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Rituximab with chemotherapy in children and adolescents with central nervous system and/or bone marrow positive Burkitt lymphoma/leukaemia: A Children's Oncology Group Report

Running head: Rituximab in high-risk Burkitt lymphoma

Stanton Goldman[1], Lynette Smith[2], Paul Galardy[3], Sherrie L. Perkins[4], J. Kimble Frazer[5], Warren Sanger[6], James R. Anderson[2], Thomas G. Gross[7], Howard Weinstein[8], Lauren Harrison[9], Bruce Shiramizu[10], Matthew Barth[11]and Mitchell S. Cairo[9, 12, 13, 14, 15]

[1]Division of Paediatric Haematology/Oncology, Medical City Children's Hospital, Dallas, TX; [2] Department of Biostatistics, University of Nebraska, College of Public Health, Omaha, NE; [3]Department Paediatric Haematology/Oncology; Mayo Clinic, Rochester, MN; [4]Department of Pathology, University of Utah, Salt Lake City, UT; [5]Section of Paediatric Haematology-Oncology, University of Oklahoma Health Sciences Center, Oklahoma City, OK ; [6] Center for Human Genetics, University of Nebraska, Omaha, NE; [67] Center for Global Health, National Cancer Institute, National Institute of Health, Rockville, MD; [8]Division of Paediatric Haematology/Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; Departments of [9]Paediatrics, [12]Medicine, [13]Pathology, [14]Microbiology and Immunology and [15]Cell Biology and Anatomy, New York Medical College, Valhalla, NY, [10]Division of Paediatric Haematology/Oncology, University of Hawaii, Honolulu, HI; [11]Department of Paediatrics, Roswell Park Cancer Institute, Buffalo, NY.

Address Correspondence:

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Mitchell S. Cairo, MD

Chief, Division of Paediatric Haematology, Oncology, and Stem Cell Transplantation

Director, Cellular Tissue and Engineering Laboratory

Professor of Paediatrics, Medicine, Pathology, Microbiology and Immunology and Cell Biology and Anatomy

Associate Chairman, Department of Paediatrics

New York Medical College

40 Sunshine Cottage Road, Skyline #IN-D12

Valhalla, NY 10595

Email: Mitchell_cairo@nymc.edu

Phone: 914-594-2150

Fax: 914-594-2151

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Summary

Children and adolescents with Burkitt Lymphoma (BL) and combined central nervous system (CNS) and bone marrow involvement still have a poor prognosis with chemotherapy alone. We therefore investigated in children and adolescents with bone marrow (≥25% blasts) and/or CNS positive Burkitt lymphoma the chemoimmunotherapy combination of rituximab (375mg/m^2) and the standard chemotherapy arm of our previously reported French-American-British LMB 96 trial. Central pathological and cytogenetic characterization was also performed. There were 40 evaluable patients with Burkitt histology (25 with leukaemia and 15 with CNS disease ± leukaemia). The chemoimmunotherapy regimen was well tolerated. The incidence of grade III/IV mucositis during induction cycles with combined chemotherapy and rituximab was 31% and 26%, respectively. The 3 year event-free survival (EFS)/overall survival (OS) was 90% (95% CI, 76-96%) in the entire cohort and 93% (95% CI, 61-99%) in patients with CNS disease. **Based on the results of this trial, an international randomized study of FAB/LMB 96 chemotherapy ± rituximab for high risk patients is currently under investigation.**

Key words: children, adolescents, Burkitt Lymphoma, Burkitt Leukaemia, chemotherapy, Rituximab

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Introduction

Approximately 1 in 4 children and adolescents with de-novo mature and Burkitt lymphoma (BL) present with high-risk disease that is either mature B-cell leukaemia (bone marrow ≥ 25% blasts [BM]) and/or have central nervous system (CNS) involvement. Both the Berlin-Frankfurt-Münster (BFM) and French-American-British (FAB) international cooperative studies have unsuccessfully attempted to reduce the overall burden of chemotherapy in this high risk group of patients. In the FAB 96 study, a randomized attempt to reduce the dose of cytarabine during consolidation and eliminate three final cycles of maintenance was halted early due to inferior event-free survival (EFS) (Cairo, *et al* 2012, Cairo, *et al* 2007) while the BFM 95 study concluded that reducing the infusion duration of methotrexate from 24 to 4 hours led to significantly inferior EFS in high risk (R3/R4) patients.(Woessmann, *et al* 2005) Subsets of children with BL, such as those with poor response to initial reduction, complex karyotypes, and those with combined BM and CNS disease, have a significantly worse prognosis (Cairo, *et al* 2012, Cairo, *et al* 2007, Poirel, *et al* 2009) .

