IFN- α 2 as a subcutaneous injection at 2×10^6 IU/m² three times per week, with allowed dose adjustments for toxicity as follows: 25% reduction in IFN- α 2 for grade 2 non-hematologic toxicity, 50% reduction in IFN- α 2 for grade 3 non-hematologic toxicity, 25% reduction in IFN- α 2 for ANC 1000-1499/ μ L. CPA was reduced by 25-50% for myelosuppression and thrombocytopenia (25% reduction for ANC 1500-2499/ μ L or platelets 100,000-149,000/ μ L and 50% reduction for ANC 1000-1499/ μ L or platelets 75,000-99,000/ μ L). Patients with ANC < 1000/ μ L or platelets < 75,000/ μ L had both agents held. Responders remained on treatment with the initial therapy for three months following documentation of maximal response. Once the maintenance phase was initiated, all subsequent responders were randomized between observation and IFN- α 2 2×10^6 IU/m² three times a week for two additional years. Patients were stratified by their original treatment and the quality of response (complete vs. partial), and randomized to observation or to maintenance treatment with IFN- α 2.

Response Assessment

Initial response assessment was conducted at twelve weeks using computed tomography (CT) scans with or without a lymphangiogram. Thereafter, patients in partial response were reassessed every 16 weeks to determine further response. Patients in complete remission were reassessed every 12 weeks. A complete response was defined as the disappearance of all measurable and evaluable disease, and resolution of symptoms and laboratory changes attributed to the lymphoma for at least four weeks. If hepatic involvement was detected histologically at diagnosis, a negative liver biopsy was required. For those who had initial bone marrow involvement, two successive negative marrow biopsies three months apart were required to confirm a complete response. A partial response required a 50% or greater decrease in the sum of the products of the two longest perpendicular dimensions of all measurable lesions lasting four or more weeks, during which no new lesion may appear and no existing lesion may enlarge. Complete resolution of all enlarged lymph nodes or masses accompanied by persistent marrow involvement was considered a partial response. A maximal response was either a complete response or a partial response in which there was no further change in measurable disease over a period of three months on continued treatment. Any regression that was less than a partial remission was considered to be treatment failure. Progressive disease or relapse was noted if there was the reappearance of an old lesion, the appearance of a new lesion, or a 25% or greater increase in residual lesions when compared with maximal regression. During the maintenance phase and for all patients at the end of therapy, disease re-evaluation was performed every 12 weeks via physical exam, bloodwork, and CT scans.

Study Endpoints and Statistical Analysis

The primary objectives of the induction therapy were to determine and compare complete and overall response rate, duration of response, time to progression, survival and toxicity. The primary objectives of the maintenance phase were to determine and compare duration of response, time to progression, survival, and toxicity. Time to progression is defined as the

interval from randomization to first evidence of progression, relapse or recurrence, or death from any cause. The duration of complete remission is the interval from the date of documentation of complete response to relapse or death. Overall survival (OS) is measured from the date of randomization to death from any cause. The randomization scheme used was a stratified random permuted blocks design with balanced assignments to each treatment.^{8,9} The patient's institution is not a stratification factor, but partial balancing within institutions is handled as proposed by Zelen.¹⁰

Due to the pattern of reasons for discontinuation of therapy in this study, a combined endpoint, event-free survival (EFS), i.e., time to treatment failure, was used in these analyses. A treatment failure is defined as progressive disease, death from any cause, early termination of protocol therapy due to an adverse event (5 patients), initiation of non-protocol therapy with stable disease (5 patients), or withdrawal from protocol treatment with no response (11 patients).

Comparisons of complete response rates between treatment groups were made using the Pearson chi-square test for contingency tables. "Time to event" distributions (event-free survival, and survival) were estimated using the product-limit method of Kaplan and Meier and Cox proportional hazards models. Estimation of "time to complete response" distributions took into account the fact that patients who progressed or died without attaining a complete response were no longer at risk for achieving complete response. The statistical significance of differences observed in the distributions of "times to event" was assessed using the log-rank test. All p-values reported are two-sided.

