CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Group Chair
Peter C. Adamson, M.D.
adamson@email.chop.edu

Group Statistician
Todd Alonzo, Ph.D.
talonzo@childrensoncologygroup.org

Group Vice Chair
Susan Blaney, M.D.
smblaney@txch.org

Chief Operating Officer
Elizabeth O'Connor, M.P.H.
econnor@childrensoncologygroup.org

Executive Director of Administration
Deborah L. Crabtree, M.S.
crabtreed@email.chop.edu

Group Chair's Office
The Children's Hospital of Philadelphia
3501 Civic Center Blvd
CTRB 10060
Philadelphia, PA 19104

P 215 590 6359
F 215 590 7544

Group Operations Center
222 E. Huntington Drive
Suite 100
Monrovia, CA 91016

P 626 447 0064
F 626 445 4334

Statistics & Data Center Headquarters
222 E. Huntington Drive
Suite 100
Monrovia, CA 91016

P 626 447 0064
F 626 445 4334

Gainesville Office
6011 NW 1st Place
Gainesville, FL 32607

P 352 273 0556
F 352 392 8162

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February 1, 2019

Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

Enclosed please find Amendment #9 to protocol ANHL12P1, *A Randomized Phase 2 Trial of Brentuximab Vedotin (SGN35, NSC# 749710), or Crizotinib (NSC#749005, commercially labeled) in Combination with Chemotherapy for Newly Diagnosed Patients with Anaplastic Large Cell Lymphoma (ALCL)* for CTEP review.

This amendment is being submitted in response to a Request for Rapid Amendment (RRA) from Dr. John J. Wright (wrighttj@ctep.nci.nih.gov), dated January 22, 2019. In this amendment, the revised CAEPR for Crizotinib (Version 2.3, October 30, 2018) has been inserted in the protocol, and the associated risk information in the informed consent document has been revised accordingly.

In addition, changes have been made in response to a RRA for SGN-35 (brentuximab vedotin) from Dr. Elad Sharon (sharone@mail.nih.gov), dated June 13, 2018. A notation has been made in the protocol to indicate that the SGN-35 arm is closed to accrual and treatment and that the CAEPR will not be updated further. The associated risk information in the informed consent document has been revised accordingly.

Revisions to the protocol and consent document are detailed in the pages below.

Please let me know if we can offer further information.

Sincerely,

Jeannette Cassar, Protocol Coordinator (for)
Eric Lowe, MD, ANHL12P1 Study Chair
Peter Adamson, MD, COG Group Chair

CHILDREN'S ONCOLOGY GROUP

SUMMARY OF CHANGES: PROTOCOL

In accordance with the above discussion, the following specific revisions have been made to the protocol.

#	Section	Page(s)	Change
1.	General	-	Updated protocol version date in the footer.
2.	Title Page	1	Update version date and amendment number
3.	6.1.10	56	Added the following notation: "The arm using SGN-35 (brentuximab vedotin, NSC 749710) is closed to accrual and treatment. The CAEPR is no longer being updated."
4.	6.2	60	• Updated the monograph date. • Removed "commercially labeled" and added the IND number.
5.	6.2.8	61-64	Updated the toxicity section with the new CAEPR and toxicity information.

SUMMARY OF CHANGES: INFORMED CONSENT

In accordance with the above discussion, the following specific revisions have been made to the consent.

#	Section	Page(s)	Change
1.	General	All	Updated version date of consent to match the current version of the protocol.
2.	Possible Side Effects of SGN-35	9	Updated the possible side effects of SGN-35 to match the NCI provided template.
3.	Possible Side Effects of Crizotinib	10-11	Updated the possible side effects of Crizotinib to match the NCI provided template.

Activated: 11/08/13
Closed:

Version Date: 02/01/2019
Amendment: 9

CHILDREN'S ONCOLOGY GROUP

ANHL12P1

A Randomized Phase 2 Trial of Brentuximab Vedotin (SGN35, NSC# 749710), or Crizotinib (NSC#749005, commercially labeled) in Combination with Chemotherapy for Newly Diagnosed Patients with Anaplastic Large Cell Lymphoma (ALCL)

A COG Groupwide Phase II Study (Limited to US sites)

NCI Supplied Agents :
Brentuximab Vedotin (SGN35, NSC# 749710)
Crizotinib (NSC#749005)

STUDY CHAIR
Eric J. Lowe, M.D.
Children's Cancer and Blood Disorder Center
Children's Hospital of the King's Daughters
601 Children's Lane
Norfolk, VA 23507
Phone: (757) 668-9772
Fax: (757) 668-6171
E-mail: eric.lowe@chkd.org

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STUDY COMMITTEE

STUDY CHAIR
Eric Jeffrey Lowe, MD
Children's Hospital-King's Daughters
Pediatric Hematology/Oncology
601 Children's Lane
Norfolk, Virginia 23507
Phone: (757) 668-7243
Fax: (757) 668-7811
E-mail: eric.lowe@chkd.org

STUDY CO-VICE CHAIR
John T. Sandlund, MD
Oncology
Saint Jude Children's Research Hospital
262 Danny Thomas Place, MS 260
Memphis, TN 38105-3678
Phone: (901) 595-2427
Fax: (901) 521-9005
E-mail: john.sandlund@stjude.org

STUDY CO-VICE CHAIR
Anne Fitzpatrick Reilly, MD
Hematology/Oncology
Children's Hospital of Philadelphia
Division of Oncology
34th & Civic Center Blvd
Philadelphia PA 19104
Phone: (215) 590-0936
Fax: (215) 590-4183
E-mail: reillya@email.chop.edu

STUDY COMMITTEE MEMBERS
Robert E. Hutchison, MD
SUNY Upstate Medical University
Pathology
750 East Adams Street
Syracuse, NY 13210
Phone: (315) 464-6771
Fax: (315) 464-7322
E-mail: hutchisb@upstate.edu

Thomas Gene Gross, MD, PhD
National Cancer Institute
NCI-Center of Global Health
9609 Medical Center Drive, 3W534
Rockville, MD 20850
Phone: (240) 276-6984
Fax: (240) 276-5820
E-mail: Thomas.Gross@nih.gov

STUDY COMMITTEE MEMBERS
Debbie A. Woods, MSN, CPNP
Nursing
University of California Davis Comprehensive Cancer Center
Pediatric Hematology/Oncology
2279 45th Street
Sacramento, CA 95817
Phone: (916) 734-4899
Fax: (916) 734-0980
E-mail: dwoods@ucdavis.edu

JoEllen Louise Weilnau, PharmD
Pharmacy
Children's Hospital Medical Center of Akron
One Perkins Square
Akron, OH 44308
Phone: (330) 543-4601
Fax: (330) 543-4436
E-mail: jweilnau@akronchildrens.org

Megan So-Young Lim, MD, PhD
Pathology
Children's Hospital of Philadelphia
Department of Pathology and Laboratory Medicine
422 Curie Blvd.
Room 609 Stellar-Chance
Philadelphia, PA 19104
Phone: (215) 898-2925
Fax: (215) 662-7529
E-mail: megan.lim@uphs.upenn.edu

Rebecca Alice Emmons Gardner, MD
Hematology/Oncology
Seattle Children's Hospital
Hematology/Oncology
M/S MB.8.501, PO Box 5371
Seattle, WA 98145
Phone: (206) 667-1317
Fax: (206) 987-3946
E-mail: rebecca.emmons@seattlechildrens.org

STUDY STATISTICIAN
Donald A. Barkauskas, PhD
Children's Oncology Group
Group Operations Center
222 E. Huntington Drive, Suite 100
Monrovia, CA 91016
Phone: (626) 241-1540
Fax: (626) 445-4334
E-mail: dbarkauskas@childrensoncologygroup.org

STUDY COMMITTEE MEMBERS
Kala Kamdar, MD
Hematology/Oncology
Baylor College of Medicine
Pediatrics
6621 Fannin Street, CC1410.00
Houston, Texas 77030
Phone: (832) 824-4163
Email: kykamdar@txch.org

Lisa Giulino Roth, MD
Hematology/Oncology
Weill Medical College of Cornell University
Pediatrics
1300 York Ave. C406
New York, NY 10065
Phone: (212) 746-6948
Email: giulinol@mskcc.org

Sabrina Whitley Wigginton, BSN, RN, CPON
Clinical Research Associates
Children's Hospital-King's Daughters
Hematology/Oncology
601 Children's Lane
Norfolk, VA 23507
Phone: (757) 668-7909
Fax: (757) 668-9782
E-mail: Sabrina.Wigginton@chkd.org

Catherine Mary Bollard, MD
Cellular Therapy
Children's National Medical Center
Center for Cancer and Blood Disorders
111 Michigan Avenue NW
5th Floor Main, Suite 5200, Room 5207
Washington, DC 20010
Phone: (202) 476-4776
Fax: (202) 476-5685
Email: cbollard@childrensnational.org

Rodney R. Miles, MD PhD
Pathology
Primary Children's Hospital
Department of Pathology
15 N. Medical Drive East, JMRB 2100
Salt Lake City, UT 84112-0565
Phone: (801) 584-5240
Fax: (801) 584-5124
Email: rodney.miles@path.utah.edu

COG RESEARCH COORDINATOR
Gisele B. Galit, MD
Children's Oncology Group
Group Operations Center
222 E. Huntington Drive. Suite 100
Monrovia, CA 91016
Phone: (626) 241-1570
Fax: (626) 445-4334
E-mail: ggalit@childrensoncologygroup.org

COG PROTOCOL COORDINATOR
Jeannette Cassar
Children's Oncology Group
Group Operations Center
222 E. Huntington Drive, Suite 100
Monrovia, CA 91016
Phone: (626) 241-1532
Fax: (626) 445-4334
E-mail: jcassar@childrensoncologygroup.org

Brentuximab Vedotin	NSC#749710	
Crizotinib (Xalkori)	NSC#749005	/Exempt
Cyclophosphamide (Cytoxan)	NSC# 26271	/Exempt
Cytarabine	NSC# 63878	/Exempt
Dexamethasone (Decadron)	NSC# 34521	/Exempt
Doxorubicin (Adriamycin)	NSC# 123127	/Exempt
Etoposide	NSC# 141540	/Exempt
Filgrastrim (GCSF)	NSC# 614629	/Exempt
Hydrocortisone	NSC# 010483	/Exempt
Ifosfamide	NSC# 109724	/Exempt
Leucovorin	NSC# 003590	/Exempt
Mesna	NSC# 113891	/Exempt
Methotrexate	NSC# 000740	/Exempt
Pegfligrastim	NSC# 725961	/Exempt

IND SPONSORS: NCI

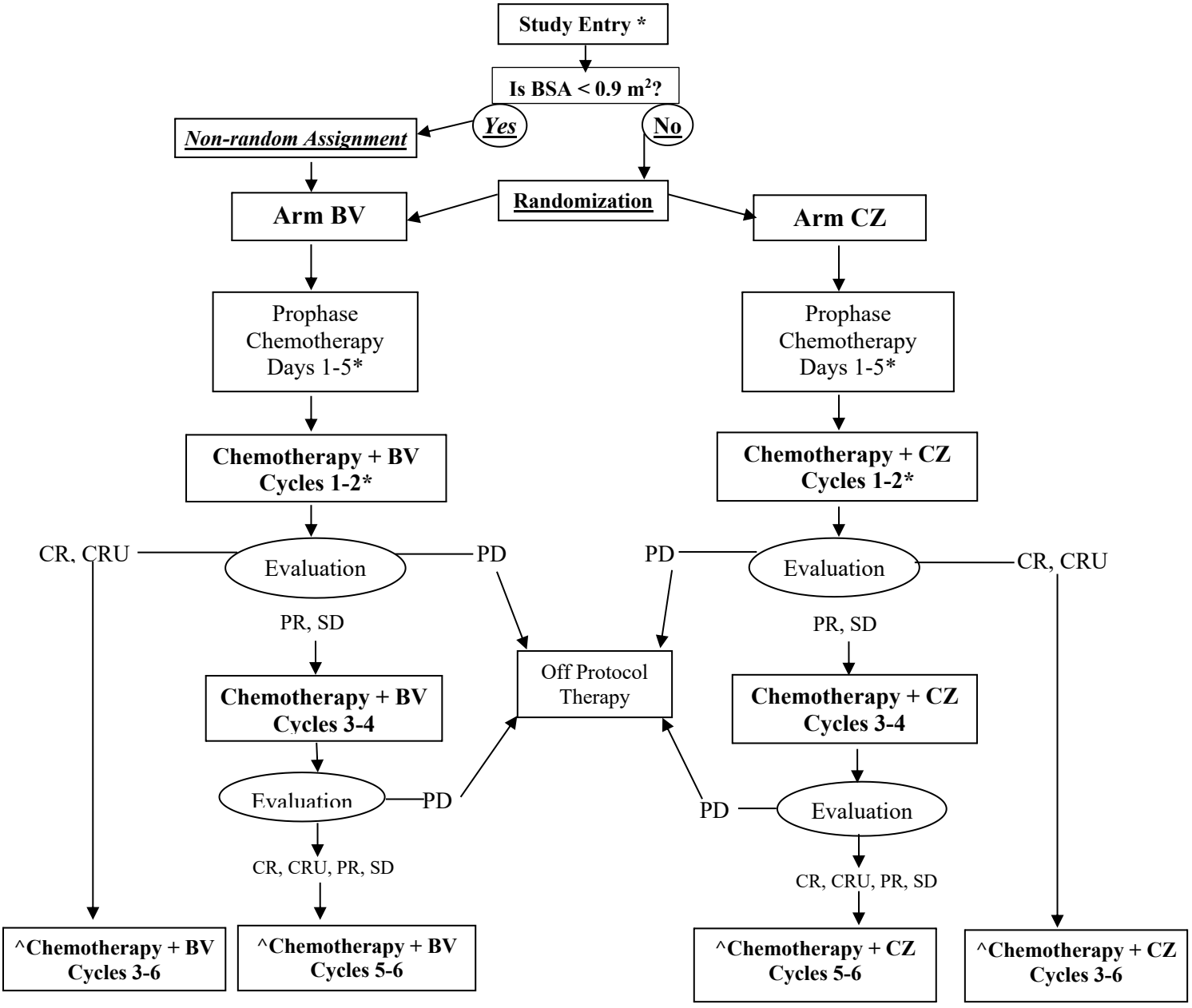
SEE SECTION 13 FOR SPECIMEN SHIPPING ADDRESSES

ABSTRACT

Despite numerous treatment strategies over the last 20 years failure rates remain 25-30% for pediatric anaplastic large cell lymphoma (ALCL). Two novel agents that have demonstrated high response rates as single agents in ALCL will be studied in this trial. Brentuximab vedotin (previously known as SGN35; currently marketed under the brand name Adcetris) is an antibody-drug conjugate containing an anti-CD30 monoclonal antibody linked to a tubulin inhibitor (monomethylauristatin E). After binding CD30, a transmembrane receptor expressed on all ALCLs, brentuximab vedotin is internalized and the drug is released into the cytoplasm where it causes cell cycle arrest and apoptosis. Tubulin inhibitors are active agents in ALCL as evidenced by responses using vincristine and vinblastine. The response rate of brentuximab vedotin in patients with relapsed/refractory ALCL is impressive and the FDA has approved brentuximab vedotin for the treatment of patients with ALCL that have failed one line of therapy. Crizotinib is an orally bioavailable small molecule inhibitor of receptor tyrosine kinases including anaplastic large cell lymphoma kinase (ALK). ALK plays a central role in the pathogenesis of ALCL due to a chromosomal translocation that results in expression of an oncogenic kinase fusion protein. Crizotinib inhibits ALK phosphorylation resulting in antitumor activity. Crizotinib has also shown impressive response rates in patients with refractory/relapsed ALK positive ALCL.

The primary aim of this pilot phase II study is to determine the toxicity and efficacy of the addition of two novel agents (brentuximab vedotin or crizotinib) to standard chemotherapy (best arm of ALCL99) in children with newly diagnosed ALCL. In this protocol, patients with newly diagnosed ALCL will be randomized to receive standard chemotherapy plus brentuximab vedotin (Arm BV) or standard chemotherapy plus crizotinib (Arm CZ). All patients will initially receive a 5 day prophase followed by 6 cycles of chemotherapy. The novel agent (either brentuximab vedotin or crizotinib) will start with Cycle 1 and be given in all 6 cycles. Each cycle lasts 21 days with the total therapy lasting approximately 19 weeks. Each arm will be evaluated for toxicity. Each arm will independently be evaluated for differences in EFS compared to historical data for ALCL99. A secondary aim of the trial will be to determine if minimal disease at diagnosis and/or minimal residual disease during treatment can identify patients at high risk of recurrence. Minimal disseminated disease (MDD) and minimal residual disease (MRD) will be measured using peripheral blood at 3 separate time points (diagnosis, after prophase, and after Cycle 1). The results from this pilot phase II study will provide necessary information to incorporate these novel agents into future trials and potentially improve the treatment of children with ALCL.

EXPERIMENTAL DESIGN SCHEMA



^Arm BV = Chemotherapy (6 cycles) + Brentuximab Vedotin Day 1 of each cycle
^Arm CZ = Chemotherapy (6 cycles) + Crizotinib Days 1-21 of each cycle
CR=Complete response/ CRU= Complete Response Unconfirmed /PR= Partial Response/ SD=Stable Disease/ PD=Progressive Disease. See Section 10.3
Cycles 1, 3, 5 = **Course A** / Cycles 2, 4, 6 = **Course B**

Prophase
Cyclophosphamide Days 1-2
Dexamethasone Days 1-5
ITT: Day 1

Course A (Cycles 1, 3, 5)
Dexamethasone Days 1-5
Ifosfamide Days 1-5
Methotrexate Day 1
Etoposide Days 4-5
Cytarabine Days 4-5

Course B (Cycles 2, 4, 6)
Dexamethasone Days 1-5
Methotrexate Day 1
Cyclophosphamide Days 1-5
Doxorubicin Days 4-5

***MDD/MRD**
Collected at 3 time points:
1) Baseline (prior to therapy)
2) Day 6 (end of prophase and before Cycle #1)
3) End of Cycle #1

1.0 GOALS AND OBEJCTIVES

1.1 Primary Aims

1.1.1 Tolerability

To determine the tolerability of brentuximab vedotin given in combination with standard chemotherapy (ALCL99) and to determine the tolerability of crizotinib given in combination with chemotherapy (ALCL99).

1.1.2 Event Free Survival

To estimate the Event Free Survival (EFS) of Arm BV and Arm CZ and contrast these to historical control data.

1.2 Secondary Aim

1.2.1 MDD/MRD

To determine the prognostic significance of minimal disseminated disease (MDD) at diagnosis and minimal residual disease (MRD) as measured by RT- polymerase chain reaction (PCR) in peripheral blood.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Anaplastic large cell lymphoma (ALCL) is a distinct form of non-Hodgkin lymphoma (NHL) which accounts for 10-15% of all childhood lymphomas.[1,2] First described in 1985 by Stein et al.,[3] ALCL is a T or null cell lymphoma characterized by the malignant cell expression of CD30 (Ki-1). Despite numerous treatment strategies, EFS remains around 70%.[2,4-10]

Protocol	Stratification	Number	Duration (months)	EFS
HM 89 / 91	None	82	8	66%
NHL-BFM 90	Disease Stage	89	5	76%
ALCL 99	Clinical Features	352	5	73%
UKCCSG	Disease Stage	72	7-8	59%
POG 9315	None	86	12	72%
CCG 5941	None	86	12	68%
LSA2-L2 modified	None	34	24	65%

ANHL0131 tested the substitution of vinblastine for vincristine in children with ALCL when given with APO (Doxorubicin, Prednisone, and Vincristine) chemotherapy (52 weeks of therapy). Results showed similar EFS to other studies and no benefit to the patients receiving the additional vinblastine (3 yr EFS of 75% for APO vs. 80% for APV, p = 0.73). The international ALCL99 trial used chemotherapy based on BFM-NHL-90 (duration of 4 months). The first randomization compared methotrexate 1 g/m^2 administered over 24 hours with intrathecal chemotherapy throughout therapy versus methotrexate 3 g/m^2 administered over 3 hours with intrathecal chemotherapy only in prophase of therapy. Overall, 352 patients were randomized. While the 2 year EFS (73% versus 75%) did not differ between the 2 arms, the toxicity from the methotrexate administered over 3 hours was significantly less and the 2 CNS relapses both occurred on the arm with 1 g/m^2 and intrathecal chemotherapy.[5] Therefore, it is now considered standard of care when using the ALCL99 regimen to use 3 g/m^2 of methotrexate over 3 hours and intrathecal chemotherapy only in the prophase. The second randomization was

for patients with clinically "high-risk features", i.e. involvement of skin, mediastinum, liver, lung and/or spleen. Patients were randomized to standard chemotherapy ± vinblastine weekly as maintenance for a total duration of 1 year of therapy. While vinblastine delayed relapses, there was no difference in the 2 year EFS (73% versus 70%) in the 217 randomized patients.[10] Thus, the ALCL99 trial demonstrated a failure rate of approximately 30%, all but initial intrathecal chemotherapy can safely be omitted when using 3 g/m^2 of methotrexate administered over 3 hours, and the addition of vinblastine maintenance did not improve EFS.