Rituximab has been shown to improve EFS and overall survival (OS) when added to cyclophosphamide, adriamycin (oncovin, prednisone-(CHOP) based therapy in adults with diffuse large B-cell lymphoma (DLBCL) and also when combined with more aggressive therapy in adults with mature B-cell (Burkitt) lymphoma (BL) (Barnes, *et al* 2011, Coiffier, *et al* 2002, Corazzelli, *et al* 2012, Dunleavy, *et al* 2013, Pfreundschuh, *et al* 2006, Thomas, *et al* 2006). Unfortunately, all of these studies of rituximab and chemotherapy in adults with BL had few or no patients with BM and/or CNS involvement. Meinhardt et al. reported the safety and efficacy of one pre-dose of rituximab prior to reduction therapy in children and adolescents with mature

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de novo BL, including 19 evaluable patients with BM and/or CNS disease (Meinhardt, *et al* 2010). We have previously reported the safety and efficacy of the combination of rituximab plus FAB/Lymphomes Malins B (LMB) 96 Group B chemotherapy in children with Stage III/IV DLBCL/BL (Goldman, *et al* 2013). However, to date there has been no prospective study investigating the combination of rituximab with FAB/LMB 96 Group C chemotherapy in children, adolescents or young adults with BL and CNS disease and/or BM involvement. Importantly, our previous study in children with BL and CNS disease only had a 75% 4 year EFS following standard systemic and intrathecal chemotherapy with FAB/LMB therapy (Cairo, *et al* 2007).

Patients and methods

General

The Children's Oncology Group (COG) ANHL01P1 investigated the addition of rituximab to the FAB 96 C1 systemic and intrathecal chemotherapy backbone (Cairo, *et al* 2007). The trial was open to all COG centers in the United States, Canada, Australia and New Zealand. The protocol was approved at each respective institutional review board. Staging classification utilised the St. Jude Staging for NHL (Murphy 1980). Parents or patients over 18 years of age signed an institutional review board-approved informed consent before study enrollment in accordance with the Declaration of Helsinki. Safety reports and interim analyses were reviewed every 6 months, then annually by the COG independent Data and Safety Monitoring Committee.

Eligibility and Evaluation

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Patients under 30 years of age with newly diagnosed de-novo mature B-cell lymphoma classified as by World Health Organization criteria were eligible (Swerdlow, *et al* 2008). CD20 positive immunohistochemistry was required for study eligibility. Group C risk was defined as patients with BM ≥25% blasts and/or CNS disease (Cairo, *et al* 2007). CNS disease was defined as any cerebral spinal fluid (CSF) blasts found on diagnostic lumbar puncture and/or isolated intracerebral mass, cranial nerve palsy, clinical spinal cord compression and parameningeal extension as we have previously described (Cairo, *et al* 2007). Carriers of hepatitis B were eligible but carefully monitored for reactivation, as we have previously described (Goldman, *et al* 2013).

Treatment

Systemic and Intrathecal Chemotherapy. The systemic and intrathecal chemotherapy backbone for group C patients was similar to that reported in the FAB/LMB 96 study for the C1 arm (Cairo, *et al* 2007). The previous study (FAB/LMB 96) initially employed a 48-hour infusion of doxorubicin during the two induction cycles and the study was amended midway for unacceptable rates of grade III/IV mucositis and the anthracycline infusion was reduced to a 6 hour infusion (Patte, *et al* 2007). The doxorubicin infusion was reduced to 30-60 minutes in the current COG ANHL01P1 group C trial. Non-alkaline hydration and one or more doses of rasburicase 0.2 mg/kg IV, generously supplied by Sanofi (Bridgewater, NJ), was administered to all patients at least 4 hours prior to initiating reduction therapy for prevention or treatment of tumour lysis syndrome. An initial reduction phase consisted of low-dose cyclophosphamide, Oncovin® (vincristine), and prednisone (COP). Induction courses consisted of COPADM1+2 (cyclophosphamide 1.5 gm/m^2/course 1 and 3 gm/m^2/course 2 - fractionated, Oncovin®,