RESULTS

Patient Characteristics

As of study closure, 581 patients had been entered on this study (Figure 1), with well-matched characteristics on both arms (Table 1). Five patients withdrew consent after randomization and prior to receiving any therapy. Forty-five patients were deemed ineligible by virtue of not fulfilling all protocol-specified eligibility criteria. An additional 95 patients, including 20 patients without submitted material for central histopathology review and 75 determined to be ineligible upon central pathology review were also ineligible (Figure 1). Histologic subtypes that were excluded following central review were grade 3 follicular lymphoma (26 patients, 5%), other indolent non-Hodgkin lymphoma, not otherwise specified (39 patients, 7%), small lymphocytic lymphoma (11 patients, 2%), and diffuse aggressive lymphomas (9 patients, 2%). Intention-to-treat analyses include all 581 patients registered, of which 293 were randomized to daily oral cyclophosphamide and 288 were randomized to cyclophosphamide plus IFN- α 2, while the 436 who were fully eligible by both clinical criteria and central histopathology review are the subjects of the analyses of the strictly eligible and treated patients (224 and 212 patients, respectively). The primary results for this study are reported from the intention-to-treat analyses. When evaluating strictly eligible patients, the study populations remained similar with no significant differences in patient characteristics (data not shown).

Response and survival following induction

Response to induction therapy by treatment arm is detailed in Table 2. The complete and overall response rates were 43% and 88% in the cyclophosphamide arm, and 43% and 84% in the cyclophosphamide plus IFN- α 2 arm, respectively. The median duration of induction was 9 months (range, 2 weeks-20 months). The median time to CR was 6 months (range, 1-30 months). Survival by induction treatment for the intent-to-treat populations is shown in Figure 2. With a median follow-up of 11.5 years (range 0.6-15.2 years), the median EFS and OS is 2.5 years (95% CI 2.2, 3.0) and 9 years (95% CI 7.7, 10.2), respectively, for the cyclophosphamide arm; the median EFS and OS is 2.4 years (95% CI 2.1, 3.1) and 8.4 years (95% CI 7.5, 11.1), respectively, for the combination arm. Of patients achieving a complete response, the median duration of response was 4.6 years (95% CI 2.9, 5.9) and 4.8 years (95% CI, 3.3, 6.2) on the single versus combination arm with no statistically significant difference between the two. As predicted, patients achieving only a PR after induction had an inferior outcome compared to CR patients.

Analysis of strictly eligible patients was similar to analysis of the entire population entered, with no major differences observed between the CPA or CPA plus IFN- α 2 arms for response to induction (91% versus 85%), median EFS (2.7 years on both arms), median OS (9.5 years versus 9.8 years), or duration of response following induction (4.6 years versus 4.4 years).

Response and survival following maintenance

204 patients (99 from the cyclophosphamide arm and 105 from the combination arm) completed the induction phase and were randomized to either observation or maintenance therapy with IFN- α 2 (Table 3). Of these 204 patients, 5 patients withdrew consent, 10 were deemed ineligible, 28 were found to be ineligible after central pathology review, and 7 had no pathology submitted. Of the remaining patients, 78 patients on the cyclophosphamide induction arm and 76 from the combination induction arm were randomized to either observation (n=84) or maintenance IFN- α 2 (n=70) (Figure 1). The duration of maintenance was 23 months (range, 1 week-9.5 years). 10% of patients discontinued maintenance by 4 months, but half the randomized patients received at least 2 years of maintenance therapy. Eight patients improved from a PR to a CR during maintenance therapy. Five of these patients were on the IFN- α 2 arm and 3 were on the observation arm. Overall, there was no difference in either EFS or OS between patients randomized to observation or IFN- α 2 maintenance following either cyclophosphamide or combined cyclophosphamide plus IFN- α 2 induction (Figure 3a). Specifically, the EFS for patients undergoing the second randomization is as follows: CPA $\rightarrow$ observation (2.4 years [95% CI: 1.6, 4.6]), CPA plus IFN $\rightarrow$ observation (3.3 years [95% CI: 1.6, 7.5]), CPA $\rightarrow$ IFN (3.9 years [95% CI: 2.2, 6.7]), CPA plus IFN $\rightarrow$ IFN (3.7 years [95% CI: 2.3, 5.5]). These differences were not statistically significant.