While studies have used a wide range of chemotherapy strategies, no intervention has been able to improve on the approximate failure rate of 25%-30% that exists regardless of treatment strategy. The addition of vinblastine, either with chemotherapy or as single agent in maintenance, failed to show any improvement in EFS in both the ANHL0131 and ALCL99 trials. CCG 5941 showed no advantage to intensifying multi-agent chemotherapy given over 11 months. Intensification with intermediate dose methotrexate and high dose cytarabine on an APO backbone did not improve outcome (POG 9315). Intensification with high dose cytarabine, etoposide and methotrexate did not improve outcome in high risk patients (NHL-BFM 95). The Italian group (AIEOP) was unable to demonstrate benefit of longer duration of therapy using a modified LSA2-L2 acute leukemia regimen (duration 2 years; 65% EFS).

In addition, progression while receiving chemotherapy portends a very poor prognosis in children with ALCL, with only 25% of patients who progress on therapy expected to survive even with aggressive salvage therapy, including allogeneic transplant.[11,12] Therefore, interventions that prevent relapse, especially on-therapy progression of disease, will have the greatest impact on overall survival and toxicity.

2.2 Brentuximab vedotin Background

The CD30 antigen is a transmembrane glycoprotein receptor that is expressed on all systemic ALCL in children.[13] Brentuximab vedotin is a CD30 targeted antibody (cAC10) conjugated to monomethyl auristatin E (MMAE). Brentuximab vedotin binds to CD30, becomes internalized, and then releases MMAE that causes apoptosis as an antitubulin agent.

Preclinical data demonstrated that MMAE binds to the same site on tubulin as vinblastine. Using mouse xenografts of a Hodgkin Lymphoma (HL), which also highly expresses CD30, cell line, Alley et al. were able to demonstrate that brentuximab vedotin had a peak tumor concentration 10-30 fold greater than MMAE or vinblastine delivered in a non-targeted fashion, or systemic administration.[14] In addition, over a three day period, the tumor exposure to the anti-tubulin agent after brentuximab vedotin was 5-10 fold higher than when given as a non-targeted agent.

There have been two phase I studies of brentuximab vedotin involving patients with relapsed HL or ALCL.[15-17] In the first phase I study, brentuximab vedotin was given every 3 weeks. Of the 45 patients enrolled, 33 (73%) had previously received a stem cell transplant. Despite this high amount of pretreatment, toxicity was tolerable. The most common toxicities were fatigue (40%), pyrexia (33%), peripheral neuropathy (31%), diarrhea (22%), nausea (22%), headache (20%), and vomiting (20%). The vast majority of these toxicities were Grade 1 or 2. In this study, the dose limiting toxicities were prostatitis, hyperglycemia, and unrelated acute renal failure. The dose recommended for future studies

was 1.8 mg/kg every 3 weeks. In addition, brentuximab vedotin was determined to be minimally immunogenic. Of the 45 patients treated, only 2 developed low levels of human anti-brentuximab vedotin antibody which showed no effect on clearance of the drug. The second phase I study gave brentuximab vedotin weekly with similar toxicities: fatigue (24%), peripheral neuropathy (18%), nausea (26%), neutropenia (18%), and hyperglycemia (12%). In these phase I trials, 6/7 patients with ALCL had a complete response and 1 had stable disease.

A phase II multicenter trial using brentuximab vedotin 1.8 mg/kg every 3 weeks for patients over 12 years of age with relapsed or refractory ALCL has recently been completed.[18,19] Brentuximab vedotin was administered over 30 minutes as an outpatient every 3 weeks. A total of 58 patients were enrolled with an overall response rate of 86% (53% CR, 33% PR) and 97% of patients demonstrated tumor reduction. There was no difference between those patients who had ALK positive versus ALK negative ALCL. The responses have been durable, with the median duration of CR for patients off treatment not having been reached. Adverse events were manageable with a toxicity profile similar to phase I study. The most common toxicities were nausea (38%), peripheral sensory neuropathy (38%), fatigue (34%), pyrexia (33%), diarrhea (29%), and neutropenia (21%). Grade 3 and 4 toxicities were rare (Grade 3/4: neutropenia 12%/9%, peripheral sensory neuropathy 10%/0%, thrombocytopenia 9%/5%, anemia 7%/0%). Because brentuximab vedotin is an anti-tubulin agent, toxicities involving neuropathy were closely monitored. Grade 1/2, 3, or 4 toxicity rates included peripheral sensory neuropathy (28%, 10%, and 0% respectively), paresthesias (5%, 0%, and 0%) and peripheral motor neuropathy (3%, 2%, and 0%). Most patients (79%) showed improvement or resolution of their symptoms over time. In addition, a phase II multicenter trial using brentuximab vedotin 1.8 mg/kg every 3 weeks for patients over 12 years of age with relapsed or refractory Hodgkin Lymphoma enrolled 102 patients and had a similar toxicity profile.

Brentuximab vedotin has recently been combined with chemotherapy for adults with newly diagnosed Hodgkin lymphoma.[20] Brentuximab vedotin was given in combination with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) to 25 patients and in combination with AVD (no bleomycin) to 19 patients. In the ABVD cohort, 10 of 25 patients developed pulmonary toxicity that prompted the change to AVD. Seven of the 10 patients who developed pulmonary toxicity went on to receive brentuximab vedotin and AVD without any further pulmonary toxicity. None of the patients in the AVD cohort have experienced pulmonary toxicity. Of note, there was minimal lung toxicity in the phase II single agent studies that included many patients who had lymphoma involvement of the lungs, suggesting that the pulmonary toxicity seen on this study was a result of the combination of brentuximab vedotin with bleomycin. Overall, 44 patients received brentuximab vedotin with chemotherapy and there were 0 DLTs observed concluding that a dose of 1.2 mg/kg every 2 weeks can be given with AVD. The most common Grade 3+ toxicities occurring in the 44 patients were neutropenia (77%), anemia (14%), fever and neutropenia (11%), pulmonary toxicity (11%), dypsnea (9%), and syncope (9%). Of note, although 52% of patients had Grade 1 or 2 peripheral neuropathy, no patient had Grade 3 or 4 neuropathy.

Brentuximab vedotin has also been given with CH-P (cyclophosphamide, doxorubicin, prednisone) chemotherapy to newly diagnosed patients with ALCL. Patients were given brentuximab vedotin at 1.8 mg/kg every 3 weeks with CH-P therapy. De-escalation was not required as none of the initial six patients enrolled on this arm experienced a Dose

Limiting Toxicities (DLTs) defined as greater than 7 day delay in chemotherapy administration. Of the 20 total patients who have received concurrent brentuximab and CH-P, the most common side effects have been rash (10%), fever neutropenia (20%), and nausea (25%). The authors conclude that the recommended dose for brentuximab with CH-P chemotherapy is 1.8 mg/kg [personal communication, T-cell Lymphoma Forum Jan. 2012].

In addition, brentuximab vedotin given in combination with gemcitabine (AHOD1221) is currently open to enrollment and will provide additional data as patients receive therapy.

2.3 Crizotinib Background

Pediatric ALCL is characterized by having the vast majority of cases express anaplastic large cell lymphoma kinase (ALK).[21] *ALK* is a gene found on chromosome 2 and translocations affecting the *ALK* gene can result in the expression of oncogenic fusion proteins. The ALK protein is a fusion protein produced by a genetic translocation most commonly t(2;5) involving the *ALK* gene on chromosome 2 and the nucleophosmine (NPM) gene on chromosome 5. The formation of ALK fusion proteins results in activation and dysregulation of the gene's expression and signaling which can contribute to increased cell proliferation and survival in tumors expressing these proteins. The ALK protein has been implicated in the pathogenesis of pediatric ALCL.[22]

Crizotinib is an inhibitor of receptor tyrosine kinases including ALK and Hepatocyte Growth Factor Receptor (HGFR, c-Met). Crizotinib inhibits ALK phosphorylation resulting in antitumor activity. Crizotinib was found to potently inhibit cell proliferation in ALK positive ALCL cells but not ALK negative cells.[23] Crizotinib has also been shown to have antitumor activity in mice expressing tumors with the ALK fusion protein.

Crizotinib has been evaluated in two single-arm adult clinical trials for the treatment of locally advanced or metastatic ALK-positive NSCLC.[24] Among the 397 patients for whom information on deaths and serious adverse reactions are available, the most common adverse reactions (≥ 25%) were vision disorder, nausea, diarrhea, vomiting, edema, and constipation. Grade 3-4 adverse reactions in at least 4% of patients in both studies included increased ALT and neutropenia. The rates of treatment-related adverse events resulting in permanent discontinuation were 6% in one study and 3% in the other. Serious adverse events in greater than or equal to 2% of patients included pneumonia, dyspnea, and pulmonary embolism.

Crizotinib is also effective in treating patients with relapsed ALCL. A report from the New England Journal of Medicine reported 2 adult patients with recurrent ALK positive ALCL who achieved CRs after receiving single agent crizotinib.[25] These authors updated their experience at the International Lymphoma Meeting in June 2011 reporting 2 additional patients with responses of CR and PR demonstrating clear activity in ALK positive ALCL.

ADVL0912 is an ongoing phase I1/II study of crizotinib in children with Relapsed/Refractory Solid Tumors, Primary CNS Tumors, and Anaplastic Large Cell Lymphoma. Seventy subjects have been enrolled on the pediatric phase 1 study of crizotinib including 8 with ALCL.[26] The toxicity profile overall has been good with DLT reached in 2/7 patients at 215 mg/m^2/dose BID and 1/6 at 365 mg/m^2/dose BID. A separate stratum of 18 patients with known ALK mutations were enrolled at 1 dose level lower than A1 stratum. One patient experienced a DLT of Grade 4 neutropenia. Eight patients with

ALCL have received crizotinib (6 at 165 mg/m^2/dose BID which is roughly equivalent to the dose used in the adult studies and 2 at 280 mg/m^2/dose BID). Of the 8 patients, there have been 7 CRs for a complete response rate of 88%. Many of these responses are ongoing as the patients are continuing to receive medication [personal communication- Y. Mosse].

ADVL1212 is a recently opened study evaluating the safety and tolerability of crizotinib administered in combination with topotecan and cyclophosphamide or vincristine and doxorubicin. As this study accrues, more information will be available to support the safety of combination chemotherapy with crizotinib.

2.4 Study Rationale

2.4.1 Rationale for ALCL99

Though APO regimen can be given as outpatient therapy, it is 52 weeks in duration. While ALCL99 therapy usually requires hospitalization, the duration is only 19 weeks. The APO regimen gives doxorubicin at a cumulative dose of 300 mg/m^2; whereas ALCL99 gives 150 mg/m^2 total of doxorubicin. Additionally, the ALCL99 study demonstrated that giving methotrexate (3 g/m^2 over 3 hours) resulted in less toxicity and no increased risk of CNS relapses, than methotrexate 1 g/m^2 given over 1 hour plus intrathecal therapy. Lastly, the BFM finding of prognostic value of minimal disease and minimal residual disease was a retrospective, subset analysis of patients on BFM-NHL-90 and ALCL99. By using the ALCL99 for the backbone of chemotherapy, we will reduce the exposure to anthracycline, reduce intrathecal chemotherapy, reduce time in treatment, have the ability to compare results directly to the largest trial in pediatric ALCL, and have the opportunity to confirm or dispute the BFM findings regarding minimal disease and minimal residual disease in a prospective fashion.

2.4.2 Rationale for eligibility

Patients must have disease that is both CD30 positive and ALK positive since these are the targets of brentuximab vedotin and crizotinib respectively. Patients with skin disease only will not be eligible as skin only disease exhibits very different characteristics than systemic disease. Since patients with central nervous system disease are rare and we do not want to cloud any neurological toxicity associated with either drug, patients with CNS disease will not be eligible. Patients with Stage II, III, and IV disease will be eligible. Attarbaschi et al. demonstrated that patients with Stage II disease have similar EFS and OS as more advanced stage disease using ALCL-99 therapy.[27] In addition, in a multivariate analysis of 225 children with ALCL of all stages, stage was not predictive of outcome.[28] While recent COG trials have not included Stage II patients, there are no data that Stage II patients have an outcome different than patients with higher stage disease.

2.4.3 Rationale for brentuximab vedotin and crizotinib

Since all cases of ALCL express CD-30, this is an ideal target for directed therapy. Brentuximab vedotin is a unique antibody drug conjugate which delivers a tubulin inhibitor directly to the tumor cells. Tubulin inhibitors are active agents in ALCL as evidenced by responses using vincristine and vinblastine. The response rate using brentuximab vedotin as a single agent for patients with relapsed/refractory ALCL is impressive. We hypothesize that the toxicity will be tolerable and that this agent will be active and this agent will advance into larger, more definitive

studies. We plan to utilize a dose of 1.8 mg/kg every 3 weeks which is the dose utilized in the phase II trials for ALCL. This dose gives similar exposure to the 1.2 mg/kg every 2 weeks that was tolerable in combination with chemotherapy in the upfront Hodgkin lymphoma trial and is the current dose being evaluated with CH-P therapy in upfront ALCL. There will be a de-escalation of the dose should patients experience delays in chemotherapy as the DLT.

Because pediatric ALCL is characterized by having the vast majority of cases express ALK and the ALK protein is postulated to be the oncogenic drive in the pathogenesis for pediatric ALCL, this is an ideal target for treatment. The rationale for the use of inhibitors directed toward oncogenic tyrosine kinases that are genetically altered is supported by many recent examples such as imatinib in gastrointestinal stromal tumors with mutant c-Kit or chronic myelogenous leukemia with BCR-Abl gene translocations. Moreover, AALL0031 demonstrated remarkable clinical efficacy when combining a targeted tyrosine kinase inhibitor (imatinib) with standard chemotherapy for Ph+ ALL. We hypothesize that the toxicity will be tolerable and that this agent will be active and this agent will advance into larger, more definitive studies. We plan to use the 165 mg/m^2/dose BID dose as this has shown reasonable toxicity in ADVL0912 with excellent response rates.

Despite numerous treatment strategies over the last 20 years, failure rates remain 25-30% for pediatric ALCL. This study proposes to randomize patients to 2 arms. Arm BV will add brentuximab vedotin to standard chemotherapy per ALCL99 (3 g/m^2 methotrexate and prophase intrathecal chemotherapy only). Arm CZ will add crizotinib to standard chemotherapy per ALCL99 (3 g/m^2 methotrexate and prophase intrathecal chemotherapy only). This design will allow for determination of toxicity of brentuximab vedotin and crizotinib with chemotherapy, as well as provide preliminary information on EFS when compared to historical controls. The results of this study will provide all the necessary information to design more definitive studies testing the benefit of novel agents in improving the outcome of children with ALCL.

2.5 Biology

2.5.1 Minimal Disseminated Disease (MDD) / Minimal Residual Disease (MRD)

Clinical and histological characteristics have limited prognostic value in children with ALCL. As the majority of ALCL in children possess a genetic translocation involving the anaplastic large cell lymphoma kinase (*ALK*) gene,[21] a polymerase chain reaction (PCR) for NPM-ALK provides an ideal platform to assess minimal disease. In a report from Damm-Welk et al., minimal disease in bone marrow or peripheral blood found by PCR at diagnosis identified a group of patients with a high incidence of relapse.[29] Overall there was a cumulative incidence of relapse of 50% for the 38 patients who were PCR positive and a cumulative incidence of relapse of 15% for the 42 patients who were PCR negative ($p < 0.001$). In multivariate analysis, the relative risk of relapse for patients with quantitative PCR positive bone marrow was 4.74 ($p=0.006$) but only 1.67 ($p = 0.32$) for the clinical risk features previously considered high risk by some groups.[28,29] In multivariate analysis, the relative risk of relapse for patients with qualitative PCR positive bone marrow was 3.47 ($p = 0.028$). Although fewer samples were tested in peripheral

blood, there was a high concordance rate (Spearman correlation coefficient = 0.84; $p < .001$) between the bone marrow PCR results and the peripheral blood PCR results. Overall, both quantitative and qualitative PCR in either peripheral blood or bone marrow identified high risk patients in this small selection of patients.

Since minimal disease at diagnosis may be prognostic, it follows that minimal residual disease during therapy may also hold prognostic significance. Defining MRD as qualitative PCR positivity, the same researchers who studied minimal disease at diagnosis, examined minimal residual disease at Day 6 and after course 1, in a very limited number of samples. Minimal residual disease at both time points identified patients at higher risk for relapse (personal communication- W. Woessman). We hypothesize that MDD/MRD will be of great importance in the future of treatment for ALCL allowing us to identify patients early in treatment who have a high risk of recurrence.

2.6 Thromboembolic Background

Thromboembolic adverse events, which are frequently multifactorial in causality, have been reported with many of the chemotherapy agents given on ANHL12P1 including crizotinib and brentuximab vedotin. Amendment #5 modified the ANHL12P1 protocol and consent document to reflect the potential risk of thromboembolic events. Further evaluation of the thromboembolic events on this trial has been undertaken. Briefly, there have been 15 thromboembolic events on ANHL12P1 as of September 27, 2017 (4 subjects had a pulmonary embolism (2 of 4 known to be catheter-related) and 11 had a catheter-related clot). Nine of the catheter-related thromboses (6 in Arm CZ and 3 in Arm BV) have been asymptomatic and discovered on routine tests (echo or CT) for other purposes. One catheter-related thrombosis (Arm CZ) was symptomatic with neck discomfort from the central line migrating position into the neck and another (Arm BV) was symptomatic with arm swelling. The incidence point estimate for a Grade 2+ Adverse Event of a catheter-related thrombosis is 17.1% (95% CI 7.2%–32.1%) on Arm CZ and 6.0% (95% CI 1.7%–14.6%) on Arm BV with the larger CI for Arm CZ mostly due to fewer patients enrolled to date on that arm. All 4 pulmonary emboli occurred on Arm CZ (giving an incidence point estimate of 9.8%; 95% CI 2.7%–23.1%). No deaths have occurred due to thromboembolic events. The increased risk of thromboembolic events in Arm CZ has resulted in the requirement to use anticoagulation for prophylaxis as of Amendment #6A.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix III for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix III.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The

CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.1.4 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment. **Patients who are started on protocol therapy on a Phase II study prior to study enrollment will be considered ineligible**.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

3.1.5 Randomization

Randomization will take place at the time a patient is enrolled via OPEN.
Eligible patients will be stratified as follows:

- **Stratum 1**: Patients with BSA ≥ 0.9 m^2
- **Stratum 2**: Patients with BSA < 0.9 m^2

Eligible patients in Stratum 1 will be randomized (1:1) to Arm BV or Arm CZ.
Eligible patients in Stratum 2 will be non-randomly assigned to Arm BV because crizotinib is only available in certain strengths.

3.1.5.1 Two exceptions to randomization:

1) If one arm is temporarily closed, patients will be non-randomly assigned to the other arm.
2) If Arm BV is temporarily closed and the patient is < 0.9 m^2, then the patient is not eligible for the study.