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prednisone, doxorubicin, high dose methotrexate [HDMTX] [8 gm/m^2 in 4-hour infusion]), as we previously described (Cairo, *et al* 2007). Patients then received two identical consolidation courses, CYVE 1+2 (continuous infusion and high dose cytarabine and etoposide) (Fig 1). **CNS negative patients received 10 prophylactic intrathecal injections while CNS positive patients received 13 intrathecal injections and an additional course of high dose methotrexate between CYVE consolidation cycles.** A disease evaluation was performed after completion of consolidation cycles with any biopsy proven residual disease considered an event and patient removed from study. Patients without disease after consolidation received four maintenance courses as previously described (Fig 1) (Cairo, *et al* 2007). No patients received cranial irradiation, including those presenting with CNS disease.

Immunotherapy. All rituximab infusions were administered at the standard dose of 375 mg/m^2. Patients were pre-medicated with combination acetaminophen and diphenhydramine. Rituximab, generously supplied by Genentech (San Francisco, CA) through the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute, was diluted in normal saline at a concentration of 1 mg/ml. The monitoring and methods of administration of rituximab was identical to what we have previously described (Goldman, *et al* 2013). During induction cycles (COPADM), rituximab was administered 48 hours prior (day –2) and repeated on the day of chemotherapy administration (day 0). During consolidation cycles (CYVE), rituximab was administered just prior to chemotherapy administration (day 0). In the initial sub-pilot, the rituximab administration began with the second induction cycle (4 total doses) (Fig 1). **The reason for initiating rituximab in the second induction cycle in the small initial cohort was to avoid any potential overlapping toxicity with the other experimental agent in the study**

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(rasburicase in reduction). After the fourth sub-pilot patient was entered, the study was temporarily closed (~ 5 months) to accrual until all subpilot patients completed consolidation chemoimunotherapy and were evaluated for toxicity. In the larger pilot study, rituximab was given beginning in the first induction cycle (6 total doses) (Fig 1).

Pathology

Central pathology review consisted of review of morphology, immunophenotype and genetic data from the original diagnostic biopsy. In addition, CD20 expression of the tumour was confirmed by immunohistochemistry. Four micron sections underwent immunoperoxidase staining for CD20 (L-26 clone, DAKO Cytomation, Carpinteria, CA) by standard methods following heat induced epitope retrieval in citrate buffer (pH6.0) on an automated stainer (ES, Ventana Medical Systems, Tucson, AZ). All steps were performed at 40°C. A case was scored as positive if >80% of the tumour cells stained for CD20.

Cytogenetics and fluorescence in situ hybridization (FISH) analysis

Cytogenetic analysis was performed, as we have previously described, with nomenclature according to the International System for Human Chromosome Nomenclature ~~(2005)~~ (Shaffer and Tommerup 2005) (Poirel, *et al* 2009). Interphase FISH analysis for *MYC* rearrangement was performed on a portion of the specimen submitted for cytogenetic analysis. A dual-color *MYC/IGH* translocation probe designed to detect t(8;14)(q24.1;q32) or a dual-color *MYC* break-apart probe designed to detect rearrangements of the *MYC* gene region at 8q24.1 with various partner chromosomes was utilized according to the COG reference laboratories standard protocols. Slides were counterstained with 4,6-diamidino-2-phenylindole (DAPI) in Antifade

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solution and the nuclei were visualized and captured using a fluorescence microscope equipped with appropriate filters and imaging software.

Statistics

The objective of this study was to estimate the toxicity of and response rate to chemoimmunotherapy in Group C patients. Stevens-Johnson Syndrome (SJS), toxic epidermal necrosis (TEN) , the frequency of Grade ≥ 4 stomatitis (Grade ≥3 stomatitis for the pilot portion), delayed recovery beyond day +42 of the induction phase, and toxic deaths were considered events in the sub-pilot and pilot studies.