However, a subset analysis comparing outcomes of patients achieving a CR versus a PR following induction, maintenance IFN- α 2 improved EFS of the PR patients, but not OS (Figure 3b and 3c; Table 4). Among 4 maintenance groups (CR with or without IFN- α 2 maintenance, PR with or without IFN- α 2 maintenance) using a Cox model, there was a statistically significant inferior outcome for PR patients randomized to observation

compared to all other groups. With this observation, a second Cox model was fitted with the binary variables: PR patients on observation compared to all others. Patients achieving a PR and randomized to observation had a median EFS of only 1.8 years (95% CI 1.3, 2.6) versus 3.9 years (95% CI 2.6, 5.2) for all other groups (PR followed by IFN- α 2 maintenance or any CR irrespective of maintenance strategy) ($p < 0.002$).

Second Malignancies

Second malignancies have been reported in 70 patients, with 37 on the CPA arm and 33 on the CPA plus IFN- α 2 arm. One patient developed myelodysplastic syndrome 6.4 years following study entry, and 2 patients had therapy-related leukemia at 6.7 and 8.5 years. There were 3 lymphoproliferative malignancies (1 Hodgkin lymphoma, 2 non-Hodgkin lymphomas), 10 non-melanoma skin cancers, and the remaining cancers were solid tumors of breast, colon, or lung.

Toxicity

This phase III therapeutic trial was monitored at least twice annually by the Data and Safety Monitoring Board, a standing committee composed of individuals from within and outside the CALGB. All adverse events were graded according to the CALGB Expanded Common Toxicity Criteria. Adverse events reported for the induction phase of treatment by treatment arm are shown in Table 5a. Grade 3 or greater leucopenia, thrombocytopenia, granulocytopenia and neurologic CNS toxicities were significantly higher in the CPA plus IFN- α 2 arm ($p < 0.001$), as were hepatic toxicities, fever without infection, and other toxicities ($p < 0.01$). Toxicities included in the “Other” category in Table 5a were all grade 3 and included fatigue ($n=24$), depressed performance status ($n=6$), weight loss ($n=3$), anorexia ($n=4$), muscle pain ($n=3$), and 1 case each of edema, hot flashes, lightheadedness, and gout. There were three treatment-related deaths, all on the combination arm, including 1 respiratory failure presumed due to CPA-induced pulmonary fibrosis, 1 due to infection, and 1 due to neutropenia.

Toxicities reported during the maintenance phase of treatment by treatment arm are shown in Table 5b for 192 available patients. Toxicities included in the “Other” category in Table 5b were all grade 3 and included 1 case each of lymphocytopenia, fatigue, night sweats, chills, and flu-like symptoms. Grade 3 or greater leukopenia ($p=0.023$) and granulocytopenia ($p < 0.001$) were significantly higher in the IFN- α 2 group.

DISCUSSION

This report is the final analysis of a large multicenter randomized trial comparing daily oral cyclophosphamide (CPA) with or without interferon alpha 2b (IFN- α 2) in patients with previously untreated indolent lymphomas, and a second randomization comparing IFN- α 2 maintenance versus observation in responding patients. With long-term follow-up, our results fail to find an advantage to the addition of IFN- α 2 to CPA in this population. Response to induction therapy, event-free and overall survival were similar in both groups, and there did not appear to be a significant advantage to adding IFN- α 2 maintenance over observation. The only subgroup to experience any benefit was partial responders randomized

to IFN- α 2 maintenance, with an improved event-free survival but no overall survival advantage compared to partial responders randomized to observation. In contrast, toxicity was increased in patients randomized to IFN- α 2. Although most toxicities were mild, grade 3 or greater hematologic toxicities were significantly increased in the combination arm. Even when excluding the large number of ineligible patients, no differences by treatment arm could be detected. Thus, although the analyses were performed in both the intent to treat population (ITT) and the strictly eligible population, only the ITT data is presented.