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record that will serve as the source document for verification at the time of audit.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, if applicable, must be obtained within 2 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).

See Section 7.1 for required studies to be obtained prior to starting protocol therapy.

INCLUSION CRITERIA

3.2.1 Age

Patient must be < 22 years of age at the time of study enrollment.

3.2.2 Diagnosis

- Newly diagnosed patients with histologically proven ALCL (ICD-0 code: 9714/3).
- Disease must be CD30 positive.
- Disease must be ALK positive (defined by local institutional standards).
- Patients must have Stage II, III, or IV disease (See Appendix I for staging).

3.2.3 Life Expectancy

Patients must have a life expectancy of ≥ 8 weeks.

3.2.4 Organ Function Requirements

3.2.4.1 Adequate Liver Function Defined As:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age.
- ALT (SGPT) < 2.5 x upper limit of normal (ULN) for age. For the purpose of this study, the ULN for ALT is 45 U/L.
- If the lab abnormality is thought to be due to the lymphoma the patient is eligible and dose adjustments should be made (See Section 5.0).

3.2.4.2 Adequate Cardiac Function Defined As:

- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by radionuclide angiogram.

3.2.4.3 Adequate Pulmonary Function Defined As:

- Patients with a history of pulmonary dysfunction must have no evidence of dyspnea at rest, no exercise intolerance due to pulmonary insufficiency, and a pulse oximetry > 92% while breathing room air unless current dysfunction is due to the lymphoma in which case the patient is eligible.

3.2.5 Exclusion Criteria

3.2.5.1 Patients with CNS disease are not eligible.

3.2.5.2 Patients with disease limited to the skin are not eligible, regardless of how wide-spread.

3.2.5.3 Patients with Stage I disease are not eligible.

3.2.5.4 Patients who have received any prior cytotoxic chemotherapy for the current diagnosis of ALCL or any cancer diagnosed previously are not eligible.

3.2.5.5 Previous steroid treatment and/or radiation treatment is not allowed unless it is for the emergent management of a mediastinal mass. Emergent steroid treatment and/or radiation treatment should stop once protocol therapy is initiated.

3.2.5.6 Intrathecal chemotherapy prior to enrollment is allowed for the current diagnosis of ALCL as long as adequate CSF is obtained prior to administration of the intrathecal chemotherapy and subsequently demonstrated to be negative for ALCL. (See Section 4.2)

3.2.5.7 Female patients who are pregnant are not eligible due to risks of fetal and teratogenic adverse events. Pregnancy tests must be obtained in girls who are post menarchal.

3.2.5.8 Lactating females are not eligible unless they have agreed not to breastfeed their infants.

3.2.5.9 Sexually active patients of reproductive potential are not eligible unless they agree to use an effective contraceptive method for the duration of treatment and for 3 months after stopping treatment.

3.2.5.10 Patients with Down syndrome are not eligible due to the amount of methotrexate and potential for side effects.

3.2.5.11 Patients with an immunodeficiency that existed prior to diagnosis such as primary immunodeficiency syndromes or organ transplant recipients are not eligible.

3.2.5.12 CYP3A4 Substrates with Narrow Therapeutic Indices: Patients chronically receiving medications known to be metabolized by CYP3A4 and with narrow therapeutic indices including pimozide, aripiprazole, triazolam, ergotamine and halofantrine are not eligible. The topical use of these medications (if applicable) is allowed. See Appendix IV.

3.2.5.13 CYP3A4 Inhibitors: Patients chronically receiving drugs that are known potent CYP3A4 inhibitors within 7 days prior to study enrollment, including but not limited to ketoconazole, itraconazole, clarithromycin, erythromycin, ritonavir, indinavir, nelfinavir, saquinavir, delavirdine, nefazodone, diltiazem, verapamil, and grapefruit juice are not eligible. The topical use of these medications (if applicable), e.g. 2% ketoconazole cream, is allowed. See Appendix IV.

3.2.5.14 CYP3A4 Inducers: Patients chronically receiving drugs that are known potent CYP3A4 inducers within 12 days prior to study enrollment, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, ritonavir, and St. John's wort are not eligible. The topical use of these medications (if applicable) is allowed. See Appendix IV.

3.2.5.15 Patients that are known to be positive for HIV are not eligible.
Note: Inclusion of HIV positive patients will be considered at a later date.

3.2.5.16 Patients who weigh < 10 kg are not eligible.

3.2.6 Regulatory Requirements

3.2.6.1 All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.6.2 All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

Eligible patients will be stratified as follows:

- Stratum 1: Patients with BSA ≥ 0.9 m^2
- Stratum 2: Patients with BSA < 0.9 m^2

At study enrollment:

- Eligible patients in Stratum 1 will be randomized (1:1) to Arm BV or Arm CZ.
- Eligible patients in Stratum 2 will be non-randomly assigned to Arm BV because crizotinib is only available in certain strengths.

Arm BV: Patients receive standard chemotherapy plus brentuximab vedotin.

Arm CZ: Patients receive standard chemotherapy plus crizotinib.

Two exceptions to randomization:

1) If one arm is temporarily closed, patients will be non-randomly assigned to the other arm.
2) If Arm BV is temporarily closed and the patient is < 0.9 m^2, then the patient is not eligible for the study.

All patients will receive a 5 day prophase followed by alternating Courses (A and B) administered every 21 days for a total of 6 cycles (3 cycles of Course A and 3 cycles of Course B). The study agents will begin on Day 1 of Cycle 1 following the prophase. Growth factors are not required but will be permitted as the standard chemotherapy backbone causes neutropenia and both brentuximab vedotin and crizotinib have been shown to cause neutropenia. If used, the use of growth factor should be reported.

4.1.1 Supportive Care Guidelines

- Thromboembolic events are known side effects of chemotherapy and/or the presence of a central venous catheter. Many thromboembolic events have multifactorial causes. Whenever possible, treating physicians should make every attempt to eliminate additional risk factors such as tobacco use, dehydration, concomitant medications, etc. that increase the risk for thrombosis.

- Tumor Lysis: Patients with massive tumor burden should be hydrated prior to initiation of chemotherapy and monitored for tumor lysis syndrome.

- Prophylactic anticoagulation is required for patients on Arm CZ due to the potential risk of thromboembolic events (see Section 2.6). Anticoagulation may be implemented according to each institution's standard of care for prophylactic anticoagulation OR utilizing low molecular weight heparin with a goal Anti-Xa of 0.1-0.3 units/mL. More information can be found at: https://childrensoncologygroup.org/downloads/COG_SC_Thrombosis_Guideline_Document.pdf.
  It is important to note potential drug interactions between the chemotherapeutic agents on Arm CZ and certain anticoagulation medications (including but not limited to warfarin, apixaban, and rivaroxaban).

- Risk of bleeding secondary to chemotherapy induced thrombocytopenia should be minimized using platelet transfusions according to each institution's standard of care for thrombocytopenic patients receiving anticoagulation.

- Central venous line: Insertion of a central venous line is recommended prior to the administration of treatment. Two lumens are preferred for ease in chemotherapy administration. This may have to be delayed in the event of a large mediastinal mass, being a contraindication to surgery.

- Mucositis: Mucositis is expected particularly after Course B (Cycles 2, 4, and 6). Patients should be instructed on the importance of meticulous oral hygiene to reduce oral infections and prevent mucositis.

- Anti-emetics: Anti-emetics should be given during each chemotherapy cycle. Steroids should not be used as anti-emetic therapy.

- *Pneumocystis jiroveci* pneumonia prophylaxis: Appropriate prophylaxis should be given per institutional standards.

  For COG Supportive Care Guidelines see:
  https://childrensoncologygroup.org/cog-supportive-care-guidelines.

4.1.2 Concomitant Therapy Restrictions

- Strong inducers or inhibitors of CYP3A enzymes should be avoided.

- See Appendix IV for full list.

- The metabolism of the two investigational agents (crizotinib and brentuximab vedotin) is predominantly mediated by the CYP3A isozymes. Co-administration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of crizotinib and/or brentuximab vedotin in humans. The chronic concurrent use of potent CYP3A inhibitors and potent CYP3A inducers (with the exception of protocol defined therapy) must be avoided until treatment discontinuation. The list of potent CYP3A4 inhibitors and inducers in Appendix IV should be avoided whenever possible, and therapeutic alternatives to these agents are recommended. Please see Appendix IV for a list of common substrates, inhibitors, and inducers of CYP3A4.

4.2 Prophase (5 days) – Arms BV and CZ

Intrathecal chemotherapy may be administered at the time of the diagnostic lumbar puncture prior to enrollment on study. No other chemotherapy should begin prior to enrollment.

Peripheral blood for MDD/MRD should be drawn prior to beginning prophase. (Time point #1)

Those patients with bulky disease may be at risk for metabolic problems associated with tumor lysis. Please use appropriate supportive care.

Cyclophosphamide: IV over 15 - 30 minutes
Days: 1 and 2
Dose: 200 mg/m^2/dose.

May be administered with or without further dilution. To avoid hypotonic solution, reconstitute Cyclophosphamide with 0.9% NaCl to a final concentration of 20 mg/mL.

Dexamethasone: PO (may administer IV if patient unable to take oral medications)
Days: 1-5
Dose: 5 mg/m^2/dose once daily on days 1 and 2.
5 mg/m^2/dose BID on days 3, 4, 5.

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation may be used temporarily as needed.

Intrathecal Triple Therapy (ITT): age appropriate dose (see below)
Day 1 (may be administered during diagnostic lumbar puncture)
Dose:

Age (yrs)	IT MTX	IT HC	IT ARAC
0-0.99	7.5 mg	7.5 mg	15 mg
1-1.99	8 mg	8 mg	16 mg
2-2.99	10 mg	10 mg	20 mg
≥ 3	12 mg	12 mg	24 mg

For IT administration, use preservative free formulation.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map (TDM) for the prophase (all Arms) is on the next page.

Cycle 1 for both arms starts on Day 6 of the prophase (i.e., Day 6 of prophase is Day 1 of Cycle 1).

Peripheral blood for minimal residual disease (MRD) should be drawn prior to beginning Cycle 1. (Time point #2)

4.2.1 **Prophase (5 days) Arm BV and CZ**	_____ Patient COG ID number	_____ DOB

*Prophase lasts 5 days. This Therapy Delivery Map is on one **(1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Cyclophosphamide (CPM)	IV over 15 - 30 minutes	200 mg/m^2/dose	1& 2		a.History b.Physical Exam (weekly) c.CBC/diff/plts (weekly) d.Electrolytes (weekly) e.Performance Status f.Cr,Bilirubin,AST,ALT g.Urinalysis **h.Blood for MRD** **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE. (See Section 7.1.)**
Dexamethasone (DEX)	PO	5 mg/m^2/dose once a day on days 1 and 2 5 mg/m^2/dose BID on days 3-5	Once daily on Days 1 & 2 BID Days 3-5	May give IV if unable to take PO.	
Intrathecal Triple Therapy (ITT): Methotrexate (IT MTX) Hydrocortisone (IT HC) Cytarabine (IT ARAC)	IT	Age(yrs) Dose 0-0.99 MTX: 7.5mg, HC: 7.5mg, ARAC: 15mg 1-1.99 MTX: 8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg, HC: 10mg, ARAC: 20mg ≥ 3 MTX: 12mg, HC: 12mg, ARAC: 24mg	Day 1	**Note age-based dosing.**	

Prophase Ht _____cm Wt _____kg BSA _____m^2 Growth Factor Used? Y/N?

Date Due	Date Given	Day	CPM ____mg	DEX ____mg ____mg$^{\$}$ $^{\$}$(BID Days 3-5)	ITT ____mg (IT MTX) ____mg (IT HC) ____mg (IT ARAC)	Studies	Comments
Enter calculated dose above and actual dose administered below.							
		1	____mg	____mg	____mg (IT MTX) ____mg (IT HC) ____mg (IT ARAC)	a – **h***	
		2	____mg	____mg			
		3		_____mg _____mg$^{\$}$			
		4		_____mg _____mg$^{\$}$			
		5		_____mg _____mg$^{\$}$			
		6/1				**h**	MRD blood draw is Day 6, before Cycle 1.

*See Section 7.1. for the full list of baseline studies that need to be done prior to starting protocol therapy, **including blood for MRD.** The studies listed on this TDM need to be completed prior to prophase.

See Section 5.0 for Dose Modifications for Toxicities and the COG website posted materials for Supportive Care Guidelines.

4.3 Course A (21 days) – Arm BV (Cycles 1, 3 and 5)

Peripheral blood for minimal residual disease (MRD) should be drawn prior to beginning Cycle 1. (Time point #2)

Cycle 1 should begin on Day 6 of the prophase. Cycles 3 and 5 should begin on Day 22 of the previous cycle when peripheral counts have recovered with ANC ≥ 500/mm^3 and platelets ≥ 50,000/mm^3 (whichever occurs later). Therapy may be delayed for severe complication. The use of growth factors should be noted if they are administered.

Brentuximab vedotin: IV over 30 minutes (Do NOT give as IV push)
Day 1
Dose: 1.8 mg/kg/dose. (Maximum dose is 180 mg)

Special precautions: Brentuximab should be administered on Day 1 prior to other chemotherapy. Brentuximab vedotin should be administered over approximately 30 minutes and cannot be mixed with other medications. **In-line filters should not be used during the IV administration.**

Dosing is based on patient weight according to the institutional standard. Actual weight will be used except for patients weighing greater than 100 kg; the dose for patients with weight greater than 100 kg will be calculated based on 100 kg.

Dilute reconstituted product in either 0.9% Sodium Chloride Injection, USP, Lactated Ringer's solution, USP, or dextrose 5% in water (D5W), USP. The final concentration of brentuximab vedotin in infusion bag should be in the range of 0.4–1.8 mg/mL. Refer to Section 6.1 for additional details.

Dexamethasone: PO (may administer IV if patient unable to take oral medications)
Days: 1-5
Dose: 5 mg/m^2/dose BID on Days 1-5.

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation may be used temporarily as needed.

Ifosfamide: IV over 60 minutes
Days: 1-5
Dose: 800 mg/m^2/dose once a day. On Day 1 administer prior to methotrexate. Mesna use as described below.

Suggested hydration: Prehydrate at 125 mL/m^2/hour with a fluid containing D5W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. Consider adding potassium and magnesium to prevent electrolyte deficiencies. After completion of ifosfamide, continue hydration with fluids as recommended for methotrexate. Following clearance of the methotrexate, patient should receive IV or oral fluids at a rate of 3000 mL/m^2/day until 12 hours after the last dose of ifosfamide.

Mesna: IV over 15 minutes (or continuous infusion as below)
Days: 1-5
Dose: 160 mg/m^2/dose IV at hours 0 (either 15 minutes prior to or concurrently with ifosfamide), 4, and 8 following ifosfamide daily.

When administered intravenously, the total daily mesna dose is equal to 60% of the daily ifosfamide dose and is administered in 3 divided doses. For example, if the dose of ifosfamide is 1000 mg, then the total daily mesna dose is 600 mg; 200 mg of mesna will be given 15 minutes before or with the ifosfamide dose (Hour 0) and 2 boluses of 200 mg each will be given at Hours 4 and 8. Mesna can also be administered as a continuous IV infusion. The continuous infusion should be started 15-30 minutes before or at the same time as the ifosfamide and finished no sooner than 8 hours after the end of the ifosfamide infusion. For example, if the dose of ifosfamide is 1000 mg, then the total daily mesna dose is 600 mg; the 600 mg mesna continuous infusion will start 15-30 minutes before or at the same time as the ifosfamide and be completed no sooner than 8 hours after the end of the ifosfamide infusion. If continuous infusion mesna is required, it should be given through a separate IV from the bicarbonate IVFs. Alternatively, mesna may be given orally as described below.

Patients able to tolerate oral mesna may receive the second and/or the third dose(s) by mouth at a dosage of 40% of the ifosfamide dose. The first dose of mesna should be given intravenously. The oral dose of mesna is twice the IV dose and each oral dose should be given 2 hours earlier than an intravenous dose would be given. For example, if the dose of ifosfamide is 1000 mg, the first MESNA dose would be 200 mg IV at the time of the ifosfamide dose, followed by oral doses of 400 mg at hours 2 and 6, rather than at hours 4 and 8. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed. If the patient vomits within 2 hours following an oral dose, repeat the oral dose or administer an IV dose of mesna.

Methotrexate: IV over 3 hours
Day 1
Dose: 3000 mg/m^2/dose.

<u>HD MTX Infusion Guidelines</u>
Methotrexate should be given on Day 1 at least 2 hours after the completion of brentuximab vedotin, after Day 1 ifosfamide dose, and when urine parameters are met.

Hold trimethoprim/sulfamethoxazole (TMP-SMX) and any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.1 µM/L.

Suggested hydration: Prehydrate with D5 ¼ NS with 30 mEq NaHCO3/L at 125 mL/m^2/hour for a minimum of 2 hours beginning after completion of brentuximab vedotin and until urine output is > 100 mL/m^2/hour and pH is ≥ 7.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine output and pH at above parameters. A bicarbonate bolus (25 mEq/m^2 over 15 minutes) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration.

Continue hydration and alkalinization throughout MTX infusion until level is < 0.1 µM/L (hydrate for a minimum of 48 hours after MTX completion). Sodium bicarbonate is incompatible with many medications; infuse via separate line or lumen unless compatibility is known.

Methotrexate levels: Hours 24, 48 and at least every 24 hours until level is < 0.1 µM/L: Draw MTX level and serum creatinine. For SCr > 125% of baseline or for MTX levels exceeding 50 µM/L at 24 hours or desired levels at any other time point, increase hydration to 200 mL/m^2/hr.

Leucovorin: IV or PO
Begin 24 hours from the start of methotrexate infusion
Dose: 15 mg/m^2/dose every 6 hours until MTX level is < 0.1 µM/L.

IV push or short infusion: Inject by IV push over a minimum of 3 minutes or by short infusion over 15 to 120 minutes. Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL solution per minute). IV leucovorin and sodium bicarbonate are incompatible.

Oral: Administer with or without food. Doses > 25 mg should be given IV due to the saturation of absorption. If the level does not fall as expected, increase the leucovorin as shown below:
Schedule for calculation of leucovorin rescue based on plasma MTX levels

MTX level µM/L	<0.1	0.1-2	2-20	20-100	>100
48 hrs	None	15 mg/m^2 q6 hr	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr
72 hrs	None	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr	1000 mg/m^2 q**3** hr*
96 hrs	None	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr	1000 mg/m^2 q**3** hr*
120 hrs	None	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr	1000 mg/m^2 q**3** hr*

For patients who have markedly delayed MTX clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G2). To obtain supplies of glucarpidase in the US contact the Voraxaze 24-hour Customer Service line at 855-786-7292. Additional information can be found at http://www.btgplc.com/products/specialty-pharmaceuticals/voraxaze regarding product availability through ASD Healthcare, Cardinal, and McKesson. Canadian sites should contact McKesson at (877) 384-7425 for further information. Sites in Australia and New Zealand should contact Hospira at 1300-046-774 (local) or medicalinformationAUS@hospira.com. Patients requiring glucarpidase rescue may remain on study, and may receive further courses of MTX at investigator discretion if renal function is adequate as per parameters above.

Cytarabine: IV over 1 – 30 minutes
Days: 4 and 5
Dose: 150 mg/m^2/dose every 12 hours for a total of 4 doses.

Etoposide: IV over 2 hours
Days: 4 and 5
Dose: 100 mg/m^2/dose once a day

Special precautions: Begin after completion of first cytarabine dose of the day. Infuse diluted solution (concentration ≤ 0.4 mg/mL); slow rate of administration if hypotension occurs. The use of an in-line filter during the infusion is suggested. Etoposide can be mixed in 0.9% NaCl or D5W.

See Section 5.0 for Dose Modifications based on Toxicities.
The therapy delivery maps (TDMs) for Arm BV Cycles 1, 3, and 5 are on the next page.
Please refer to Section 7.0 for required observations.