Statistical considerations for the sub-pilot study for Group C patients.

If a single toxic death occurred during the period from the second cycle of induction through the end of the second maintenance course among **the 4 sub-pilot patients**, the Study Committee would review the events and determine if the study would continue or if it would be modified or permanently stopped.

Statistical considerations for assessing toxicity in the pilot.

A 2-stage stopping rule was used to terminate this study if too many Group C patients experienced Grade ≥3 stomatitis during either cycle of COPADM + rituximab therapy (Induction). A rate greater than 70%, the observed rate in FAB LMB 96, was considered too high. The pilot study also monitored for the occurrence of SJS and toxic epidermal necrosis with any incidence of either during induction leading to temporary closure and review of the event. A 2-stage stopping rule was used to close the study for toxic deaths (> 1.2%) from after the

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reduction phase until completion of second maintenance course of therapy. If any stopping rule was triggered, it was to be followed by a review by the Study Committee and COG Data and Safety Monitoring Committee.

EFS was defined as the time from enrollment to the first occurrence of disease progression, relapse after response or death from any cause. OS was defined as the time from enrollment to death from any cause. Time to event for patients not experiencing an event was censored at their time of last follow-up. Estimates of the EFS and OS distributions were calculated using the Kaplan and Meier method. Ninety-five percent confidence intervals (CI95) for the Kaplan-Meier estimates of EFS and OS were calculated using standard errors according to Greenwood (Greenwood 1926).

Results

Patient demographics

Four sub-pilot and forty-two pilot patients were enrolled, however, four pilot patients were determined to be ineligible (all prior to receiving rituximab) for the following reasons: chemotherapy started prior to enrollment (2 patients) and major informed consent deficiencies (2 patients). In addition, 2 initially eligible patients were excluded for incorrect staging in one patient and parental withdrawal of consent prior to study therapy. Thus, 36 pilot and 4 sub-pilot patients were included in the final analysis making a total of 40 patients that were evaluated for the planned endpoints. The results of the pharmacokinetics of rituximab and the incidence and grade of tumour lysis syndrome (TLS) have been previously been reported in this patient population, respectively (Barth, *et al* 2013, Galardy, *et al* 2013b).

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The mean age at study entry was 11 years (range 3-23). Eighty percent of patients were between 4 and 15 years. The male to female ratio was 4:1. Sixty-three percent of patients had isolated BM involvement (≥25% blasts); **18% (7/40) had CNS disease with BL (< 25% BM blasts)** and 20% (8/40) had combined CNS and BM disease. Seventy-eight percent of patients had elevated lactate dehydrogenase ≥2 X upper institutional limit of normal at diagnosis (Table 1).

Safety

There were two toxic deaths among the 40 evaluable patients. The first death occurred in a teenager whom had been ill for several weeks prior to arrival at the COG center for therapy of Burkitt leukaemia. This patient died of pre-existing pulmonary aspergillosis soon after reduction therapy. The second death on study was secondary to grade V typhlitis and infection and occurred in a patient during the second induction cycle. The institutional investigator graded the typhlitis as probably related to rituximab. **Although the study required leucovorin rescue and alkaline hydration until the serum methotrexate level was less than 0.1 micromol/L, the patient was discharged from the hospital with a methotrexate level of 0.12 micromol/L. This second toxic death triggered a prespecified study suspension. Enhanced methotrexate guidelines as well added recommendations for aneorbic treatment of suspected typhlitis and mandatory notification of study chair of infectious complications were amended to the study. After a ten month suspension, the study was reopened after approval of the data safety monitoring board without any subsequent toxic deaths.**

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Table 2 details the most common recurrent non-haematological grade III/IV toxicities by cycle of therapy with combined chemotherapy and rituximab. There were 54 reports in 13 patients (33%) of serious adverse events (SAE). Of these, only 1 SAE of grade 3 infusion reaction was definitely attributed to rituximab (total of 227 rituximab infusions). Of the remaining 53 SAE only 1 had a probable attribution to rituximab which was grade V typhlitis in the previously mentioned patient. The specified stopping rules for mucositis/stomatitis and SJS/TEN were not met during the conduct of the study. **The focus on SJS/TEN was based on rare but highly morbid incidence reported in adult lymphoma and concern about combining with other skin and mucus membrane toxic agents such as high dose methotrexate (Foran*, et al* 2000).** The incidence of grade III/IV mucositis during induction cycles with combined chemotherapy and rituximab was 31% and 26% in COPADM1 and COPADM2, respectively.