The rationale to use IFN- α 2 in this population is based on its potential complementary mechanism of action to chemotherapy. IFN- α 2 demonstrates some single agent activity, but the effects are generally not durable, and most investigators have evaluated IFN- α 2 in combination with cytotoxic agents. When IFN- α 2 has been combined with chemotherapy, conflicting results have been found, with some studies supporting a survival benefit with IFN- α 2 and others showing either no benefit or an inferior outcome.¹¹⁻¹⁵ A meta-analysis of 1,922 patients from ten phase III randomized controlled trials evaluated the role of IFN- α 2 in follicular lymphoma when given at any point in the overall treatment plan.¹⁶ The studies included were quite variable, with some using IFN- α 2 with chemotherapy of differing intensities, others using IFN- α 2 purely as a maintenance, and still others using IFN- α 2 both concomitantly and following chemotherapy. Studies with two separate randomizations, including ours, were analyzed as two separate components in order to avoid bias in favor of IFN- α 2 when the maintenance was only given to responding patients. The analysis showed that the use of IFN- α 2 at any point in treatment improved survival by 5.5% at 5 years and 8% at 10 years. However, several factors influenced the magnitude of benefit including increased intensity of initial chemotherapy, an IFN- α 2 dose $\geq$ 5 million units (MIU), a cumulative IFN- α 2 dose greater than 36 MIU per month, and when IFN- α 2 was given concurrently with chemotherapy. The low-dose daily administration of CPA along with the relatively lower daily and total dose of IFN- α 2 administered used in this trial may have been insufficient to generate potential synergy.

A major unanswered question is whether or not IFN- α 2 still has a role in modern regimens containing rituximab and other biologic agents. IFN- α 2 increases antigen expression and augments ADCC. Several exploratory analyses have shown the feasibility and potential efficacy of combining rituximab plus IFN. A multicenter single-arm phase II study combined IFN with rituximab in 38 patients with relapsed and refractory indolent lymphomas, the vast majority of whom were rituximab-naïve.¹⁷ IFN- α 2 5 MIU three times weekly was delivered for 12 continuous weeks, with rituximab 375 mg/m² weekly on weeks 5 through 8. The overall response rate was 45% with 11% complete responses, and a median duration of response 22.3 months. The mean number of IFN- α 2 doses delivered was 31 instead of 36 intended doses, primarily due to hematologic toxicities. An Italian cooperative group designed a combination study of IFN with rituximab for patients with relapsed indolent lymphomas, this time using escalating weekly dosing of IFN (1.5 MIU daily $\times$ 5 days and increasing to 6 MIU by week 4 and 5) with rituximab 375 mg/m² weekly for 4 doses starting on the third week.¹⁸ They reported an overall response rate of 70% (33% complete response) and a median duration of response of 19 months. Both of these studies comment that the results are not substantially different from those obtained with single agent rituximab in this population, but that the combination appears feasible and should be studied

in a randomized trial to determine the true contribution of IFN with rituximab. The Nordic Lymphoma Group gave rituximab for four weeks, followed by a phase II randomized study of rituximab for an additional four weeks with or without IFN- α 2 for partial responders.¹⁹ The combination group had more patients converting from partial or minor response to complete response ($p<0.05$) and were able to maintain their response for greater than 24 months (72% versus 50%). A greater number of molecular responses were also observed in the combination group. However, substantially more cytopenias were observed in the combination arm, requiring dose reductions of the IFN- α 2.

In summary, CALGB 8691 was unable to demonstrate an improvement in response rate, progression-free or overall survival by the addition of IFN- α 2 to daily oral cyclophosphamide in treatment-naïve patients with follicular lymphoma. We observe that some partial responders may benefit from the addition of IFN- α 2 maintenance with an improved event-free survival, but that this benefit did not occur for patients already in complete remission following induction and did not confer an overall survival advantage. Newer information regarding IFN- α 2 mechanisms of action may help identify specific patient subsets where the activity of combination therapies would be more robust. As the significance of the lymphoma microenvironment composition becomes better understood,^{20,21} IFN- α 2 could still have a role in management of follicular lymphoma patients worthy of further study, perhaps in combination with rituximab or other immunomodulatory agents. However, IFN- α 2 following low-dose daily oral cyclophosphamide did not improve clinical outcomes for patients with treatment-naïve follicular lymphomas.

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Figure 1.

Number of patients entered and assigned to specific treatment arms. Abbreviations: CPA (cyclophosphamide), IFN (IFN- α 2), ITT (intent-to-treat).

Figure 2. Event-free survival and overall survival by induction treatment for the intent-to-treat populations. There was no statistical difference in either EFS or OS for the cyclophosphamide (CPA) or combination arm (CPA plus IFN- α 2).