4.3.1 **Course A (21 days) - Arm BV (Cycles 1, 3 & 5)**	_____ Patient COG ID number	_____ DOB

*Cycle 1 should begin on Day 6 of the Prophase. Cycles 3 and 5 should begin on Day 22 following the previous cycle when peripheral counts have recovered with ANC ≥ 500/mm³ and platelets ≥ 50,000/mm³. This Therapy Delivery Map is on one **(1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Brentuximab vedotin (BREN)	IV over 30 minutes	1.8 mg/kg/dose (Max dose 180 mg)	Day 1	Do NOT give as IV push Do not use an in-line filter.	a. Hx; Performance Status b. Physical Exam (weekly in Cycle 1 then prior to each cycle) c. CBC/diff/plts (weekly) d. Electrolytes (weekly in Cycle 1 then prior to each cycle) e. Cr,Bilirubin,AST,ALT f. Urinalysis **g. Blood for MRD (End of Cycle 1 only!)** **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** (See **Section 7.1**)
Dexamethasone (DEX)	PO	5 mg/m²/dose BID	Days 1-5	May give IV if unable to take PO.	
Ifosfamide (IFOS)	IV over 60 minutes	800 mg/m²/dose once a day	Days 1-5	On Day 1 administer prior to MTX. Mesna use as described below.	
Mesna	IV	160 mg/m²/dose (total of 480 mg/m²/DAY)	Days 1-5	At hours 0, 4, and 8 following Ifosfamide daily.	
Methotrexate (MTX)	IV over 3 hours	3000 mg/m²/dose	Day 1	See Section 4.3 for administration guidelines.	
Leucovorin (LCV)	IV or PO*	15 mg/m²/dose every 6 hrs	Begin Day 2	See Section 4.3 for administration guidelines. 24 hrs after the START of IV MTX and q6 hours until the MTX level falls below 0.1µM/L. *	
Cytarabine (ARAC)	IV over 1 – 30 minutes	150 mg/m²/dose every 12 hours	Days 4 & 5	Give over 1 – 30 minutes every 12 hours for total of 4 doses.	
Etoposide (ETOP)	IV over 2 hours	100 mg/m²/dose once a day	Days 4 & 5	Begin after completion of 1st Cytarabine dose each day.	

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m² Growth Factor Used?: Y /N

Date Due	Date Given	Day	BREN ____mg	DEX _____mg _____mg	IFOS _____mg	Mesna ____mg/ day	MTX ____mg	LCV ____mg	ARAC ____mg	ETOP ____mg	Studies	Comm-ents
			Enter calculated dose above and actual dose administered below.									
		1	____mg	____mg ____mg	____mg	____mg/ day	____mg				a-f	
		2		____mg ____mg	____mg	____mg/ day		____*				
		3		____mg ____mg	____mg	____mg/ day						
		4		____mg ____mg	____mg	____mg/ day			____mg ____mg	____mg		
		5		____mg ____mg	____mg	____mg/ day			____mg ____mg	____mg		
		8									b,c,d#	
		15									b,c,d#	
		22	**Each cycle should begin on Day 22 of the previous cycle when peripheral counts have recovered with ANC ≥ 500/mm³ and platelets ≥ 50,000/mm³ (whichever occurs later)**								**g**	MRD is end of Cycle 1 only

* Please document the number of doses of Leucovorin administered. See Section 5.0 for Dose Modifications for Toxicities and the COG website posted materials for Supportive Care Guidelines.

\# Physical Exam and Electrolytes are weekly in cycle 1 only, then prior to each cycle.

4.4 Course B (21 days) – Arm BV (Cycles 2, 4 and 6)

Peripheral blood for minimal residual disease (MRD) should be drawn prior to beginning Cycle 2. (Time point #3)

Each cycle should begin on Day 22 of the previous cycle when peripheral counts have recovered with ANC $\geq$ 500/mm^3 and platelets $\geq$ 50,000/mm^3 (whichever occurs later). Therapy may be delayed for severe complication.

The use of growth factors should be noted if they are administered.

Brentuximab vedotin: IV over 30 minutes (Do NOT give as IV push)
Day 1
Dose: 1.8 mg/kg/dose. (Maximum dose is 180 mg)

Special precautions: Brentuximab should be administered on Day 1 prior to other chemotherapy. Brentuximab vedotin should be administered over approximately 30 minutes and cannot be mixed with other medications. **In-line filters should not be used during the IV administration.**

Dosing is based on patient weight according to the institutional standard. Actual weight will be used except for patients weighing greater than 100 kg; the dose for patients with weight greater than 100 kg will be calculated based on 100 kg.

Dilute reconstituted product in either 0.9% Sodium Chloride Injection, USP, Lactated Ringer's solution, USP, or dextrose 5% in water (D5W), USP. The final concentration of brentuximab vedotin in infusion bag should be in the range of 0.4–1.8 mg/mL.

Dexamethasone: PO (may administer IV if patient unable to take oral medications)
Days 1-5
Dose: 5 mg/m^2/dose BID on Days 1-5.

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation may be used temporarily as needed.

Cyclophosphamide: IV over 15 - 30 minutes
Days 1-5
Dose: 200 mg/m^2/dose. Give prior to methotrexate on Day 1.

May be administered with or without further dilution. To avoid hypotonic solution, reconstitute Cyclophosphamide with 0.9% NaCl to a final concentration of 20 mg/mL

Hydration: Patient will receive hydration for methotrexate. Following clearance of the methotrexate, patient should receive IV or oral fluids at a rate of 3000 mL/m^2/day until 12 hours after the last dose of cyclophosphamide.

Methotrexate: IV over 3 hours
Day 1
Dose: 3000 mg/m^2/dose.

HD MTX Infusion Guidelines
Methotrexate should be given on Day 1 at least 2 hours after the completion of brentuximab vedotin, after Day 1 cyclophosphamide dose, and when urine parameters are met.

Hold trimethoprim/sulfamethoxazole (TMP-SMX) and any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.1 µM/L.

Suggested hydration: Prehydrate with D5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour for a minimum of 2 hours beginning after completion of brentuximab vedotin and until urine output is > 100 mL/m^2/hour and pH is ≥ 7.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine output and pH at above parameters. A bicarbonate bolus (25 mEq/m^2 over 15 minutes) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration. Continue hydration and alkalinization throughout MTX infusion until level is < 0.1 µM/L (hydrate for a minimum of 48 hours after MTX completion). Sodium bicarbonate is incompatible with many medications; infuse via separate line or lumen unless compatibility is known.

Methotrexate levels: Hours 24, 48 and at least every 24 hours until level is < 0.1 µM/L: Draw MTX level and serum creatinine.

For SCr > 125% of baseline or for MTX levels exceeding 50 µM/L at 24 hours or desired levels at any other time point, increase hydration to 200 mL/m^2/hr.

Leucovorin: IV or PO
Begin 24 hours from the start of methotrexate infusion
Dose: 15 mg/m^2/dose every 6 hours until MTX level is < 0.1 µM/L.

IV push or short infusion: Inject by IV push over a minimum of 3 minutes or by short infusion over 15 to 120 minutes. Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL solution per minute). IV leucovorin and sodium bicarbonate are incompatible.

Oral: Administer with or without food. Doses > 25 mg should be given IV due to the saturation of absorption.

If the level does not fall as expected, increase the leucovorin as shown below:

Schedule for calculation of leucovorin rescue based on plasma MTX levels

MTX level µM/L	< 0.1	0.1-2	2-20	20-100	>100
48 hrs	None	15 mg/m^2 q6 hr	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr
72 hrs	None	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr	1000 mg/m^2 q**3** hr*
96 hrs	None	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr	1000 mg/m^2 q**3** hr*
120 hrs	None	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr	1000 mg/m^2 q**3** hr*

For patients who have markedly delayed MTX clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G2). To obtain supplies of glucarpidase in the US contact the Voraxaze 24-hour Customer Service line at 855-786-7292. Additional information can be found at http://www.btgplc.com/products/specialty-pharmaceuticals/voraxaze regarding product availability through ASD Healthcare, Cardinal, and McKesson. Canadian sites should contact McKesson at (877) 384-7425 for further information. Sites in Australia and New Zealand should contact Hospira at 1300-046-774 (local) or medicalinformationAUS@hospira.com. Patients requiring glucarpidase rescue may remain on study, and may receive further courses of MTX at investigator discretion if renal function is adequate as per parameters above.

DOXOrubicin: IV over 1-15 minutes
Days: 4 and 5
Dose: 25 mg/m^2/dose.

Administer at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 15 minutes. Infusion times may be lengthened slightly (up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D5W or 0.9% NaCl and that it is infused into a large vein or central venous access device.

Special precautions: Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. The conventional and liposomal formulations are NOT interchangeable.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery maps (TDMs) for Arm BV Cycles 2, 4, and 6 are on the next page.

Please refer to Section 7.0 for required observations.

4.4.1 **Course B (21 days) – Arm BV (Cycles 2, 4 and 6)**	_____ Patient COG ID number	_____ DOB

*Each cycle should begin on Day 22 following the previous cycle when peripheral counts have recovered with ANC ≥ 500/mm³ and platelets ≥ 50,000/mm³. This Therapy Delivery Map is on one **(1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Brentuximab vedotin (BREN)	IV over 30 minutes	1.8 mg/kg/dose (Max dose 180 mg)	Day 1	Do NOT give as IV Push Do not use an in-line filter.	a. Physical Exam (weekly for Cycle 2, then prior to each cycle) b. Hx, Performance Status c. CBC/diff/plts (weekly) d. Electrolytes including Ca++, PO_4, Mg++ (weekly for Cycle 2, then prior to each cycle) e. Creatinine, Bilirubin, LFTs f. CXR (PA + Lateral), CT or MRI, Bone Scan (for bone primary disease only), FDG-PET Scan (recommended-not mandatory)^ g. Urinalysis h. BM Aspirate/Biopsy (Bilateral) # i. Echo/EKG (prior to Cycles 4 and 6 only) ^All sites of disease should be evaluated after Cycle 2 and after Cycle 4 if not in CR or CRU after Cycle 2. #After Cycle 2, if positive at diagnosis **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** (See Section 7.1)
Dexamethasone (DEX)	PO	5 mg/m²/dose BID	Days 1-5	May give IV if unable to take PO.	
Cyclophosphamide (CPM)	IV over 15 - 30 minutes	200 mg/m²/dose	Days 1-5	Give prior to MTX on Day 1.	
Methotrexate (MTX)	IV over 3 hours	3000 mg/m²/dose	Day 1	See Section 4.4 and for administration guidelines.	
Leucovorin (LCV)	IV or PO*	15 mg/m²/dose every 6 hrs	Begin Day 2	See Section 4.4 and for administration guidelines. 24 hrs after the START of IV MTX and q6 hours until the MTX level falls below 0.1μM/L. *	
DOXOrubicin (DOXO)	IV over 1-15 minutes	25 mg/m²/dose	Days 4 & 5		

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m² Growth Factor Used? Y/N

Date Due	Date Given	Day	BREN mg	DEX mg mg	CPM mg	MTX mg	LCV mg	DOXO mg	Studies	Comments
		1	____mg	____mg ____mg	____mg	____mg			a-e, g and i	
		2		____mg ____mg	____mg		____*			
		3		____mg ____mg	____mg					
		4		____mg ____mg	____mg			____mg		
		5		____mg ____mg	____mg			____mg		
		8							a,c,d$	
		15							a,c,d$	
		22	**Each cycle should begin on Day 22 of the previous cycle when peripheral counts have recovered with ANC ≥ 500/mm³ and platelets ≥ 50,000/mm³ (whichever occurs later)**						a,c,d$,f^, h#	
			For end of therapy (end of cycle 6) studies, see Section 7.1 for complete list.							

*Please document the number of doses of Leucovorin administered. See Section 5.0 for Dose Modifications for Toxicities and the COG website posted materials for Supportive Care Guidelines

$ Physical Exam and Electrolytes are weekly in Cycle 2 only, then prior to each cycle.

^ All sites of disease should be evaluated after Cycle 2 and after Cycle 4 if not in CR or CRU after Cycle 2.

#After Cycle 2, if positive at diagnosis.

4.5 Course A (21 days) – Arm CZ (Cycles 1, 3 and 5)

Prophylactic anticoagulation is required for all patients on Arm CZ starting with the first dose of crizotinib. See Sections 2.6 and 4.1.1 for detail.

Peripheral blood for minimal residual disease (MRD) should be drawn prior to beginning Cycle 1. (Time point #2)

Cycle 1 should begin on Day 6 of the prophase. Cycles 3 and 5 should begin on Day 22 of the previous cycle when peripheral counts have recovered with ANC $\geq$ 500/mm^3 and platelets $\geq$ 50,000/mm^3 (whichever occurs later). Therapy may be delayed for severe complication.

The use of growth factors should be noted if they are administered.

Crizotinib: PO BID
Day: 1-21
Dose: 165 mg/m^2/dose (Refer to Appendix V for dosing nomogram)

For patients receiving crizotinib, the capsules should not be opened and must be swallowed whole. If a dose is missed or forgotten at the due time, it can be taken up to (but not greater than) 6 hours later to help prevent missed doses. If a patient vomits after a dose, it should not be repeated. See Section 6.2 regarding administration instructions. Refer to the dosing nomogram in Appendix V for correct dose. Drug doses should be adjusted based on the BSA determined based on height and weight obtained within one week prior to the beginning of each cycle.

Dexamethasone: PO (may administer IV if patient unable to take oral medications)
Days: 1-5
Dose: 5 mg/m^2/dose BID on Days 1-5.

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation may be used temporarily as needed.

Ifosfamide: IV over 60 minutes
Days: 1-5
Dose: 800 mg/m^2/dose once a day. On Day 1 administer prior to methotrexate. Mesna use as described below.

Suggested hydration: Prehydrate at 125 mL/m^2/hour with a fluid containing D5W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity $\leq$ 1.010 prior to start of ifosfamide. Consider adding potassium and magnesium to prevent electrolyte deficiencies. After completion of ifosfamide, continue hydration with fluids as recommended for methotrexate. Following clearance of the methotrexate, patient should receive IV or oral fluids at a rate of 3000 mL/m^2/day until 12 hours after the last dose of ifosfamide.

Mesna: IV over 15 minutes (or continuous infusion as below)
Days: 1-5
Dose: 160 mg/m^2/dose IV at hours 0, 4, and 8 following ifosfamide daily.

When administered intravenously, the total daily mesna dose is equal to 60% of the daily ifosfamide dose and is administered in 3 divided doses. For example, if the dose of ifosfamide is 1000 mg, then the total daily mesna dose is 600 mg; 200 mg of mesna will be given 15 minutes before or with the ifosfamide dose (Hour 0) and 2 boluses of 200 mg each will be given at Hours 4 and 8. Mesna can also be administered as a continuous IV infusion. The continuous infusion should be started 15-30 minutes before or at the same time as the ifosfamide and finished no sooner than 8 hours after the end of the ifosfamide infusion. For example, if the dose of ifosfamide is 1000 mg, then the total daily mesna dose is 600 mg; the 600 mg mesna continuous infusion will start 15-30 minutes before or at the same time as the ifosfamide/cyclophosphamide and be completed no sooner than 8 hours after the end of the ifosfamide infusion. If continuous infusion mesna is required, it should be given through a separate IV from the bicarbonate IVFs. Alternatively, mesna may be given orally as described below.

Patients able to tolerate oral mesna may receive the second and/or the third dose(s) by mouth at a dosage of 40% of the ifosfamide dose. The first dose of mesna should be given intravenously. The oral dose of mesna is twice the IV dose and each oral dose should be given 2 hours earlier than an intravenous dose would be given. For example, if the dose of ifosfamide is 1000 mg, the first MESNA dose would be 200 mg IV at the time of the ifosfamide dose, followed by oral doses of 400 mg at hours 2 and 6, rather than at hours 4 and 8. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed. If the patient vomits within 2 hours following an oral dose, repeat the oral dose or administer an IV dose of mesna.

Methotrexate: IV over 3 hours
Day 1
Dose: 3000 mg/m^2/dose.

<u>HD MTX Infusion Guidelines</u>
Methotrexate should be given on Day 1 after Day 1 ifosfamide dose and when urine parameters are met.

Hold trimethoprim/sulfamethoxazole (TMP-SMX) and any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.1 µM/L.

Suggested hydration: Prehydrate with D5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour for a minimum of 2 hours and until urine output is > 100 mL/m^2/hour and pH is ≥ 7.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine output and pH at above parameters. A bicarbonate bolus (25 mEq/m^2 over 15 minutes) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration. Continue hydration and alkalinization throughout MTX infusion until level is < 0.1 µM/L (hydrate for a minimum of 48 hours after MTX completion). Sodium bicarbonate is incompatible with many medications; infuse via separate line or lumen unless compatibility is known.

Methotrexate levels: Hours 24, 48 and at least every 24 hours until level is < 0.1 µM/L: Draw MTX level and serum creatinine. For SCr > 125% of baseline or for MTX levels exceeding 50 µM/L at 24 hours or desired levels at any other time point, increase hydration to 200 mL/m^2/hr.

Leucovorin: IV or PO
Begin 24 hours from the start of methotrexate infusion
Dose: 15 mg/m^2/dose every 6 hours until MTX level is < 0.1 µM/L.

IV push or short infusion: Inject by IV push over a minimum of 3 minutes or by short infusion over 15 to 120 minutes. Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL solution per minute). IV leucovorin and sodium bicarbonate are incompatible.

Oral: Administer with or without food. Doses > 25 mg should be given IV due to the saturation of absorption.

If the level does not fall as expected, increase the leucovorin as shown below:

Schedule for calculation of leucovorin rescue based on plasma MTX levels

MTX level µM/L	< 0.1	0.1-2	2-20	20-100	> 100
48 hrs	None	15 mg/m^2 q6 hr	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr
72 hrs	None	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr	1000 mg/m^2 q**3** hr*
96 hrs	None	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr	1000 mg/m^2 q**3** hr*
120 hrs	None	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr	1000 mg/m^2 q**3** hr*

For patients who have markedly delayed MTX clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G2). To obtain supplies of glucarpidase in the US contact the Voraxaze 24-hour Customer Service line at 855-786-7292. Additional information can be found at http://www.btgplc.com/products/specialty-pharmaceuticals/voraxaze regarding product availability through ASD Healthcare, Cardinal, and McKesson. Canadian sites should contact McKesson at (877) 384-7425 for further information. Sites in Australia and New Zealand should contact Hospira at 1300-046-774 (local) or medicalinformationAUS@hospira.com. Patients requiring glucarpidase rescue may remain on study, and may receive further courses of MTX at investigator discretion if renal function is adequate as per parameters above.

Cytarabine: IV over 1 – 30 minutes
Days: 4 and 5
Dose: 150 mg/m^2/dose every 12 hours for a total of 4 doses.

Etoposide: IV over 2 hours
Days: 4 and 5
Dose: 100 mg/m^2/dose once a day

Special precautions: Begin after completion of first cytarabine dose of the day. Infuse diluted solution (concentration ≤ 0.4 mg/mL); slow rate of administration if hypotension occurs. The use of an in-line filter during the infusion is suggested. Etoposide can be mixed in 0.9% NaCl or D5W.

See Section 5.0 for Dose Modifications based on Toxicities.
The therapy delivery maps (TDMs) for Arm CZ Cycles 1, 3, and 5 are on the next page.