Haematopathology

Adequate tissue for centrally reviewed histology was available in 73% (29/40) of patients enrolled. All of the patients had classical BL (World Health Organization) or Burkitt leukaemia (as defined by >25% BM involvement) (Swerdlow, *et al* 2008). The remaining 11 cases had classical BL by report of the local pathologist. CD20 was strongly and uniformly expressed on all centrally reviewed cases.

FISH analysis

Conventional cytogenetic studies were attempted on 36 cases, and resulted in abnormal findings in 26 (72%). Normal karyotypes were observed in 2 cases (5.5%), and 8 cases (22%) failed to yield metaphase cells for analysis. Cytogenetically, 25/26 (96%) abnormal karyotypes exhibited

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a *MYC* rearrangement. The various *MYC* rearrangements detected included, a t(2;8)(p11.2;q24.1) in 1/25 cases (4%), a t(8;22)(q24.1;q11.2) in 3/25 cases (12%) and t(8;14)(q24.1;q32) in 21/25 cases (84%). Secondary cytogenetic abnormalities were observed in 58% of the cases, of which the most frequent was gain of 1q (8/26, 31%). Other recurrent secondary changes included, loss of 13q (5/26, 19%), loss of 6q (5/26, 19%), gain of 7q (4/26, 15%) and loss of 17p (3/26, 12%). All ten cases that had a normal karotype or failed in culture were positive for *MYC* rearrangement by FISH.

EFS and OS in total cohort of patients

The outcome of the COP reduction therapy with rasburicase prophylaxis and treatment of tumour lysis syndrome has been previously reported (Galardy, *et al* 2013a). All evaluable patients were able to receive chemoimmunotherapy after reduction and control of tumour lysis. Of the 40 evaluable patients there were 4 deaths, two toxic and two due to recurrent disease at 6 months and 8 months post study enrollment, respectively. Both patients who developed recurrent disease initially achieved complete responses to chemoimmunotherapy. The median follow-up for the 36 surviving patients was 3.6 years, range (1-6). The 3-year EFS/OS for all evaluable patients was 90% (CI95: 76-96%) (Fig 2A).

EFS and OS in CNS positive patients

Details of CNS positive patients' presentations are shown in Tables 3A and 3B. Among CNS positive BL patients (n=15) the 3-year EFS is 93% (CI95: 61-99%) (Fig 2B). Eight CNS positive BL cases had CSF blasts [WBC median 35 (range 1-1104)]. Of the 7 CNS positive patients without BM disease, 100% had no evidence of disease (mean of 50 months [range 22-66]). In the

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8 CNS^+ Burkitt leukaemia cases, 7 (88%) had no evidence of disease with a mean of 41 months (range, 14-72 months). One CSF positive patient with initial cranial nerve palsy and BM involvement recurred with both systemic and CNS disease.

Discussion

This study demonstrates for the first time that rituximab can be combined safely with FAB C1 systemic and intrathecal chemotherapy. There were, however, two toxic deaths on study. The first patient's death due to pulmonary aspergillosis and multi-organ failure was most likely related to pre-existing aspergillosis. The second death which occurred during the recovery phase after the second induction cycle was due to severe mucositis/typhlitis and sepsis and considered possibly related to rituximab therapy. Although rituximab may have contributed to additional mucosal breakdown and resultant sepsis, the patient did not receive the required leucovorin rescue following HDMTX (8 gm/m^2) clearance. The 2 of 40 toxic deaths (5%) is nearly identical to the rates reported in the same population of patients treated with FAB96 C1 without rituximab (Cairo, *et al* 2007, Woessmann, *et al* 2005). **In the previous FAB/LMB 96 group C trial, there were 11 protocol deaths not directly related to disease progression (5 infectious, 3 hemorrhage, 1 thrombosis and 2 other).** The incidence of grade III/IV mucositis in the previous FAB 96 high-risk study was 68% and 52% during the two induction cycles, respectively. That latter study utilized a doxorubicin infusion time of 6- 48 hours (Cairo, *et al* 2007). For this reason, we empirically reduced the doxorubicin infusion to 30-60 minutes in the current study and with the incorporation of rituximab and carefully monitored for excess rates of grade III/IV mucositis. The decrease in anthracycline infusion time appeared to have a dramatic