Figure 3.

a. Event-free survival and overall survival of patients randomized to observation or IFN- α 2 maintenance following either cyclophosphamide or combined cyclophosphamide plus IFN- α 2 induction. **Figure 3b and 3c.** Event-free survival and overall survival by response to induction treatment and assignment to maintenance arm. Patients with a PR to induction randomized to IFN- α 2 had a similar event-free survival as CR patients whereas patients with a PR to induction randomized to observation had an inferior event-free survival compared to all other groups ($p < 0.002$). There was no difference in overall survival between any of the groups.

Table 1

Patient characteristics for induction phase (intent-to-treat). Abbreviations: CPA (cyclophosphamide), IFN (interferon- α 2), FL (follicular lymphoma), SLL (small lymphocytic lymphoma), DLBCL (diffuse large B-cell lymphoma).

Characteristic	No. of Patients				
	CPA (n=293)	CPA+IFN (n=288)	Total (n=581)		
Sex					
Male	146	149	295	51%	
Female	147	139	286	49%	
Age					
< 40	38	41	79	14%	
40-49	61	81	142	24%	
50-59	80	57	137	24%	
60-69	80	79	159	27%	
70+	34	30	64	11%	
Median/Range	55	25-80	55	24-90	
Race					
White	277	260	537	92%	
Black	11	18	29	5%	
Hispanic	4	4	8	1%	
Other	1	5	6	1%	
Missing		1	1	<1%	
Performance Status					
0	199	189	388	67%	
1	86	84	170	30%	
2	6	13	19	3%	
Missing	2	3	5		
Stage					
III	71	77	148	26%	
IV	220	207	427	74%	

	No. of Patients				
Characteristic	CPA (n=293)		CPA + IFN (n=288)		Total (n=581)
Missing	2		4		6
B Symptoms					
No	230	79%	213	75%	443
Yes	61	21%	72	25%	133
Missing	2		3		5
Other Symptoms					
No	213	73%	208	73%	421
Yes	77	27%	76	27%	153
Missing	3		4		7
Stage/Symptoms					
IIIA	58	20%	56	20%	114
IIIB	13	5%	21	7%	34
IVA	172	59%	156	55%	328
IVB	48	16%	51	18%	99
Missing	2		4		6
Pathology (Central Review)					
IWF A (SLL)	4	1%	7	3%	11
IWF B (FL, gr 1)	139	50%	146	53%	285
IWF C (FL, gr 2)	102	36%	85	31%	187
IWF D (FL, gr 3)	13	5%	13	5%	26
IWF E,F,G (DLBCL)	3	1%	6	2%	9
IWF K (other)	19	7%	20	7%	39
Missing	13		11		24

* There were no statistically significant differences between the groups (p=NS).

Table 2

Response Following Induction Therapy. Abbreviations: PCR (pathologic complete response), CCR (clinical complete response), PR (partial response), SD (stable disease), ORR (overall response rate), CPA (cyclophosphamide), IFN (interferon- α 2), NE (not evaluable)

There was no statistically significant difference in either complete, partial, or overall response rates.

Treatment	PCR/CCR	PR	SD	PD/NE	ORR
<i>Intent to treat</i>					
CPA (n=293)	125 (43%)	133 (45%)	15 (5%)	20 (7%)	258 (88%)
CPA + IFN (n=288)	123 (43%)	118 (41%)	16 (6%)	31 (11%)	241 (84%)
<i>Strictly eligible</i>					
CPA (n=224)	99 (44%)	105 (47%)	10 (4%)	10 (4%)	204 (91%)
CPA + IFN (n=212)	98 (46%)	83 (39%)	11 (5%)	20 (9%)	181 (85%)

Table 3

Patient characteristics of 204 patients randomized to maintenance therapy (intent-to-treat analysis). Abbreviations: CPA (cyclophosphamide), IFN (interferon- α 2), FL (follicular lymphoma), SLL (small lymphocytic lymphoma).