4.5.1 Course A (21 days) – Arm CZ (Cycles 1, 3 and 5)

Patient COG ID number _____ DOB _____

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Crizotinib (CRIZ)	PO	165 mg/m^2/dose BID	Days 1-21	See Appendix V for dosing. See Section 4.1.1 for required prophylactic anticoagulation.	a. Hx; Performance Status b. Physical Exam (weekly in cycle 1 then prior to each cycle) c. CBC/diff/plts (weekly) d. Electrolytes (weekly in cycle 1 then prior to each cycle) e. Cr, Bilirubin, AST, ALT f. Urinalysis **g. Blood for MRD (End of Cycle 1 only!)** **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** (See Section 7.1)
Dexamethasone (DEX)	PO	5 mg/m^2/dose BID	Days 1-5	May give IV if unable to take PO.	
Ifosfamide (IFOS)	IV over 60 minutes	800 mg/m^2/dose once a day	Days 1-5	On Day 1 administer prior to MTX. Mesna use as described below.	
Mesna	IV	160 mg/m^2/dose	Days 1-5	At hours 0, 4, and 8 following Ifosfamide daily.	
Methotrexate (MTX)	IV over 3 hours	3000 mg/m^2/dose	Day 1	See Section 4.5 for administration guidelines.	
Leucovorin (LCV)	IV or PO*	15 mg/m^2/dose every 6 hrs	Begin Day 2	See Section 4.5 for administration guidelines. 24 hrs after the START of IV MTX and q6 hours until the MTX level falls below 0.1µM/L. *	
Cytarabine (ARAC)	IV over 1 – 30 minutes	150 mg/m^2/dose every 12 hours	Days 4 & 5	Give over 1 – 30 minutes every 12 hours for total of 4 doses.	
Etoposide (ETOP)	IV over 2 hours	100 mg/m^2/dose once a day	Days 4 & 5	Begin after completion of 1st Cytarabine dose each day.	

*Cycle 1 should begin on Day 6 of the prophase. Cycles 3 and 5 should begin on Day 22 following the previous cycle when peripheral counts have recovered with ANC ≥ 500/mm3 and platelets ≥ 50,000/mm3. This Therapy Delivery Map is on one **(I)** page.*

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2 Growth Factor Used?: Y / N

Date Due	Date Given	Day	CRIZ ___mg ___mg	DEX ___mg ___mg	IFOS ___mg	Mesna ___mg/ day	MTX ___mg	LCV __mg	ARAC ___mg ___mg	ETOP ___mg	Studies	Comment
			Enter calculated dose above and actual dose administered below.									
		1	___mg ___mg	___mg ___mg	____mg	____mg/day	____mg				a-f	
		2	___mg ___mg	___mg ___mg	____mg	____mg/day		___*				
		3	___mg ___mg	___mg ___mg	____mg	____mg/day						
		4	___mg ___mg	___mg ___mg	____mg	____mg/day			___mg ___mg	___mg		
		5	___mg ___mg	___mg ___mg	____mg	____mg/day			___mg ___mg	___mg		
		6	___mg ___mg									
		7	___mg ___mg									
		8	___mg ___mg								a,b,c,d#	
		9	___mg ___mg									
		10	___mg ___mg									
		11	___mg ___mg									
		12	___mg ___mg									
		13	___mg ___mg									
		14	___mg ___mg									
		15	___mg ___mg								a,b,c,d#	
		16	___mg ___mg									
		17	___mg ___mg									
		18	___mg ___mg									
		19	___mg ___mg									
		20	___mg ___mg									
		21	___mg ___mg									
		22	**Begin next cycle on Day 22 of the previous cycle when peripheral counts have recovered with ANC ≥ 500/mm^3 and platelets ≥ 50,000/mm^3 (whichever occurs later).**								a,b, c,d#,**g**	

* Please document the number of doses of Leucovorin administered. See Section 5.0 for Dose Modifications for Toxicities and the COG website posted materials for Supportive Care Guidelines. # Physical Exam and Electrolytes are weekly in Cycle 1 only, then prior to each cycle.

4.6 Course B (21 days) – Arm CZ (Cycles 2, 4 and 6)

Prophylactic anticoagulation is required for all patients on Arm CZ starting with the first dose of crizotinib. See Sections 2.6 and 4.1.1 for detail.

Peripheral blood for MDD/MRD should be drawn prior to beginning Cycle 2. (Time point #3)

Each cycle should begin on Day 22 of the previous cycle when peripheral counts have recovered with ANC $\geq 500/mm^3$ and platelets $\geq 50{,}000/mm^3$ (whichever occurs later). Therapy may be delayed for severe complication.

The use of growth factors should be noted if they are administered.

Crizotinib: PO BID
Day: 1-21
Dose: 165 mg/m^2/dose (Refer to Appendix V for dosing nomogram.)

For patients receiving crizotinib, the capsules should not be opened and must be swallowed whole. If a dose is missed or forgotten at the due time, it can be taken up to (but not greater than) 6 hours later to help prevent missed doses. If a patient vomits after a dose, it should not be repeated. See Section 6.2 regarding administration instructions. Refer to the dosing nomogram in Appendix V for correct dose group. Drug doses should be adjusted based on the BSA determined based on height and weight obtained within one week prior to the beginning of each cycle.

Dexamethasone: PO (may administer IV if patient unable to take oral medications)
Days 1-5
Dose: 5 mg/m^2/dose BID on Days 1-5.

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation may be used temporarily as needed.

Cyclophosphamide: IV over 15 - 30 minutes
Days 1-5
Dose: 200 mg/m^2/dose. Give prior to methotrexate on Day 1.

May be administered with or without further dilution. To avoid hypotonic solution, reconstitute Cyclophosphamide with 0.9% NaCl to a final concentration of 20 mg/mL

Hydration: Patient will receive hydration for methotrexate. Following clearance of the methotrexate, patient should receive IV or oral fluids at a rate of 3000 mL/m^2/day until 12 hours after the last dose of cyclophosphamide.

Methotrexate: IV over 3 hours
Day 1
Dose: 3000 mg/m^2/dose.

HD MTX Infusion Guidelines
Methotrexate should be given on Day 1 after Day 1 cyclophosphamide dose and when urine parameters are met.

Hold trimethoprim/sulfamethoxazole (TMP-SMX) and any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.1 µM/L.

Suggested hydration: Prehydrate with D5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour for a minimum of 2 hours and until urine output is > 100 mL/m^2/hour and pH is ≥ 7.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine output and pH at above parameters. A bicarbonate bolus (25 mEq/m^2 over 15 minutes) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration. Continue hydration and alkalinization throughout MTX infusion until level is < 0.1 µM/L (hydrate for a minimum of 48 hours after MTX completion). Sodium bicarbonate is incompatible with many medications; infuse via separate line or lumen unless compatibility is known.

Methotrexate levels: Hours 24, 48 and at least every 24 hours until level is < 0.1 µM/L: Draw MTX level and serum creatinine.

For SCr > 125% of baseline or for MTX levels exceeding 50 µM/L at 24 hours or desired levels at any other time point, increase hydration to 200 mL/m^2/hr.

Leucovorin: IV or PO
Begin 24 hours from the start of methotrexate infusion
Dose: 15 mg/m^2/dose every 6 hours until MTX level is < 0.1 µM/L.

IV push or short infusion: Inject by IV push over a minimum of 3 minutes or by short infusion over 15 to 120 minutes. Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL solution per minute). IV leucovorin and sodium bicarbonate are incompatible.

Oral: Administer with or without food. Doses > 25 mg should be given IV due to the saturation of absorption.

If the level does not fall as expected, increase the leucovorin as shown below:

Schedule for calculation of leucovorin rescue based on plasma MTX levels

MTX level µM/L	< 0.1	0.1-2	2-20	20-100	> 100
48 hrs	None	15 mg/m^2 q6 hr	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr
72 hrs	None	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr	1000 mg/m^2 q**3** hr*
96 hrs	None	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr	1000 mg/m^2 q**3** hr*
120 hrs	None	15 mg/m^2 q6 hr	10 mg/m^2 q**3** hr	100 mg/m^2 q**3** hr	1000 mg/m^2 q**3** hr*

For patients who have markedly delayed MTX clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G2). To obtain supplies of glucarpidase in the US contact the Voraxaze 24-hour Customer Service line at 855-786-7292. Additional information can be found at http://www.btgplc.com/products/specialty-pharmaceuticals/voraxaze regarding product availability through ASD Healthcare, Cardinal, and McKesson. Canadian sites should contact McKesson at (877) 384-7425 for further information. Sites in Australia and New Zealand should contact Hospira at 1300-046-774 (local) or medicalinformationAUS@hospira.com. Patients requiring glucarpidase rescue may remain on study, and may receive further courses of MTX at investigator discretion if renal function is adequate as per parameters above.

DOXOrubicin: IV over 1-15 minutes
Days: 4 and 5
Dose: 25 mg/m^2/dose.

Administer at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 15 minutes. Infusion times may be lengthened slightly (up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D5W or 0.9% NaCl and that it is infused into a large vein or central venous access device.

Special precautions: Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. The conventional and liposomal formulations are NOT interchangeable.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery maps (TDMs) for Arm CZ Cycles 2, 4, and 6 are on the next page.

Please refer to Section 7.0 for required observations.

4.6.1 Course B (21 days) – Arm CZ (Cycles 2, 4 & 6)

_____ Patient COG ID number _____ DOB

Each cycle should begin on Day 22 following the previous cycle when peripheral counts have recovered with ANC ≥ 500/mm^3 and platelets ≥ 50,000/mm^3. This Therapy Delivery Map is on one **(1)** page.

DRUG	ROUTE	DOSAGE	DAYS	NOTES	OBSERVATIONS
Crizotinib (CRIZ)	PO	165 mg/m^2/dose BID	Days 1-21	See Appendix V for dosing. See Section 4.1.1 for required prophylactic anticoagulation.	a. Physical Exam (weekly for Cycle 2, then prior to each cycle) b. Hx, Performance Status (prior to each cycle) c. CBC/diff/plts (weekly) d. Electrolytes including Ca++, PO_4, Mg++ (weekly for Cycle 2, then prior to each cycle) e. Creatinine, Bilirubin, LFTs (prior to each cycle) f. CXR(PA + Lateral), CT or MRI, Bone Scan (for bone primary disease only), FDG-PET Scan (recommended-not mandatory)^ g. Urinalysis (prior to each cycle) h. BM Aspirate/Biopsy (Bilateral) # i. Echo/EKG (prior to Cycles 4 and 6 only) ^All sites of disease should be evaluated after Cycle 2 and after Cycle 4 if not in CR or CRU after Cycle 2. #After Cycle 2, if positive at diagnosis **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** (See Section 7.1)
Dexamethasone (DEX)	PO	5 mg/m^2/dose BID	Days 1-5	May give IV if unable to take PO.	
Cyclophosphamide (CPM)	IV over 15 - 30 minutes	200 mg/m^2/dose	Days 1-5	Give prior to MTX on Day 1.	
Methotrexate (MTX)	IV over 3 hours	3000 mg/m^2/dose	Day 1	See Section 4.6 for administration guidelines.	
Leucovorin (LCV)	IV or PO*	15 mg/m^2/dose every 6 hrs	Day 2	See Section 4.6 for administration guidelines. 24 hrs after the START of IV MTX and q6 hours until the MTX level falls below 0.1µM/L.	
DOXOrubicin (DOXO)	IV over 1-15 minutes	25 mg/m^2/dose	Days 4 & 5		

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2 Growth Factor Used? Y / N

Date Due	Date Given	Day	CRIZ ___mg ___mg	DEX ___mg ___mg	CPM ___mg	MTX ___mg	LCV ___mg	DOXO ___mg	Studies	Comment
Enter calculated dose above and actual dose administered below.										
		1	___mg ___mg	___mg ___mg	___mg	___mg			a-e, g and i	
		2	___mg ___mg	___mg ___mg	___mg		___*			
		3	___mg ___mg	___mg ___mg	___mg					
		4	___mg ___mg	___mg ___mg	___mg			___mg		
		5	___mg ___mg	___mg ___mg	___mg			___mg		
		6	___mg ___mg							
		7	___mg ___mg							
		8	___mg ___mg						a,c,d$	
		9	___mg ___mg							
		10	___mg ___mg							
		11	___mg ___mg							
		12	___mg ___mg							
		13	___mg ___mg							
		14	___mg ___mg							
		15	___mg ___mg						a,c,d$	
		16	___mg ___mg							
		17	___mg ___mg							
		18	___mg ___mg							
		19	___mg ___mg							
		20	___mg ___mg							
		21	___mg ___mg						a,c,d$, f^,h#	
		22		**Each cycle should begin on Day 22 of the previous cycle when peripheral counts have recovered with ANC ≥ 500/mm^3 and platelets ≥ 50,000/mm^3 (whichever occurs later)**						
				For end of therapy (end of Cycle 6) studies, see Section 7.1 for complete list.						

* Please document the number of doses of Leucovorin administered. See Section 5.0 for Dose Modifications for Toxicities and the COG website posted materials for Supportive Care Guidelines.

$ Physical Exam and Electrolytes are weekly in Cycle 1 only, then prior to each cycle.

^ All sites of disease should be evaluated after Cycle 2 and after Cycle 4 if not in CR or CRU after Cycle 2.

After Cycle 2, if positive at diagnosis.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

The Study Chair must be notified of any dosage modification. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for grading and reporting adverse events.

5.1 Brentuximab vedotin (SGN-35)

5.1.1 Suggested Dose Modifications/Delays guidelines

Intrapatient Dose Reductions for Starting Dose of 1.8 mg/kg Every 3 Weeks
Treatment Modification Guidelines for SGN-35 Related Adverse Events

Dose Level	Dose
Starting Dose	1.8mg/kg (max dose 180 mg)
Dose Reduction #1	1.2 mg/kg (max dose 120 mg)
Dose Reduction #2	0.8 mg/kg (max dose 80 mg)

Event	CTCAE.v4.0 Grade	Action to be Taken
Allergic reactions, or Acute infusional reactions/ cytokine release syndrome	Grade 1-2	For first reaction: • Hold the infusion and wait 30 to 60 minutes (depending upon the reaction severity). • Treat reactions with diphenhydramine 1 mg/kg (max 50 mg), or follow local institution guidelines. Depending on the reaction severity, dexamethasone 0.2 mg/kg (max 10 mg) IV should be used. • Upon resolution of the symptoms, at the physician's discretion, it may be possible to resume treatment by administering an H2 blocker approximately 30 minutes before restarting the infusion. Acetaminophen can also be considered. Dosing of SGN-35 should be administered at half of the previously administered rate. For subsequent doses: • Utilize diphenhydramine with or without acetaminophen as pre-treatment for all subsequent infusions. • Dosing should be administered over the shortest period that was well tolerated. If Grade 1-2 infusion reactions recur despite the above measures, either during re-challenge or subsequent treatments: • Take the measures outlined above. • With subsequent dosing, add dexamethasone 0.2 mg/kg (max 10 mg) IV or equivalent to medications above prior to infusion.

Event	CTCAE.v4.0 Grade	Action to be Taken
	Grade 3	• Stop infusion immediately. • Administer diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated. • Once symptoms recover, brentuximab vedotin should not be resumed for that course. • Subsequent courses of brentuximab vedotin may be considered at physicians' discretion, after a discussion and approval by CTEP. • All subsequent infusions should use the following premedications prior to infusion, diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent). In addition, the infusion should be administered at 50% of the previous infusion rate.
	Grade 4	• Stop infusion immediately. • Administer diphenhydramine hydrochloride 1 mg/kg (max 50 mg) IV, dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), and other anaphylaxis medications as indicated. • Epinephrine or bronchodilators should be administered as indicated. • Hospital admission for observation may be indicated. • Discontinue SGN-35.
Anaphylaxis	Any Grade	• If anaphylaxis occurs, immediately and permanently discontinue administration of SGN-35 and administer appropriate medical therapy.
Pancreatitis	Grade 2	• Withhold dose until toxicity has returned to baseline, then continue on protocol therapy but should resume at one dose reduction. • If Grade 2 pancreatitis recurs after one dose reduction, the patient must be removed from protocol therapy.
	Grade 3-4	• Permanently discontinue brentuximab vedotin.
Peripheral Neuropathy	Grade 1	• Continue at same dose level.
	Grade 2	• Reduce dose by one level and continue treatment. If already dose reduced previously then continue dosing at that level.
	Grade 3	• Treatment should be delayed up to 1 week after all other parameters to proceed are met to see if neuropathy improves to ≤ Grade 2. If neuropathy returns to ≤ Grade 2 then proceed with next treatment reduced by one dose level. If neuropathy remains Grade 3 then SGN-35 should be held and then reduced by one dose level for subsequent treatments assuming neuropathy has returned to ≤ Grade 2. • Patients who develop Grade 3 neuropathy after dose reduction of SGN-35 will have SGN-35 discontinued
	Grade 4	• Discontinue SGN-35.

Event	CTCAE.v4.0 Grade	Action to be Taken
Pneumonitis	Grade 1	• Continue at same dose level.
	Grade 2	• If suspected, strongly consider administration of 100 mg of oral or intravenous prednisolone in single daily or two divided doses. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. • Upon occurrence of pneumonitis, study therapy should be held, and the Study Chair and Research Coordinator should be notified within 48 hours. • CTEP must be notified within 7 days of study chair notification of each instance of Grade 2 pneumonitis. The Study Chair and CTEP will review the history of the affected patient and the pulmonary toxicity for the trial as a whole before proceeding with the recommendation to resume protocol therapy at a lower dose level. Failure to discuss a case of pulmonary toxicity will lead to suspension of accrual.
	Grade 3-4	• If suspected, strongly consider administration of 100 mg of oral or intravenous prednisolone in single daily or two divided doses. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. • Discontinue brentuximab vedotin. • The Study Chair and Research Coordinator should be notified within 48 hours. • **CTEP must be notified within 7 days of the notification of the Study Chair.**
Progressive Multifocal Leukoencephalopathy (PML)	Any Grade	If PML is suspected, a diagnostic work-up should be performed. The work-up may include, but is not limited to the following: • Neurologic examinations and neurology consultation, as warranted. • Brain MRI. Features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, which are typically non-enhancing and do not have mass effect. • PCR analysis. JCV DNA, detectable in CSF or in a brain biopsy, is suggestive of PML. Brentuximab vedotin dosing should be held if PML is suspected. If PML is confirmed, brentuximab vedotin should be permanently discontinued.
Lymphopenia	Grade 1-4	• Continue at same dose level.
Neutropenia	Grade 1-2	• Continue at same dose level.
	Grade 3-4	• Neutropenia is to be expected on this protocol. Patients who are unable to start a cycle > 35 days after the start of the previous cycle (>14 day delay) due to neutropenia with no other dose-limiting toxicity should receive the same dose in the next cycle with myeloid growth factor support. • Patients who are unable to start a cycle > 35 days after the start of the previous cycle (>14 day delay) with myeloid growth factor support due to neutropenia with no other dose-limiting toxicity should have SGN-35 reduced by 1 dose level.

Event	CTCAE.v4.0 Grade	Action to be Taken
Thrombocytopenia	Grade 1-2	• Continue at same dose level.
	Grade 3-4	• Thrombocytopenia is expected on this protocol. Continue at current dose level.
Non-hematologic events (except electrolyte abnormalities and those noted elsewhere in table) that are probably or definitely related	Grade 1-2	• Continue at same dose level.
	Grade 3-4	• Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then continue on protocol therapy but should resume at one dose reduction. • If same non-hematological Grade 3-4 toxicity recurs after one dose reduction, SGN-35 should be omitted.
Electrolyte Abnormalities	Grade 1-4	• Continue at same dose level, provided electrolyte toxicity is not medically consequential and has been readily corrected. • If electrolyte abnormality is medically consequential, refer to guidelines above for non-hematologic events.
Renal Impairment		• Omit for patients with severe renal impairment (CLcr < 30mL/min)
Mucositis	Grade 1-3	• Continues at same dose level
	Grade 4	• Withold drug until toxicity is ≤ Grade 2, then resume treatment reduced by one dose level

5.2 Crizotinib

5.2.1 Hematological Toxicity

Patients who are unable to start a cycle > 35 days after the start of the previous cycle (> 14 day delay) due to neutropenia with no other dose-limiting toxicity should receive the same dose in the next cycle with myeloid growth factor support.

Patients who are unable to start a cycle > 35 days after the start of the previous cycle (> 14 day delay) with myeloid growth factor support due to neutropenia with no other dose-limiting toxicity should have crizotinib reduced by 1 dose level.

5.2.2 Therapy Delay

Crizotinib should only be given for 21 days each cycle. If the next cycle is delayed due to other reasons, crizotinib should not be given until the next cycle is started.