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effect on the incidence of grade III/IV mucositis with an almost 50% reduction in the current trial despite the addition of targeted immunotherapy.

The 3 year EFS of 93% in CNS positive patients (without cranial radiation) is encouraging and at least as efficacious as previous reports in pediatric CNS positive mature B cell leukemia/lymphoma. This pilot was not powered to compare outcomes to the previous FAB 96 trial (Cairo, *et al* 2012, Cairo, *et al* 2007, Corazzelli, *et al* 2012, Meinhardt, *et al* 2010, Thomas, *et al* 2006, Woessmann, *et al* 2005). **Among CNS positive patients who relapsed on the previous FAB 96 trial, 44% had isolated systemic recurrence and 11% combined CNS and systemic disease at relapse. The remaining 45% had recurrent disease in the CNS only (Cairo et al 2007).** Rituximab has poor (~ 0.1%) CNS penetration when given intravenously, but may have reduced the incidence of systemic relapse (Cairo, *et al* 2007, Rubenstein, *et al* 2003). Our results in CNS positive Burkitt patients compares favorably to the results of combined aggressive chemotherapy and rituximab in adults published by multiple adult groups. Three recent reports of combination aggressive chemotherapy (including infusional high dose methotrexate and intrathecal therapy) with the addition of rituximab reported improved efficacy of therapy with the addition of rituximab compared to past historical series in adult BL and Burkitt leukaemia. This included the MD Anderson hyper-CVAD regimen, a regimen of CODOX-M/ IVAC, and a German short intensive chemotherapy regimen (Barnes, *et al* 2011, Intermesoli, *et al* 2013, Pfreundschuh, *et al* 2006). Rituximab led to an improved event free survival in these three adult series for the entire patient cohorts. However, the outcomes for CNS positive adult patients with BL (n= 24; all three series combined) were poor with 3 year EFS in the three reports of 50%, 50% and 40%, respectively (Barnes, *et al* 2011, Intermesoli, *et al* 2013,

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Pfreundschuh, *et al* 2006). A recent uncontrolled prospective series of low-intensity EPOCH-R, which does not include any infusional HDMTX, reported excellent efficacy in BL but of note only one patient with CNS disease was included in this report (Dunleavy, *et al* 2013). Other potential CNS-directed therapy such as longer acting intrathecal therapy (e.g. liposomal ara-c) or direct administration of immune therapy into the CNS may need to be studied to improve CNS outcomes in adults with BL (Corazzelli, *et al* 2012, Rubenstein, *et al* 2003).

In summary, we have demonstrated that rituximab can be safely added to the modified group FAB group C1 chemotherapy backbone in children and adolescents with advanced de-novo mature B-cell BL/Burkitt leukaemia. The 3-year EFS/OS of 90% is encouraging given the patient population including ultra-high risk subgroups, such as patients with combined BM and CNS disease and complex cytogenetics. **Based on the results of this trial, an international randomized study of FAB/LMB 96 chemotherapy ± rituximab for high risk patients is currently under investigation.**

Authorship and Disclosures.

SG designed and performed the research, analyzed the results and wrote the paper; LS and JRA analyzed the data and wrote the paper; SLP analyzed the data and critically reviewed the paper; PG analyzed the data and critically reviewed the paper; JKF analyzed the data and critically reviewed the paper; BS analyzed the data and critically reviewed the paper; TGG analyzed the data and critically reviewed the paper; WS analyzed the data and critically reviewed the paper; HW analyzed the data and critically reviewed the paper; LH performed the research, analyzed

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the data and wrote the paper; MB analyzed the data and critically reviewed the paper; and MSC designed and performed the research, analyzed the results and wrote the paper. T. G. is on the Scientific Advisory Boards for Genentech/Roche & Boehringer Ingelheim Pharma GmbH & Co. M.S.C. is a consultant and on the Speakers Bureau for Sanofi and on a Scientific Advisory Board for Genentech/Roche.