Characteristic	No. of Patients			
	IFN (n=99)	Obs (n=105)	Total (n=204)	
Sex				
Male	54	50	104	51%
Female	45	55	100	49%
Age				
< 40	14	13	27	13%
40-49	23	37	60	29%
50-59	32	26	58	28%
60-69	28	22	50	25%
70+	2	7	9	4%
Median/Range	53 25-77	50 24-75	51 24-77	
Race				
White	92	95	187	92%
Black	5	6	11	5%
Hispanic	1	2	3	1%
Other	1	2	3	1%
Performance Status				
0	74	82	156	76%
1	24	22	46	23%
2	1	1	2	1%
Stage				
III	21	31	52	25%
IV	78	74	152	75%
B Symptoms				
No	81	85	166	81%

Characteristic	No. of Patients					
	IFN (n=99)		Obs (n=105)		Total (n=204)	
Yes	18	18%	20	19%	38	19%
Other Symptoms						
No	84	85%	83	79%	167	82%
Yes	15	15%	22	21%	37	18%
Stage/Symptoms						
IIIA	18	18%	25	24%	43	21%
IIIB	3	3%	6	6%	9	4%
IVA	63	64%	60	57%	123	60%
IVB	15	15%	14	13%	29	14%
Pathology (Central Review)						
IWF A (SLL)	2	2%	4	4%	6	3%
IWF B (FL, gr 1)	47	49%	62	61%	109	55%
IWF C (FL, gr 2)	31	32%	27	27%	58	29%
IWF D (FL, gr 3)	10	10%	2	2%	12	6%
IWF K (other)	6	6%	6	6%	12	6%
Missing	3		4		7	
Response to induction						
PCR/CCR	63	64%	69	66%	132	65%
PR	36	36%	36	34%	72	35%

* There were no statistically significant differences between the groups (p=NS).

Table 4

Estimated probabilities of event-free and overall survival by maintenance arm (intent-to-treat analysis). All probabilities are from the date of randomization to maintenance.

	IFN		Obs	
	Event-Free Survival			
Year	Probability	95% CI	Probability	95% CI
1	0.80	0.70,0.86	0.78	0.69,0.85
2	0.66	0.55,0.74	0.57	0.51,0.63
5	0.43	0.33,0.52	0.37	0.27,0.46
10	0.31	0.22,0.40	0.26	0.19,0.36
Median	3.9	2.4,5.2	2.6	1.8,4.6
	Survival			
Year	Probability	95% CI	Probability	95% CI
1	0.98	0.92,0.99	0.98	0.93,0.99
2	0.94	0.87,0.97	0.92	0.85,0.96
5	0.78	0.68,0.85	0.81	0.72,0.87
10	0.55	0.44,0.64	0.60	0.49,0.68
Median	11.1	8.0,---	na	-----

Table 5

Comparison of toxicities by treatment arm for both the induction phase (6A) and maintenance phase (6B).

A				
		Grade		
	Arm	1-2	3-5	p value
Leukopenia	CPA	157 (54%)	110 (38%)	<.0001
	CPA+IFN	74 (26%)	210 (74%)	
Thrombocytopenia	CPA	124 (43%)	20 (7%)	<.0001
	CPA+IFN	139 (49%)	52 (18%)	
Granulocytopenia	CPA	165 (57%)	85 (29%)	<.0001
	CPA+IFN	113 (40%)	166 (58%)	
Anemia	CPA	147 (51%)	27 (9%)	0.0007
	CPA+IFN	171 (60%)	41 (14%)	
Hemorrhage	CPA	9 (3%)	5 (2%)	0.004
	CPA+IFN	26 (9%)	2 (1%)	
Infection	CPA	89 (31%)	17 (6%)	0.199
	CPA+IFN	95 (33%)	26 (9%)	
GU	CPA	94 (32%)	14 (5%)	0.732
	CPA+IFN	100 (35%)	15 (5%)	
Hepatic	CPA	107 (37%)	4 (1%)	0.006
	CPA+IFN	104 (36%)	18 (6%)	
Nausea	CPA	133 (46%)	10 (3%)	0.065
	CPA+IFN	146 (51%)	18 (6%)	
Other GI	CPA	93 (32%)	8 (3%)	0.004
	CPA+IFN	128 (45%)	16 (6%)	
Pulmonary	CPA	55 (19%)	6 (2%)	0.030
	CPA+IFN	74 (26%)	12 (4%)	
Cardiac	CPA	11 (4%)	0 (0%)	0.001
	CPA+IFN	26 (9%)	5 (2%)	
Neurologic, CNS	CPA	70 (24%)	3 (1%)	<0.0001
	CPA+IFN	122 (43%)	21 (7%)	
Neurologic, PNS	CPA	287 (99%)	4 (1%)	<0.0001
	CPA+IFN	57 (20%)	12 (4%)	
Skin/mucosa	CPA	55 (19%)	2 (1%)	<0.0001
	CPA+IFN	110 (39%)	8 (3%)	
Allergy	CPA	5 (2%)	1 (< 1%)	0.305
	CPA+IFN	9 (3%)	3 (1%)	
Fever w/o infection	CPA	29 (10%)	3 (1%)	<0.0001
	CPA+IFN	121 (42%)	16 (6%)	
Alopecia	CPA	85 (29%)	5 (2%)	0.216