5.2.3 Hepatic Toxicity

Patients are expected to have temporary increases in liver enzymes secondary to other chemotherapeutic agents.

Patients with Grade 3-4 liver enzyme elevation, including ALT/AST/GGT, will have crizotinib held until levels recover to ≤ Grade 1 (< 2.5 X ULN) or baseline. See below table for adjustments.

5.2.4 Renal Cyst

The development of complex renal cysts has been reported in some patients with NSCLC treated with crizotinib. These cysts may be symptomatic or asymptomatic, and have usually developed within the first several months of starting crizotinib. The precise nature and significance of these cysts is unclear; however, while no

evidence of malignancy has been found based on aspiration of cyst fluid and biopsy in the reported cases, complex renal cysts may be associated with renal malignancy, and thus consultation with an urologist or suitable alternate medical expert is recommended. Monitoring of complex renal cysts with appropriate imaging should be performed as scheduled per protocol with contrast-enhanced CT scanning or magnetic resonance imagining assuring full visualization of the kidneys.

Event	CTCAE.v4.0 Grade	Action to be Taken
Hepatic toxicity: Increased ALT	Grades 3 – 4	Patients with Grade 3-4 liver enzyme elevation, including ALT/AST/GGT, will have crizotinib held until levels recover to ≤ Grade 1 (< 2.5 X ULN) or baseline. • If levels recover within 7 days of study drug interruption, this is not considered dose limiting and crizotinib will be continued at the same dose. • If levels recover > 7 days after interruption of study drug but < 21 days from the planned start of the next cycle, the patient may continue on protocol therapy but should receive subsequent doses of crizotinib at the next lower dose level (see Appendix V and reduce by one dose group). • If levels do not meet criteria within 21 days after the planned start of the next treatment cycle, this is a DLT and the patient should not receive any further crizotinib.
Left ventricular systolic dysfunction	Grades 1 – 2	• Continue at the same dose level.
	Grades 3 – 4	• Discontinue treatment and do not retreat.
Pneumonitis (in absence of disease progression in the lung, infection, other pulmonary disease, or radiation effect)	Grade 1	• Continue at the same dose level.
	Grade 2	• If suspected, strongly consider administration of 100 mg of oral or intravenous prednisolone in single daily or two divided doses. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. • Upon occurrence of pneumonitis, study therapy should be held, and the Study Chair and Research Coordinator should be notified within 48 hours. • **CTEP must be notified within 7 days of study chair notification of each instance of Grade 2 pneumonitis. The Study Chair and CTEP will review the history of the affected patient and the pulmonary toxicity for the trial as a whole before proceeding with the recommendation to resume protocol therapy at a lower dose level. Failure to discuss a case of pulmonary toxicity will lead to suspension of accrual.**

Event	CTCAE.v4.0 Grade	Action to be Taken
	Grades 3 – 4	• If suspected, strongly consider administration of 100 mg of oral or intravenous prednisolone in single daily or two divided doses. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. • Discontinue crizotinib and do not retreat. • The Study Chair and Research Coordinator should be notified within 48 hours. • **CTEP must be notified within 7 days of the notification of the Study Chair.**
Prolonged QTc interval (as confirmed by a cardiologist at the site)	Grade 1	• Continue at the same dose level.
	Grade 2	• Continue at the same dose level. Assess electrolytes (particularly Ca++, K+, Mg+) and concomitant medications • Correct any electrolyte abnormalities.
	Grade 3	• Withhold current dose until recovery to Grade ≤1. Assess and correct electrolytes (particularly Ca++, K+, Mg+) and concomitant medications. Upon recovery to Grade ≤1, resume treatment by reducing the dose by 1 dose level if no other cause for QTc prolongation is found, otherwise resume at the same dose.
	Grade 4	• Discontinue treatment and do not retreat.
Thromboembolic Events	Grade 1	• Continue at same dose level.
	Grades 2-3	• Crizotinib should be held at least 1 week and up to 2 weeks. If the thrombosis is considered controlled on anticoagulation and the patient is able to proceed with chemotherapy then proceed with treatment reduced by one dose level. If after 2 weeks patient still has clinical symptoms from the event, then crizotinib should be discontinued permanently. • Patients who develop a subsequent Grade 2-4 event after dose reduction will have crizotinib discontinued permanently.
	Grade 4	• Discontinue crizotinib treatment permanently.
Non-hematologic events (except electrolyte abnormalities and those noted elsewhere in table) that are probably or definitely related	Grades 1 – 2	• Continue at same dose level.
	Grades 3 – 4	• Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then continue on protocol therapy but should receive subsequent doses of crizotinib at the next lower dose level (see Appendix V and reduce by one dose group). • If same non-hematological Grade 3-4 toxicity recurs after one dose reduction (as stated above), crizotinib should be omitted.
Visual Disturbance	Grades 1-2	• Continue at the same dose level. Repeat Ophthalmologic examination.
	Grade 3	• Interrupt crizotinib until recovery. Repeat ophthalmologic examination[+]. Resume treatment by reducing by one dose level.
	Grade 4	• Discontinue treatment and do not retreat. Repeat ophthalmologic examination[+].

Event	CTCAE.v4.0 Grade	Action to be Taken
Mucositis	Grade 1-3	• Continues at same dose level
	Grade 4	• Withold drug until toxicity is ≤ Grade 2, then resume treatment reduced by one dose level

5.3 Cyclophosphamide

5.3.1 Hematuria

Omit in the presence of macroscopic hematuria. If there is a history of previous significant hematuria, hydrate before cyclophosphamide until specific gravity is < 1.010 and hydrate at 125 mL/m^2/hr for 24 hours after dose. If mesna was initially given in 3 separate boluses, change administration to continuous IV infusion. The continuous infusion should be started 15-30 minutes before or at the same time as cyclophosphamide and finished no sooner than 8 hours after the end of cyclophosphamide infusion. If the patient develops hematuria while receiving mesna continuous IV infusion at 60% dosing, increase mesna dosing to 100% of the cyclophosphamide dose. If hematuria persists with 100% mesna administration by continuous infusion, omit remaining doses during that cycle.

5.3.2 Renal Dysfunction

If creatinine clearance or radioisotope GFR is < 10 mL/min/1.73 m^2, reduce dose of cyclophosphamide by 50%. Prior to dose adjustment of cyclophosphamide, the creatinine clearance should be repeated with good hydration.

5.4 Dexamethasone

5.4.1 Hypertension

Dose should not be reduced. Sodium restriction and anti-hypertensives should be employed in an effort to control hypertension. Avoid calcium channel blockers due to their potential prohemorrhagic effect.

5.4.2 Hyperglycemia

Dose should not be reduced for hyperglycemia. Rather, insulin therapy should be employed to control the blood glucose level.

5.4.3 Pancreatitis

Do not modify dose for asymptomatic elevations of amylase and/or lipase. Discontinue steroids, except for stress doses, in the presence of hemorrhagic pancreatitis or severe pancreatitis.

5.4.4 Varicella

Steroids should be held during active infection except during Cycles 1 and 2. Do not hold during incubation period following exposure.

5.4.5 Inability to use oral doses

For dexamethasone, substitute the IV preparation mg for mg.

5.5 Doxorubicin

5.5.1 Cardiac Toxicity
If prolongation of the QTc interval (> 0.48 sec.), or a decrease in the shortening fraction to < 27% is observed, the doxorubicin-containing chemotherapy should be postponed 1 week, any existing malnutrition corrected and the tests repeated. If the abnormalities persist, doxorubicin should be discontinued.

5.5.2 Hyperbilirubinemia
If direct bilirubin is between 1.2 mg/dL and 3 mg/dL, give 50% of the dose, if between 3.1 mg/dL and 5 mg/dL, give 25% of the dose, and if > 5 mg/dL omit dose.

5.5.3 Mucositis
If patient has severe infection or severe mucositis (Grade 3-4), may delay start of cycle. Doses should be given at full dose.

5.6 Etoposide

5.6.1 Allergic Reaction
Premedicate with diphenhydramine (1-2 mg/kg slow IV push, maximum dose is 50 mg; if unavailable, other H1 antagonists may be used as appropriate). If symptoms persist, add hydrocortisone 100-300 mg/m^2. Continue to use premedication before etoposide in the future. Also consider substituting an equimolar amount of etoposide phosphate, in the face of significant allergy and/or hypotension. Etoposide phosphate is a water soluble prodrug that does not contain polysorbate 80 and polyethyleneglycol, the solubilizing agent in etoposide that may induce allergic reactions and hypotension. Etoposide phosphate is rapidly converted to etoposide in vivo and provides total drug exposure, as represented by AUC (0-infinity) that is statistically indistinguishable from that measured for etoposide at equimolar doses.

5.6.2 Hypotension
If diastolic or systolic blood pressure (BP) falls 20 mm Hg during infusion, reduce infusion rate by 50%. Start a simultaneous infusion of NS 10 mL/kg if BP fails to recover or falls further. Stop infusion if BP does not recover, continue NS. If the patient has had any episode of hypotension, prehydrate with 0.9% NaCl at 10 mL/kg/hr for 2 hours prior to any subsequent infusion.

5.6.3 Renal Insufficiency
If renal function decreases, adjust etoposide as follows: CrCl/GFR 10-50 mL/min/1.73 m^2, decrease dose by 25%; if CrCl/GFR < 10 mL/min/1.73 m^2, decrease dose by 50%.

5.6.4 Hyperbilirubinemia
If direct bilirubin is > 2 mg/dL, decrease dose by 50%. If direct bilirubin is > 5 mg/dL, hold etoposide.

5.7 Ifosfamide

5.7.1 Hematuria

Omit in the presence of macroscopic hematuria. If there is a history of previous significant hematuria, hydrate before ifosfamide until specific gravity is < 1.010 and hydrate at 125 mL/m^2/hr for 24 hours after dose. If mesna was initially given in 3 separate boluses, change administration to continuous IV infusion. The continuous infusion should be started 15-30 minutes before or at the same time as ifosfamide and finished no sooner than 8 hours after the end of ifosfamide infusion. If the patient develops hematuria while receiving mesna continuous IV infusion at 60% dosing, increase mesna dosing to 100% of the ifosfamide dose. If hematuria persists with 100% mesna administration by continuous infusion, omit remaining doses during that cycle.

5.7.2 Neurotoxicity

This is an organic brain syndrome, manifestations of which range from mild confusion and disorientation to seizures, ataxia, and coma. It may be aggravated by impaired renal function, low serum albumin and possibly other conditions such as large tumor burden in the pelvis, short infusion times, or prior CNS disease. It usually, but does not always, resolve spontaneously; it may or may not recur with subsequent doses. Methylene blue has been reported to reverse the ifosfamide-related-encephalopathy syndrome in some, but not all, patients. If other causes for the neurological symptoms have been ruled out and Grade III or greater neurotoxicity is present, methylene blue may be administered until symptoms improve. Since ifosfamide-induced neurotoxicity may not recur, ifosfamide therapy may be continued with the next scheduled cycle.

5.7.3 Nephrotoxicity

If estimated CrCl/GFR is < 50 mL/min/1.73 m^2 and the patient is well-hydrated, defer ifosfamide containing chemotherapy for 1 week. If after a 1 week delay the estimated CrCl/GFR is still < 50 mL/min/1.73 m^2 (in a well-hydrated patient), hold ifosfamide. Estimated creatinine clearance should be repeated with good hydration. A timed, 24 hour urine collection for creatinine clearance or radionuclide GFR should be performed to confirm renal dysfunction

5.8 Methotrexate

5.8.1 Nephrotoxicity

For patients with CrCl/GFR < 60 mL/min/1.73 m^2, delay further courses of methotrexate until CrCl/GFR ≥ 60 mL/min/1.73 m^2.

5.8.2 Hepatic Toxicity

ALT or AST < 20 times normal give full dose. ALT or AST ≥ 20 times normal of upper limits, check every 48 hours until < 10 times normal, then give full dose. If not recovered by 1 week after cycle is due, hold methotrexate.

6.0 DRUG INFORMATION

Please see Appendix VI for drug interactions associated with the drugs used in this study.

6.1 Brentuximab vedotin 11/09/15

(SGN35, AdcetrisTM, NSC#749710)

6.1.1 Structure and molecular weight

Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC) consisting of three components: the chimeric IgG1 antibody cAC10, specific for human CD30, the microtubule disrupting agent MMAE, and a protease-cleavable linker that covalently attaches MMAE to cAC10. Approximately 4 molecules of MMAE are attached to each antibody molecule. Brentuximab vedotin is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells, and the small molecule components are produced by chemical synthesis. Brentuximab vedotin has an approximate molecular weight of 153 kDa.

6.1.2 Supplied by

Seattle Genetics, Inc. and the Division of Cancer Treatment and Diagnosis (DCTD), NCI. **Do NOT use commercial supply.**

6.1.3 Formulation

The agent is supplied as a sterile, white to off-white preservative-free lyophilized cake or powder in individually-boxed single-use vials containing 50 mg brentuximab vedotin per vial.

6.1.4 Storage

Store vial dry under refrigeration at 2-8°C (36-46°F) in the original carton to protect from light until reconstitution and use.

6.1.5 Solution Preparation

Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.

Please note that the dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

Preparation consists of 2 steps: dilution of the stock solution and dilution of the final solution.

Step 1: **Make a 5 mg/mL concentration**. **Use vials from the same Lot number for each dose**.

1. Reconstitute the 50 mg lyophilized powder brentuximab vedotin with 10.5 mL Sterile Water for Injection, USP. Final concentration is 5 mg/mL (Note: total volume is 11 mL).
2. Swirl the vial gently. Do not shake.
3. Let the reconstituted vial settle for one minute to eliminate bubbles. The reconstituted solution should be colorless, clear to slightly opalescent and should NOT have visible particulates.

4. Store the reconstituted vial under refrigeration (2° – 8° C) and protect from light if not used immediately. Discard after 8 hours.

Step 2: **Further dilute the IV solution**.

1. Withdraw the calculated amount of drug from the 5 mg/mL reconstituted vial in step 1.
2. Inject the required amount of drug into 0.9% NS, Lactated Ringer's Solution, USP, or dextrose 5% in Water (D5W), USP to a final concentration between **0.4 – 1.8 mg/mL**.
3. Brentuximab vedotin solution is compatible in polyvinylchloride (PVC), ethylene vinyl acetate (EVA), polyolefin, or polyethylene.
4. Do not shake. Gently invert the bag (or syringe) to mix.
5. The prepared IV bag (or syringe) is to be stored at refrigeration (2° – 8° C) and must be used within 24 hours of initial product reconstitution (or sooner per institutional practice for agents without a preservative). Protect the prepared IV solution from direct sunlight if not used immediately.
6. Prior to administration, inspect the IV bag (or syringe) for discoloration or floating particulates. Do not use the IV solution if the solution is discolored or/and have particulates.

6.1.6 Stability

The stability testing of the intact vials is ongoing. Reconstituted agent must be diluted and administered within 24 hours.

CAUTION: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, the reconstituted product (from Step 1) should be discarded within 8 hours after initial entry/puncture.

6.1.7 Administration

Infuse the prepared IV solution over 30 minutes. Do not mix with other medications. Do not administer as an IV push or bolus. Do not use an in-line filter for the IV administration. The IV bag (or syringe) does NOT need light protection during the IV administration.

6.1.8 Potential drug interactions:

In vitro data indicates that the active metabolite of brentuximab vedotin, monomethyl auristatin E (MMAE) is a substrate and an inhibitor of CYP3A4 but is neither a sensitive substrate nor a strong inhibitor/inducer of CYP3A4. However, patients should be monitored for potential drug-interaction when administered drugs known to be a strong CYP 3A4 inhibitor/inducer with brentuximab vedotin. In vitro, MMAE is a substrate of P-gp transporter and is not an inhibitor of P-gp. See Appendix IV for a list of CYP3A4 inducers and inhibitors.

6.1.9 Patient Care Implications

- New signs and symptoms of CNS system abnormalities may indicate progressive multifocal leukoencephalopathy (PML).
- Tumor lysis syndrome, particularly in patients with highly proliferative tumors or high tumor burden prior to treatment.
- Infusion-related reactions, including anaphylaxis, may occur.
- Signs and symptoms of peripheral neuropathy may include tingling or numbness of the hands, feet, or any muscles weakness.
- Steven-Johnson syndrome.
- High fever (≥ 100.5° F) or other signs of potential infection.

6.1.10 Toxicity

Comprehensive Adverse Events and Potential Risks list (CAEPR) for SGN-35 (brentuximab vedotin, NSC 749710)

The arm using SGN-35 (brentuximab vedotin, NSC 749710) is closed to accrual and treatment. The CAEPR is no longer being updated.

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 555 patients.* Below is the CAEPR for SGN-35 (brentuximab vedotin).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, October 2, 2015[1]

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 4.0 Term) [n= 555]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 4.0 Term) [n= 555]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Blood and lymphatic system disorders - Other (lymphadenopathy)		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		
Nausea			***Nausea (Gr 2)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
	Edema limbs		
Fatigue			***Fatigue (Gr 2)***
Fever			***Fever (Gr 2)***
	Pain		
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (hepatotoxicity)[2]	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infections and infestations - Other (herpes zoster)		
	Lung infection		
Upper respiratory infection			***Upper respiratory infection (Gr 2)***
INVESTIGATIONS			
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		
	Weight loss		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Bone pain		
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 2)***

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 4.0 Term) [n= 555]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy)	
	Paresthesia		
	Peripheral motor neuropathy		***Peripheral motor neuropathy (Gr 2)***
Peripheral sensory neuropathy			***Peripheral sensory neuropathy (Gr 2)***
PSYCHIATRIC DISORDERS			
	Anxiety		
	Depression		
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
		Respiratory, thoracic and mediastinal disorders - Other (pulmonary toxicity)[3]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		
	Hyperhidrosis		
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Hepatotoxicity may manifest as increased ALT/AST, bilirubin, alkaline phosphatase, and/or GGT.

[3]Pulmonary toxicity, which may manifest as pneumonitis, interstitial lung disease, or adult respiratory distress syndrome (ARDS), has been observed in patients treated in brentuximab vedotin monotherapy trials as well as in combination with bleomycin.

Adverse Events also reported on SGN-35 (brentuximab vedotin) trials but for which there is insufficient evidence to suggest that there was a reasonable possibility that SGN-35 (brentuximab vedotin) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Myocardial infarction; Pericardial effusion; Sinus tachycardia
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Infusion related reaction; Non-cardiac chest pain
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (oral candidiasis); Meningitis; Pharyngitis; Sepsis; Sinusitis; Skin infection; Urinary tract infection
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Investigations - Other (blood LDH increased); Lymphocyte count decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia;

Hypocalcemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness; Myositis; Neck pain
NEOPLASMS BENIGN, MALIGNANT, AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Myelodysplastic syndrome
NERVOUS SYSTEM DISORDERS - Dysesthesia; Encephalopathy; Seizure; Syncope
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (pyelonephritis)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (groin pain)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome[3]; Pleural effusion[3]; Pneumothorax[3]; Productive cough; Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain)
VASCULAR DISORDERS - Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: SGN-35 (brentuximab vedotin) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

6.1.11 Clinical Drug Request

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application at https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email pmbafterhours@mail.nih.gov anytime.

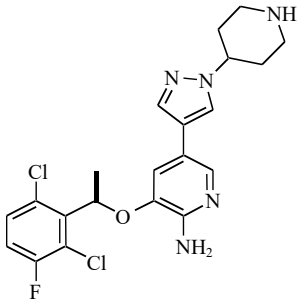
6.1.12 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record (DAR) Form. (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form).

6.2 Crizotinib **01/23/2019**
(XALKORI®, PF-02341066, PF-02341066-004) NSC# 749005)

6.2.1 Structure and molecular weight
The chemical name for the drug substance is (*R*)-3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(1-piperidin-4-yl-1*H*-pyrazol-4-yl)-pyridin-2-ylamine.