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Figure Legends

Figure 1. Treatment Schema. Sub-pilot and Pilot Group C patients were treated with identical FAB/LMB96 C1 systemic and intrathecal chemotherapy backbones (Patte, *et al* 2007). Sub-pilot schema: Rituximab 375 mg/m^2/dose was administered on day -2 and day 0 of 2nd Induction cycle and day 0 of both consolidation cycles (4 total doses). Pilot schema: Rituximab 375 mg/m^2/dose was administered on day -2 and day 0 of both induction cycles and day 0 of both consolidation cycles (6 total doses) No rituximab was administered during maintenance.

Figure 2. (A) EFS and OS in all patients. Probability of EFS and OS in children and adolescents with BM and/or CNS disease with de-novo mature B-NHL treated with Rituximab and FAB Group C1 Chemotherapy Pilot on COG-ANHL01P1 as determined by Kaplan-Meier method. **(B) EFS in CNS positive and CNS negative patients.** Probability of EFS in children and adolescents with BM and/or CNS positive and negative disease with advanced de-novo mature B-NHL treated with Rituximab and FAB Group C1 chemotherapy stratified by CNS+ vs. CNS- on COG-ANHL01P1 as determined by Kaplan-Meier method.

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Figure 1.

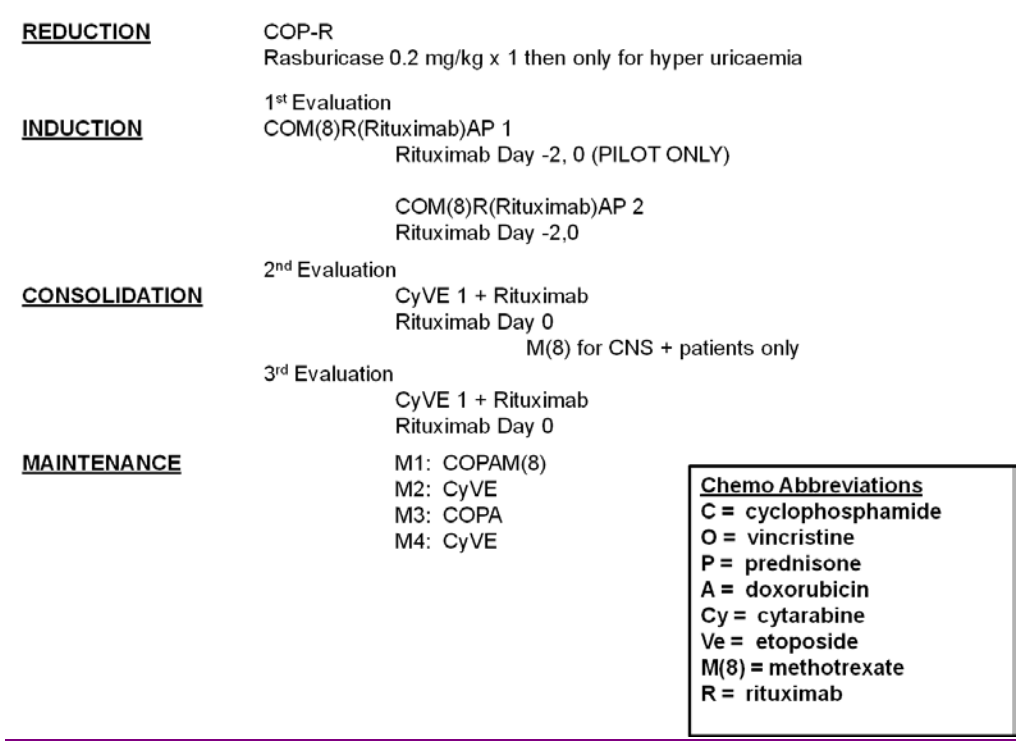

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Figure 2A.