A				
		Grade		
	Arm	1-2	3-5	p value
	CPA+IFN	88 (31%)	11 (4%)	
Local	CPA	20 (7%)	0 (0%)	0.020
	CPA+IFN	36 (12%)	1 (< 1%)	
Other*(see text)	CPA	145 (50%)	11 (4%)	<0.0001
	CPA+IFN	210 (74%)	35 (12%)	
Maximum Toxicity	CPA	130 (45%)	159 (55%)	<0.0001
	CPA+IFN	29 (10%)	256 (90%)	

B				
		Grade		
	Arm	1-2	3-4	p-value
Leukopenia				
	IFN	69 (73%)	13 (14%)	<0.0001
	OBS	33 (34%)	1 (1%)	
Thrombocytopenia				
	IFN	44 (46%)	7 (7%)	<0.0001
	OBS	10 (10%)	4 (4%)	
Granulocytopenia				
	IFN	62 (65%)	13 (14%)	<0.0001
	OBS	16 (16%)	1 (1%)	
Anemia				
	IFN	41 (43%)	1 (1%)	<0.0001
	OBS	9 (9%)	1 (1%)	
Hemorrhage				
	IFN	94 (99%)	0 (0%)	0.497
	OBS	96 (100%)	0 (0%)	
Infection				
	IFN	19 (20%)	3 (3%)	<0.0001
	OBS	3 (3%)	0 (0%)	
GU				
	IFN	16 (83%)	0 (0%)	0.005
	OBS	92 (96%)	0 (0%)	
Hepatic				
	IFN	24 (25%)	2 (2%)	0.002
	OBS	8 (8%)	1 (1%)	
Nausea				
	IFN	25 (26%)	0 (0%)	<0.0001
	OBS	2 (2%)	0 (0%)	

B				
		Grade		
	Arm	1-2	3-4	p-value
Other GI				
	IFN	24 (26%)	2 (2%)	<0.0001
	OBS	4 (4%)	0 (0%)	
Pulmonary				
	IFN	16 (17%)	1 (1%)	0.0002
	OBS	2 (2%)	0 (0%)	
Cardiac				
	IFN	5 (5%)	0 (0%)	0.118
	OBS	1 (1%)	0 (0%)	
Neurologic CNS				
	IFN	38 (40%)	3 (3%)	<0.0001
	OBS	1 (1%)	0 (0%)	
Neurologic PNS				
	IFN	13 (14%)	1 (1%)	0.016
	OBS	4 (4%)	0 (0%)	
Skin/Mucosa				
	IFN	25 (27%)	0 (0%)	<0.0001
	OBS	4 (4%)	0 (0%)	
Allergy				
	IFN	3 (3%)	0 (0%)	0.119
	OBS	0 (0%)	0 (0%)	
Fever w/o Infection				
	IFN	27 (29%)	5 (5%)	<0.0001
	OBS	5 (5%)	0 (0%)	
Alopecia				
	IFN	13 (86%)	0 (0%)	0.023
	OBS	4 (4%)	0 (0%)	
Local				
	IFN	12 (13%)	1 (1%)	0.0007
	OBS	1 (1%)	0 (0%)	
Other*(see text)				
	IFN	64 (65%)	7 (7%)	<0.0001
	OBS	16 (15%)	0 (0%)	
Maximum Toxicity				
	IFN	54 (57%)	39 (41%)	<0.0001
	OBS	49 (51%)	7 (7%)	