The structure of crizotinib is shown in the diagram below:



Molecular Weight: 450.34 Daltons

6.2.2 Supplied by
For US sites: Division of Cancer Treatment and Diagnosis (DCTD), NCI. Do NOT use commercial supply.

6.2.3 Formulation
Capsules will be used in this study. The capsules are available in strengths of 200 mg and 250 mg.

6.2.4 Storage
The capsules should be stored according to labeled conditions. Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned medication should be stored separately from medication that needs to be dispensed.

6.2.5 Handling
Crizotinib must be handled and administered with care.

To minimize exposure, patients should be instructed to keep their medication in the bottles provided to them by the study site. Bottles dispensed by the study site should be labeled in accordance with the appropriate regulatory requirements. Study site staff should provide guidance to patients and/or patient caregivers on safe handling practices.

6.2.6 Stability
Crizotinib should be stored according to the labeled conditions. To minimize exposure, patients should be instructed to keep their medication in its original container and stored according to the labeled conditions.

6.2.7 Administration

General Information:

Crizotinib is given orally and may be administered on an outpatient basis. Patients should be instructed to take their medication at approximately the same time each day and to not take more than the prescribed dose at any time. The dose may be taken with or without food or beverage. If a dose is missed or forgotten at the due time, it can be taken up to (but not greater than) 6 hours later to help prevent missed doses. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of crizotinib. If a patient vomits after a dose of crizotinib, that dose will not be repeated; wait until the next scheduled time to administer a dose. Crizotinib is a substrate for and moderate inhibitor of CYP3A4/5; refer to Appendix IV for information regarding concomitant medication restrictions.

Oral capsules

Swallow capsules whole (do not crush, dissolve, or open capsules). May be administered with or without food.

6.2.8 Toxicity

Comprehensive Adverse Events and Potential Risks list (CAEPR)
For Crizotinib (PF-02341066, NSC 749005)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2058 patients.* Below is the CAEPR for Crizotinib (PF-02341066).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, October 30, 2018[1]

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 5.0 Term) [n= 2058]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
		Febrile neutropenia	
CARDIAC DISORDERS			
		Heart failure	
	Sinus bradycardia		
ENDOCRINE DISORDERS			
		Testosterone deficiency	
EYE DISORDERS			

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 5.0 Term) [n= 2058]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Eye disorders - Other (vision disorders)[2]			***Eye disorders - Other (vision disorders)[2] (Gr 2)***
Periorbital edema			***Periorbital edema (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colonic perforation	
Constipation			***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		
		Esophageal ulcer	
		Esophagitis	
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Edema face			***Edema face (Gr 2)***
Edema limbs			***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
Generalized edema			***Generalized edema (Gr 2)***
Localized edema			***Localized edema (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
		Hepatobiliary disorders - Other (hepatotoxicity)	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
		Blood bilirubin increased	
	Creatinine increased		
		Electrocardiogram QT corrected interval prolonged	
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Muscle cramp		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 5.0 Term) [n= 2058]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Headache		
	Nervous system disorders - Other (neuropathy)[3]		***Nervous system disorders - Other (neuropathy)[3] (Gr 2)***
		Syncope	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (renal cyst)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash[4]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Vision disorders may include the following: Chromatopsia, Diplopia, Halo vision, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual brightness, Visual impairment, Vitreous floaters, and Visual perseveration.

[3]Neuropathy may include the following: Acute polyneuropathy, Amyotrophy, Areflexia, Autoimmune neuropathy, Autonomic failure syndrome, Autonomic neuropathy, Axonal neuropathy, Biopsy peripheral nerve abnormal, Burning feet syndrome, Burning sensation, Decreased vibratory sense, Demyelinating polyneuropathy, Dysesthesia, Electromyogram abnormal, Formication, Gait disturbance, Genital hypoesthesia, Guillain-Barre syndrome, Hyperesthesia, Hypoesthesia, Hyporeflexia, Hypotonia, Ischemic neuropathy, Loss of proprioception, Miller Fisher syndrome, Mononeuritis, Mononeuropathy, Mononeuropathy multiplex, Motor dysfunction, Multifocal motor neuropathy, Muscle atrophy, Muscular weakness, Myelopathy, Nerve conduction studies abnormal, Nerve degeneration, Neuralgia, Neuritis, Neuromuscular toxicity, Neuromyopathy, Neuropathy peripheral, Neuropathy vitamin B6 deficiency, Neurotoxicity, Paresthesia, Peripheral motor neuropathy, Peripheral nerve lesion, Peripheral nerve palsy, Peripheral nervous system function test abnormal, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Peroneal muscular atrophy, Peroneal nerve palsy, Phrenic nerve paralysis, Polyneuropathy, Polyneuropathy chronic, Polyneuropathy idiopathic progressive, Radiation neuropathy, Sensorimotor disorder, Sensory disturbance, Sensory loss, Skin burning sensation, Temperature perception test decreased, Tinel's sign, Toxic neuropathy, and Ulnar neuritis.

[4]Treatment-related rash may include erythematous rash, rash maculo-papular, and pruritus.

Adverse events reported on crizotinib (PF-02341066) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that crizotinib (PF-02341066) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (basophilia); Disseminated intravascular coagulation; Eosinophilia; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Myocarditis; Pericardial effusion; Supraventricular tachycardia
EYE DISORDERS - Cataract; Optic nerve disorder; Papilledema
GASTROINTESTINAL DISORDERS - Colitis; Dysphagia; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal amyloidosis); Ileus

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Fever; General disorders and administration site conditions - Other (failure to thrive); Malaise; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (cholestasis); Hepatobiliary disorders - Other (hepatitis)
IMMUNE SYSTEM DISORDERS - Autoimmune disorder
INFECTIONS AND INFESTATIONS - Abdominal infection; Infections and infestations - Other (peridiverticular abscess); Kidney infection; Lung infection; Sepsis; Skin infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (traumatic lung injury); Spinal fracture; Wound complication
INVESTIGATIONS - Blood lactate dehydrogenase increased; CPK increased; GGT increased; Investigations - Other (monocyte count increased); Investigations - Other (platelet count increased); Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (hypoproteinemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Musculoskeletal and connective tissue disorder - Other (myopathy); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor hemorrhage
NERVOUS SYSTEM DISORDERS - Intracranial hemorrhage; Ischemia cerebrovascular; Pyramidal tract syndrome; Seizure; Stroke
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS - Pregnancy loss
PSYCHIATRIC DISORDERS - Confusion; Delirium; Euphoria
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Renal calculi; Urinary retention
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Dyspnea; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (respiratory distress)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hematoma; Hypotension; Phlebitis; Thromboembolic event; Vasculitis

Note: Crizotinib (PF-02341066) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

6.2.9 Agent Ordering and Agent Accountability

NCI supplied agents may be requested by the responsible investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Biosketch, Agent Shipping Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

6.2.10 Clinical Drug Request

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application at https://eapps-

ctep.nci.nih.gov/OAOP/pages/login.jspx. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability call (240) 276-6575. Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

6.2.11 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record (DAR) Form. (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form).

6.3 CYCLOPHOSPHAMIDE - INJECTION (03/13/13)

(Cytoxan) NSC #26271

Source and Pharmacology:

Cyclophosphamide is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P450 isoenzymes (CYP2B6, CYP2C9, and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent *in vitro* than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug. The plasma half-life ranges from 4.1 to 16 hours after IV administration.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Anorexia, nausea & vomiting (acute and delayed)	Abdominal discomfort, diarrhea	Transient blurred vision, nasal stuffiness with rapid administration, arrhythmias (rapid infusion), skin rash, anaphylaxis, SIADH
Prompt: Within 2-3 weeks, prior to the next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, hemorrhagic cystitis (L)	Cardiac toxicity with high dose (acute – CHF hemorrhagic myocarditis, myocardial necrosis) (L), hyperpigmentation, nail changes, impaired wound healing, infection secondary to immune suppression
Delayed: Any time later during therapy	Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent)[1] (L)	Amenorrhea[1]	Gonadal dysfunction: ovarian failure[1] (L), interstitial pneumonitis, pulmonary fibrosis[2] (L)

Late: Any time after completion of treatment			Secondary malignancy (ALL, ANLL, AML), bladder carcinoma (long term use > 2 years), bladder fibrosis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects.		

[1] *Dependent on dose, age, gender, and degree of pubertal development at time of treatment.*
[2] *Risk increased with pulmonary chest irradiation and higher doses.*
(L) Toxicity may also occur later.

Formulation and Stability:
Cyclophosphamide for injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 g, and 2 g vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide. Storage at or below 25ºC (77ºF) is recommended. The product will withstand brief exposures to temperatures up to 30ºC (86ºF).

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

Cyclophosphamide for Injection: If the drug will be administered as undiluted drug at the 20 mg/mL concentration, then reconstitute to 20 mg/mL with NS ONLY to avoid a hypotonic solution. If the drug will be further diluted prior to administration, then first reconstitute with NS, SWFI, or Bacteriostatic Water for Injection (paraben preserved only) to a concentration of 20 mg/mL. Following reconstitution further dilute in dextrose or saline containing solutions for IV use.

Supplier: Commercially available from various manufacturers. See package insert for further information

6.4 CYTARABINE
(Cytosine arabinoside, Ara-C, Cytosar®) NSC #63878 (07/13/15)

Source and Pharmacology:
Cytarabine appears to act through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate (Ara-CTP), an effective inhibitor of DNA polymerase. Ara-CTP is inactivated by a pyrimidine nucleoside deaminase, which converts it to the nontoxic uracil derivative (Ara-U). It appears that the balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine. It has an initial distributive phase $t_{½}$ of about 10 minutes, with a secondary elimination phase $t_{½}$ of about 1 to 3 hours. Peak levels after intramuscular or subcutaneous administration of cytarabine occur about 20 to 60 minutes after injection and are lower than IV

administration. Intrathecally administered doses are metabolized and eliminated more slowly with a t½ of about 2 hours.

Toxicity: (Intravenous, SubQ, IM)

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, anorexia *With High Dose*: conjunctivitis	Flu-like symptoms with fever, rash	Ara-C syndrome (fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, malaise, conjunctivitis), anaphylaxis, swelling, pain and redness at the site of the medication injection (SubQ or IM injection) *With High Dose:* cardiomyopathies (vasculitis, and pericarditis), cerebral and cerebellar dysfunction including: encephalopathy, aseptic meningitis, ataxia, dysphasia, nystagmus, a decreased level of consciousness, personality changes, somnolence, seizures
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (anemia, thrombocytopenia, leukopenia, megaloblastosis, reticulocytopenia), stomatitis, alopecia	Diarrhea, hypokalemia, hypocalcemia, hyperuricemia *With High D*ose: capillary pulmonary leak syndrome (RDS, pulmonary edema)	Hepatotoxicity, sinusoidal obstruction syndrome (SOS, formerly VOD), urinary retention, renal dysfunction, pain and erythema of the palms and soles
Delayed: Any time later during therapy, excluding the above conditions			Asymptomatic nonoliguric rhabdomyolysis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cytarabine have been noted in humans. It is unknown whether the drug is excreted in breast milk.		

Formulation: Cytarabine for Injection is available in vials of 100 mg, 500 mg, 1 g, and 2 g containing a sterile powder for reconstitution. It is also available at a 20 mg/mL concentration with benzyl alcohol (25 mL per vial) or as a preservative free solution (5 mL, 50 mL per vial), and at a 100 mg/mL concentration with benzyl alcohol (20 mL vial) or as preservative free solution (20 mL vial). Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Cytarabine solutions should be protected from light.

Guidelines for Administration: See Treatment and Dose Modifications section of the protocol.

IV Infusion:
Reconstitute the lyophilized powder with Bacteriostatic Water for Injection or NS injection. Solution containing bacteriostatic agent should not be used for the preparation of doses > 200 mg/m^2. May be further diluted with dextrose or sodium chloride containing solutions. May give by IV push injection, by IV infusion, or by continuous infusion.

Low Dose (≤ 200 mg/m²/dose): For administration by IV push, reconstitute to a concentration of 20-100 mg/mL.

Stability: When reconstituted with Bacteriostatic Water for Injection, cytarabine is stable for 48 hours at room temperature. Solutions reconstituted without a preservative should be used immediately. Discard if solution appears hazy. Diluted solutions in D5W or NS are stable for 8 days at room temperature; however, the diluted cytarabine should be used within 24 hours for sterility concerns.

Supplier: Commercially available from various manufacturers. See package insert for further information.

6.5 DEXAMETHASONE

(Decadron®, Hexadrol®, Dexone®, Dexameth®) NSC #34521 (05/09/11)

Source and Pharmacology:
Dexamethasone is a synthetic fluorinated glucocorticoid devoid of mineralocorticoid effects. Dexamethasone, 0.75 mg, has potent anti-inflammatory activity equivalent to approximately 5 mg of prednisone. Glucocorticoids produce widespread and diverse physiologic effects on carbohydrate, protein, and lipid metabolism, electrolyte and water balance, functions of the cardiovascular system, kidney, skeletal muscle, and the nervous systems. Glucocorticoids reduce the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. Glucocorticoids selectively bind to the cortisol receptors on human lymphoid cells which are found in larger numbers on leukemic lymphoblasts. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. The specific cellular mechanisms that act to halt DNA synthesis are thought to be related to inhibition of glucose transport or phosphorylation, retardation of mitosis, and inhibition of protein synthesis. Elimination half-lives for the following age groups have been reported to be: infants and children under 2 years of age: 2.3 to 9.5 hours, 8 to 16 years: 2.82 to 7.5 hours, and adults (age not specified): 3 to 6 hours. The biologic half-life is 36-72 hours. It is primarily metabolized in the liver and excreted by the kidneys.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Insomnia, hyperphagia	Gastritis	Hyperuricemia
Prompt: Within 2-3 weeks, prior to the next course	Immunosuppression, personality changes (mood swings, euphoria, anxiety, depression), pituitary-adrenal axis suppression, acne (L)	Hyperglycemia, facial erythema, poor wound healing, infections (bacterial, fungal, parasitic, viral), edema	Pancreatitis (L), increased intraocular pressure (L), hypertension, psychosis, vertigo, headache
Delayed: Any time later during therapy	Cushing's syndrome (moon facies, truncal obesity)	Striae and thinning of the skin, easy bruising, muscle weakness, osteopenia	Spontaneous fractures (L), growth suppression, peptic ulcer and GI bleeding, pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the femoral and humeral heads (L), urolithiasis[1] (L)
Late: Any time after completion of treatment		Cataracts (which may be reversible on discontinuation of dexamethasone in children)	
Unknown Frequency and Timing:	**Fetal and teratogenic toxicities**: dexamethasone crosses the placenta with 54% metabolized by enzymes in the placenta. In animal studies, large doses of cortisol administered early in pregnancy produced cleft palate, stillborn fetuses, and decreased fetal size. Chronic maternal ingestion during the first trimester has shown a 1% incidence of cleft palate in humans. There are no reports of dexamethasone excretion into breast milk in humans; however, it is expected due to its low molecular weight that it would partition into breast milk.		

[1] ***Mainly reported in pediatric patients with ALL. Howard SC et al. Urolithiasis in pediatric patients with acute lymphoblastic leukemia. Leukemia 2003; 17: 541-6.*** *(L) Toxicity may also occur later.*

Formulation and Stability:

Oral:
Available in 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg tablets; liquid formulations are available in 0.5 mg/5 mL and 1 mg/1 mL concentrations. Inactive ingredients vary depending on manufacturer but tablet formulations may include: calcium or magnesium stearate, corn starch, lactose, and various dyes. Liquid formulations may include: 5%-30% alcohol, benzoic acid, sorbitol, sodium saccharin, glycerin, purified water, and various dyes.

Injection:
Dexamethasone Sodium Phosphate Solution for Injection is available as 4 mg/mL (1 mL, 5 mL, and 30 mL vials) and 10 mg/mL (1 mL and 10 mL vial sizes). Vials are available in multi-dose vials as well as unit of use vials and syringes. Inactive ingredients vary depending on manufacturer but include creatinine, sodium citrate, sodium hydroxide to adjust pH, Water for Injection, sodium sulfite, bisulfite and metabisulfite, methyl and propyl paraben, benzyl alcohol, and EDTA.

Guidelines for Administration: See Treatment and Dose Modifications section of the protocol.

Dexamethasone Sodium Phosphate for Injection may be given IV, or IM undiluted. For IV use, it may be further diluted in dextrose or saline containing solutions. Avoid using benzyl alcohol-containing dexamethasone solutions in neonates. Diluted solutions that contain no preservatives should be used within 24 hours, but maintain stability for at least 14 days in PVC bags at room temperature protected from light.

Supplier: Commercially available from various manufacturers. See package insert for further information.

6.6 DOXORUBICIN

(Adriamycin®) NSC #123127 (05/09/11)

Source and Pharmacology:
An anthracycline antibiotic isolated from cultures of *Streptomyces peucetius*. The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytocidal activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases, and dehydrogenases generate highly reactive species including the hydroxyl free radical (OH•). Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both. Doxorubicin serum decay pattern is multiphasic.

The initial distributive $t_{½}$ is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal $t_{½}$ of 20 to 48 hours reflects a slow elimination from tissues. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. The P450 cytochromes which appear to be involved with doxorubicin metabolism are CYP2D6 and CYP3A4. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, pink or red color to urine, sweat, tears, and saliva	Hyperuricemia, facial flushing, sclerosis of the vein	Diarrhea, anorexia, erythematous streaking of the vein (flare reaction), extravasation (rare) but if occurs = local ulceration, anaphylaxis, fever, chills, urticaria, acute arrhythmias
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (leukopenia, thrombocytopenia, anemia), alopecia	Mucositis (stomatitis and esophagitis), hepatotoxicity	Radiation recall reactions, conjunctivitis and lacrimation
Delayed: Any time later during therapy		Cardiomyopathy[1] (CHF occurs in 5-20% at cumulative doses ≥ 450 mg/m²) (L)	Cardiomyopathy[1] (CHF occurs in < 5% at cumulative doses ≤ 400 mg/m²) (L), ulceration and necrosis of colon, hyper-pigmentation of nail bed and dermal crease, onycholysis
Late: Any time after completion of treatment	Subclinical cardiac dysfunction	CHF (on long term follow up in pediatric patients)	Secondary malignancy (in combination regimens)
Unknown Frequency and Timing:	Fetal and teratogenic toxicities. Carcinogenic and mutagenic effects of doxorubicin have been noted in animal models. Doxorubicin is excreted into breast milk in humans		

[1] Risk increases with cardiac irradiation, exposure at a young or advanced age.
(L) Toxicity may also occur later.

Formulation and Stability:
Doxorubicin is available as red-orange lyophilized powder for injection in 10 mg[1], 20 mg[1], 50 mg[1]vials and a preservative-free 2 mg/mL solution in 10 mg[1], 20 mg[1], 50 mg[1], 200 mg[2] vials.
[1]: Contains lactose monohydrate, 0.9 NS, HCl to adjust pH to 3. The Adriamycin RDF® (rapid dissolution formula) also contains methylparaben, 1 mg per each 10 mg of doxorubicin, to enhance dissolution.
[2] Multiple dose vial contains lactose, 0.9% NS, HCl to adjust pH to 3.

Aqueous Solution: Store refrigerated 2°-8°C, (36°-46°F). Protect from light. Retain in carton until contents are used.

Powder for Injection: Store unreconstituted vial at room temperature, 15°-30°C (59°-86°F). Retain in carton until contents are used. Reconstitute with preservative-free NS to a final concentration of 2 mg/mL. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and 15 days under refrigeration, 2°-8°C (36°-46°F) when protected from light. Doxorubicin further diluted in 50 – 1000 mL of NS or D5W is stable for up to 48 hours at room temperature (25°C) when protected from light.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.

Administer IV through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl preferably into a large vein. Protect the diluted solution from sunlight. To avoid extravasation, the use of a central line is suggested.

Supplier: Commercially available from various manufacturers. See package insert for further information.