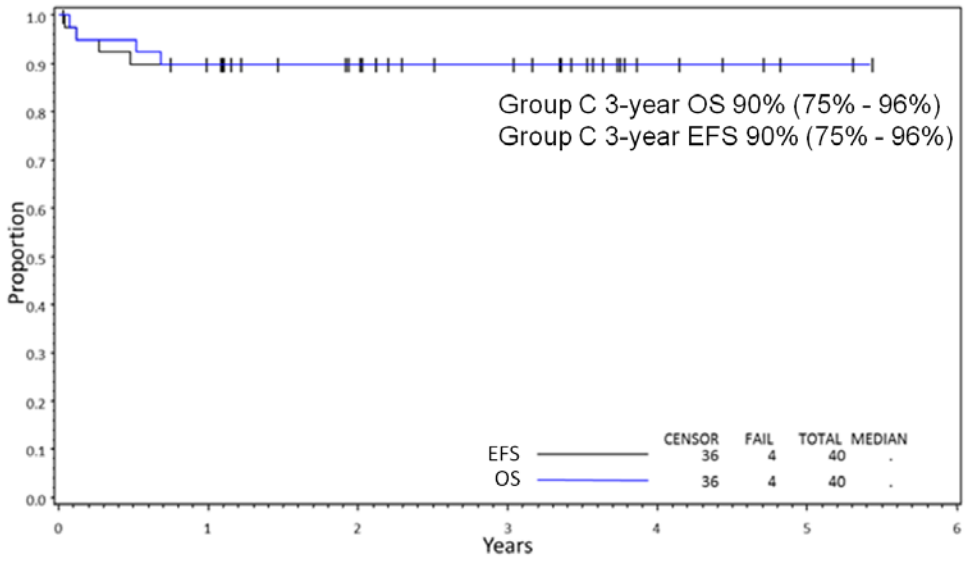

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Figure 2B.

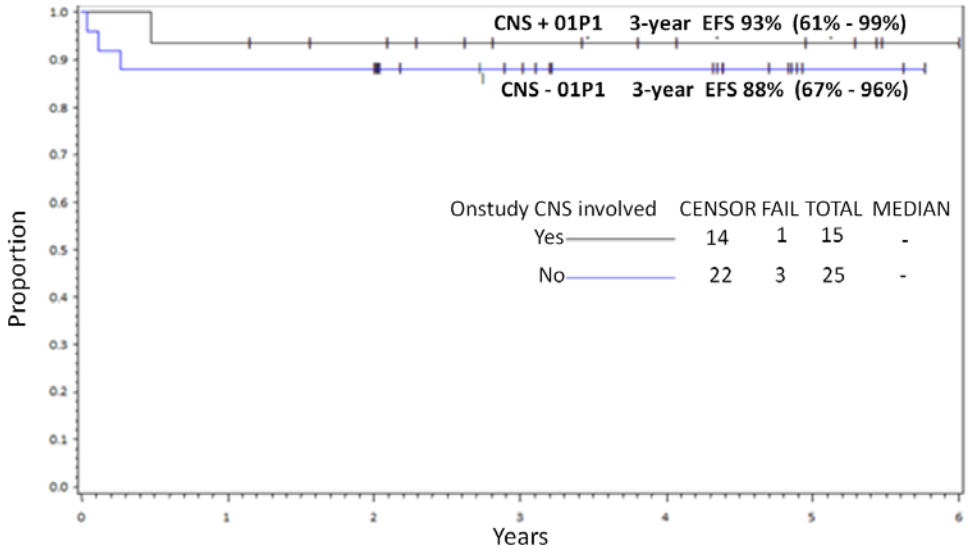

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Table 1: Patient Demographics of Evaluable Patients

		Total N (%)
N		40
Gender	Male	32 (80%)
Age, years	Mean±SD years	11±5.5
Pathological diagnosis	Burkitt	40 (100%)
Sites of Disease	BM+/CNS-	25 (62.5%)
	BM+/CNS+	8 (20%)
	BM-/CNS+	7 (17.5%)
LDH	≥ 2 times Upper Limit of Normal	31 (77.5%)

BM +: Bone marrow with > 25 % blasts by morphology
CNS+: Central nervous system involvement (See text for details);
COG, Children's Oncology Group

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