6.7 ETOPOSIDE - INJECTION

(Toposar®, Etopophos®, VP-16) NSC #141540 (11/15/16)

Source and Pharmacology:
A semisynthetic derivative of podophyllotoxin that forms a complex with topoisomerase II and DNA which results in single and double strand DNA breaks. Its main effect appears to be in the S and G_2 phase of the cell cycle. The initial $t_{½}$ is 1.5 hours and the mean terminal half-life is 4 to 11 hours. It is primarily excreted in the urine. In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m² or about 35% of the total body clearance over a dose range of 80 to 600 mg/m². Etoposide, therefore, is cleared by both renal and non-renal processes, i.e., metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known. Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the non-renal clearance of etoposide.

The maximum plasma concentration and area under the concentration time curve (AUC) exhibit a high degree of patient variability. Etoposide is highly bound to plasma proteins (~94%), primarily serum albumin. Pharmacodynamic studies have shown that etoposide systemic exposure is related to toxicity. Preliminary data suggests that systemic exposure for unbound etoposide correlates better than total (bound and unbound) etoposide. There is poor diffusion into the CSF < 5%.

Etoposide phosphate is a water soluble ester of etoposide which is rapidly and completely converted to etoposide in plasma. Pharmacokinetic and pharmacodynamic data indicate that etoposide phosphate is bioequivalent to etoposide when it is administered in molar equivalent doses.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting	Anorexia	Transient hypotension during infusion; anaphylaxis (chills, fever, tachycardia, dyspnea, bronchospasm, hypotension)
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression (anemia, leukopenia), alopecia	Thrombocytopenia, diarrhea, abdominal pain, asthenia, malaise, rashes and urticaria	Peripheral neuropathy, mucositis, hepatotoxicity, chest pain, thrombophlebitis, congestive heart failure, Stevens-Johnson Syndrome, exfoliative dermatitis
Delayed: Any time later during therapy			Dystonia, ovarian failure, amenorrhea, anovulatory cycles, hypomenorrhea, onycholysis of nails
Late: Any time after completion of treatment			Secondary malignancy (preleukemic or leukemic syndromes)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of etoposide have been noted in animals at 1/20th of the human dose. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:
Etoposide for Injection is available as a 20 mg/mL solution in sterile multiple dose vials (5 mL, 25 mL, or 50 mL each). The pH of the clear, nearly colorless to yellow liquid is 3 to 4. Each mL contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg modified polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. Vial headspace contains nitrogen. Unopened vials of etoposide are stable until expiration date on package at controlled room temperature (20°-25°C or 68°-77°F).

Etoposide phosphate for injection is available for intravenous infusion as a sterile lyophilized powder in single-dose vials containing etoposide phosphate equivalent to 100 mg etoposide, 32.7 mg sodium citrate *USP*, and 300 mg dextran 40. Etoposide phosphate must be stored under refrigeration (2°-8°C or 36°-46°F). Unopened vials of etoposide phosphate are stable until the expiration date on the package.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.

Etoposide:
Dilute etoposide to a final concentration ≤ 0.4 mg/mL in D5W or NS. Etoposide infusions are stable at room temperature for 96 hours when diluted to concentrations of 0.2 mg/mL; stability is 24 hours at room temperature with concentrations of 0.4 mg/mL. The time to precipitation is highly unpredictable at concentrations > 0.4 mg/mL. Use in-line filter during infusion secondary to the risk of precipitate formation. However, the use of an in-line filter is not mandatory since etoposide precipitation is unlikely at concentrations of 0.1-0.4 mg/mL. **Do not administer etoposide by rapid intravenous injection.** Slow rate of administration if hypotension occurs.

Leaching of diethylhexyl phthalate (DEHP) from polyvinyl chloride (PVC) bags occurred with etoposide 0.4 mg/mL in NS. To avoid leaching, prepare the etoposide solution as close as possible, preferably within 4 hours, to the time of administration or alternatively as per institutional policy; glass or polyethylene-lined (non-PVC) containers and polyethylene-lined tubing may be used to minimize exposure to DEHP.

Etoposide Phosphate:
Reconstitute the 100 mg vial with 5 or 10 mL of Sterile Water for Injection, D5W, NS, Bacteriostatic Water for Injection with Benzyl Alcohol, or Bacteriostatic Sodium Chloride for Injection with Benzyl Alcohol for a concentration equivalent to 20 mg/mL or 10 mg/mL etoposide equivalent (22.7 mg/mL or 11.4 mg/mL etoposide phosphate), respectively. **Use diluents without benzyl alcohol for neonates and infants < 2 years of age or patients with hypersensitivity to benzyl alcohol.**

When reconstituted as directed, etoposide phosphate solutions can be stored in glass or plastic containers under refrigeration for 7 days. When reconstituted with a diluent containing a bacteriostat, store at controlled room temperature for up to 48 hours. Following reconstitution with SWFI, D5W, or NS store at controlled room temperature for up to 24 hours.

Following reconstitution, etoposide phosphate may be further diluted to a concentration as low as 0.1 mg/mL of etoposide with D5W or NS. The diluted solution can be stored under refrigeration or at controlled room temperature for 24 hours.

Supplier: Commercially available from various manufacturers. See package insert for more detailed information.

CANADIAN SITES
Etoposide for Injection is available as a 20 mg/mL solution.

Etopophos® (etoposide phosphate) is not commercially available in Canada. Sites may purchase and import the USA commercial supply from Bristol Laboratories via an International Distributor (Pharma Exports LLC, phone: 1-412-885-3700, fax: 1-412-885-8022, email: pharexp@aol.com) under the authority of the protocol's No Objection Letter (NOL). Drug Accountability Log (DAL) must record Lot #'s and expiry dates of shipments received and doses dispensed. Sites may use their own DAL as long as it complies with all elements of ICH GCP and Division 5 of the Food and Drugs Act. Each site is responsible for the procurement (import +/- purchase) of Etoposide Phosphate (Etopophos). Sites may import and manage a single clinical trial supply for multiple protocols as long as each protocol has an NOL and the protocol the patient is registered on is recorded on the DAL.

6.8 FILGRASTIM, TBO-FILGRASTIM, FILGRASTIM-SNDZ

(Granulocyte Colony-Stimulating Factor, r-metHuG-CSF, G-CSF, Neupogen®, Granix®, Zarxio®) NSC #614629 (11/15/16)

Source and Pharmacology:
Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein with a molecular weight of 18,800 daltons manufactured by recombinant DNA technology utilizing E coli bacteria into which has been inserted the human granulocyte colony stimulating factor

gene. It differs from the natural protein in that the N- amino acid is methionine and the protein is not glycosylated. G-CSF is a lineage specific colony-stimulating factor, which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens). Filgrastim exhibits nonlinear pharmacokinetics with clearance dependent on filgrastim concentration and neutrophil count. Filgrastim is cleared by the kidney. The elimination half-life is similar for subcutaneous and intravenous administration, approximately 3.5 hours. The time to peak concentration when administered subcutaneously is 2-8 hours.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Local irritation at the injection site, headache	Allergic reactions (more common with IV administration than subq):skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea) and cardiovascular (hypotension, tachycardia), low grade fever
Prompt: Within 2-3 weeks, prior to the next course	Mild to moderate medullary bone pain	Increased: alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia	Splenomegaly, splenic rupture, rash or exacerbation of pre-existing skin rashes, sickle cell crises in patients with SCD, excessive leukocytosis, Sweet's syndrome (acute febrile neutrophilic dermatosis)
Delayed: Anytime later during therapy			Cutaneous vasculitis, ARDS
Late: Anytime after completion of treatment			MDS or AML (confined to patients with severe chronic neutropenia and long term administration)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of filgrastim in humans are unknown. Conflicting data exist in animal studies and filgrastim is known to pass the placental barrier. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:
Neupogen® supplied as a clear solution of 300 mcg/mL in 1 mL or 1.6 mL vials. Neupogen® vials are preservative free single use vials. Discard unused portions of open vials.

Neupogen®, Granix®, and Zarxio® are also available as single use prefilled syringes containing 300 mcg/0.5 mL or 480 mcg/0.8 mL of filgrastim for subcutaneous administration.

Store refrigerated at 2º-8ºC (36º-46ºF). Protect from light. Do not shake. Prior to injection, filgrastim and filgrastim-sndz may be allowed to reach room temperature for a maximum of 24 hours (infusion must be completed within 24 hours of preparation). TBO-filgrastim may be removed from 2°C-8°C (36°F-46°F) storage for a single period of up to 5 days between 23°C to 27°C (73°F to 81°F). Avoid freezing and temperatures > 30ºC.

For IV use, dilute filgrastim (Neupogen®) and tbo-filgrastim (Granix®) in D5W only to concentrations >15 mcg/mL. Filgrastim-sndz (Zarxio®) may be diluted in D5W to concentrations between 5 mcg/mL and 15 mcg/mL. At concentrations below 15 mcg/mL, human serum albumin should be added to make a final albumin concentration of 0.2% (2 mg/mL) in order to minimize the adsorption of filgrastim to plastic infusion containers and equipment for all 3 products (communication on file from Teva Pharmaceuticals USA). Filgrastim or filgrastim-sndz dilutions of 5 mcg/mL or less are not recommended. Tbo-filgrastim dilutions below 2 mcg/mL are not recommended. Diluted filgrastim biosimilar products should be stored at 2º-8ºC (36º-46ºF) and used within 24 hours. Do not shake.

Do not dilute with saline-containing solutions at any time; precipitation will occur.

Guidelines for Administration:
See Treatment, Dose Modifications and Supportive Care sections of the protocol. Filgrastim biosimilar products should not be administered within 24 hours of (before AND after) chemotherapy.

Supplier: Commercially available from various manufacturers. See package insert for further information

6.9 IFOSFAMIDE

(Isophosphamide, Iphosphamide, Z4942, Ifex®) NSC #109724 (05/09/11)

Source and Pharmacology:
Ifosfamide is a structural analogue of cyclophosphamide. Ifosfamide requires hepatic microsomal activation (P450 3A isoenzymes) for the production of the reactive 4-hydroxyoxazaphorine intermediate which serves as a carrier molecule for the ultimate intracellular liberation of acrolein and phosphoramide mustard which is an active bifunctional alkylating species. Acrolein is thought to be the cause of the hemorrhagic cystitis as seen with cyclophosphamide. Ifosfamide demonstrates dose-dependent pharmacokinetics whereby the terminal half-life ranges from 7 to 16 hours at doses of 1.6-2.4 g/m² to 3.8-5 g/m², respectively. At 1.6-2.4 g/m²/d, 12 to 18% of the dose was excreted as unchanged drug in the urine, whereas at a 5 g/m² single-dose, 61% was excreted in the urine as the parent drug. Evidence also exists to suggest that ifosfamide metabolism is inducible, with more rapid clearance occurring in the second and later doses when a course of therapy is given as fractionated doses over 3 to 5 days. There is more chloroethyl side chain oxidation of ifosfamide (up to 50%) than of cyclophosphamide (< 10%), and the degree of such metabolism is more variable than with cyclophosphamide. Oxidation of the chloroethyl groups produces chloroacetaldehyde, which is thought to be responsible for the neurotoxicity and renal toxicity that have been seen with ifosfamide therapy.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea & vomiting (acute and delayed)	CNS toxicity (somnolence, depressive psychosis and confusion)	Anorexia, diarrhea, constipation, encephalopathy which may progress to coma (L), seizure, SIADH, phlebitis, hypokalemia
Prompt: Within 2-3 weeks, prior to next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, cardiac toxicities (arrhythmia, asymptomatic ECG changes), microscopic hematuria, metabolic acidosis	↑ liver enzymes, ↑ bilirubin, hemorrhagic cystitis with macroscopic hematuria, dysuria, cystitis and urinary frequency (< 5% with mesna and vigorous hydration) (L), bladder fibrosis
Delayed: Any time later during therapy	Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent)[1] (L)		Renal failure acute or chronic, renal tubular acidosis, Fanconi-like syndrome gonadal dysfunction, ovarian failure[1] (L), CHF
Late: Any time after completion of treatment	Moderate nephrotoxicity (↓ in glomerular filtration rate, renal tubular threshold for phosphate, and serum bicarbonate)		Secondary malignancy, hypophosphatemic rickets
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of ifosfamide have been noted in animals. Ifosfamide is excreted into breast milk.		

[1] *Dependent on dose, age, gender and degree of pubertal development at time of treatment*
(L) Toxicity may also occur later.

Formulation and Stability:
Ifosfamide is available in 1 g and 3 g single dose vials of lyophilized white powder without preservatives and as a 50 mg/mL solution in 20 mL and 60 mL vials.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.
Reconstitute ifosfamide lyophilized powder with sterile water for injection or bacteriostatic water for injection(use 20 mL for the 1 g vial and 60 mL for the 3 g vial) to produce a final concentration of 50 mg/mL. **Use sterile water for injection without benzyl alcohol for neonates and infants < 2 years of age or patients with hypersensitivity to benzyl alcohol.** Although the reconstituted product is stable for 7 days at room temperature and up to 6 weeks under refrigeration, the manufacturer recommends refrigeration and use within 24 hours to reduce the possibility of microbial contamination. Store unreconstituted vials at room temperature 20°-25°C (68°-77°F). Protect from temperatures above 30°C (86° F). Ifosfamide may liquefy at temperatures > 35°C.
Reconstituted solutions of ifosfamide or ifosfamide solution should be diluted further to concentrations of 0.6 to 20 mg/mL in dextrose or saline containing solutions. Such admixtures, when stored in large volume parenteral glass bottles, Viaflex bags or PAB

bags, are physically and chemically stable for 1 week at 30°C (86°F) or 6 weeks at 5°C (41°F). The manufacturer recommends refrigeration and use within 24 hours to reduce the possibility of microbial contamination. Mesna must always be administered in conjunction with ifosfamide. Adequate hydration is required. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. Refer to the Chemotherapy Administration Guidelines for additional information.

Supplier: Commercially available from various manufacturers. See package insert for further information

6.10 INTRATHECAL TRIPLES (05/08/12)

(Methotrexate/Hydrocortisone/Cytarabine, IT-3)

Source and Pharmacology:

The intrathecal route of administration of a drug produces more consistent CSF drug concentrations at relatively smaller doses because of the volume difference between the CSF and blood compartments (140 mL vs. 3500 mL in an adult). (The CSF volume of children after the first 3 years is equivalent to that of an adult). Drug half-lives are longer as well because clearance is related to flow rather than metabolism or protein binding. Intrathecal methotrexate has a biphasic elimination curve from the CSF with a $t_{½}$ of 4.5 and 14 hours respectively. Following IT injection of cytarabine the elimination of the drug from the CSF is biphasic with a $t_{½}$ of 1 and 3.4 hours respectively which is 8-fold longer than the clearance from plasma. The elimination of hydrocortisone is similarly prolonged.

Intrathecal Triple Therapy (Methotrexate/ Hydrocortisone/Cytarabine) Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, fever, headache	Arachnoditis: (headache, fever, vomiting, meningismus and pleocytosis)	Rash, anaphylaxis (L), paresis, bleeding into subarachnoid or subdural space (risk > with platelet counts < 20,000), confusion, fatigue, disorientation, seizures
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, somnolence, ataxia, cranial nerve palsy, transient and rarely permanent paraplegia (L), speech disorders
Delayed: Any time later during therapy, excluding the above condition		Cognitive disturbances (L), learning disabilities (L)	Demyelating leukoencephalopathy[1] (L), blindness[1]
Late: Any time after the completion of treatment			Progressive CNS deterioration[1]

[1] May be enhanced by systemic therapy such as high dose methotrexate or cytarabine and/or cranial irradiation. (L) Toxicity may also occur later.

Formulation and Stability:
Methotrexate 25 mg/mL **preservative free** 2 mL vial or methotrexate 20 mg preservative free sterile powder for injection vial. Cytarabine 100 mg preservative free sterile powder for injection. Hydrocortisone sodium succinate 100 mg vial sterile powder for injection.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.

For intrathecal administration, dilute each agent with 5-10 mL preservative free NS, lactated ringers or Elliot's B solution or as per institutional standard of practice. The volume of CSF removed should be equal to at least half the volume delivered.

Of note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Supplier: Commercially available from various manufacturers. See package insert for further information.

6.11 LEUCOVORIN CALCIUM (05/09/11)

(LCV, Wellcovorin®, citrovorum factor, folinic acid) NSC #003590

Source and Pharmacology:
Leucovorin is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). The biologically active compound of the mixture is the (-)- l-isomer, known as Citrovorum factor or (-)-folinic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties. Administration of leucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase. In contrast, leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as 5-fluorouracil. Leucovorin is readily converted to another reduced folate, 5, 10-methylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyuridylic acid (an active metabolite of 5-FU) to thymidylate synthase and thereby enhances the inhibition of this enzyme. Peak serum levels of 5-methyl THF (an active metabolite) were reached at approximately 1.3-1.5 hours (IV/IM) and 2.3 hours for the oral form. The terminal half-life of total reduced folates was approximately 6.2 hours. Following oral administration, leucovorin is rapidly absorbed and expands the serum pool of reduced folates. At a dose of 25 mg, almost 100% of the *l*-isomer (the biologically active form) but only 20% of the *d*-isomer is absorbed. Oral absorption of leucovorin is saturable at doses above 25 mg. The apparent bioavailability of leucovorin was 97% for 25 mg, 75% for 50 mg, and 37% for 100 mg doses. Both oral and parenteral leucovorin raise the CSF folate levels.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug			Anaphylaxis, urticaria, seizure
Unknown Frequency and timing:	Fetal toxicities and teratogenic effects of leucovorin in humans are unknown. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:
Leucovorin calcium for injection is supplied as a sterile ready to use liquid and a sterile powder for injection. The 10 mg/mL preservative free liquid is available in 50 mL vials containing sodium chloride 400 mg/vial. Store preservative free liquid in the refrigerator at 2°-8°C (36°-46°F) protected from light. The powder for injection is available in 50 mg, 100 mg, 200 mg, and 350 mg vials. Store at room temperature 15°-25°C (59°-77°F) protected from light. Reconstitute the sterile powder with sterile water for injection or bacteriostatic water for injection to a concentration of 10 mg/mL leucovorin calcium. **Do not use diluents containing benzyl alcohol for doses >10 mg/m² or in infants < 2 years of age or patients with allergy to benzyl alcohol.** When Bacteriostatic Water is used, the reconstituted solution is good for 7 days. If reconstituted with SWFI, use solution immediately as it contains no preservative. One milligram of leucovorin calcium contains 0.004 mEq of leucovorin and 0.004 mEq of calcium.

The oral form of leucovorin is available as 5 mg, 10 mg, 15 mg, and 25 mg tablets. Inactive ingredients vary depending on manufacturer but tablet formulations may include: corn starch, dibasic calcium phosphate, magnesium stearate, pregelatinized starch, lactose, microcrystalline cellulose, and sodium starch glycolate.

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

Injection:
Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL solution per minute). IV leucovorin and sodium bicarbonate are incompatible.

Oral:
Oral leucovorin should be spaced evenly (e.g., every six hours) throughout the day and may be taken without regard to meals. Doses > 25 mg should be given IV due to the saturation of absorption.

Leucovorin should not be administered < 24 hours after intrathecal injections which contain methotrexate unless there are special circumstances.

Supplier: Commercially available from various manufacturers. See package insert for further information.

6.12 MESNA - INJECTION (11/15/16)

(sodium 2-mercaptoethane sulfonate, UCB 3983, Mesnex®) NSC #113891

Source and Pharmacology:
Mesna was developed as a prophylactic agent to reduce the risk of hemorrhagic cystitis induced by ifosfamide. Mesna is rapidly oxidized to its major metabolite, mesna disulfide (dimesna). Mesna disulfide remains in the intravascular compartment and is rapidly eliminated by the kidneys. In the kidney, the mesna disulfide is reduced to the free thiol compound, mesna, which reacts chemically with the urotoxic ifosfamide metabolites (acrolein and 4-hydroxy-ifosfamide) resulting in their detoxification. The first step in the detoxification process is the binding of mesna to 4-hydroxy-ifosfamide forming a nonurotoxic 4-sulfoethylthioifosfamide. Mesna also binds to the double bonds of acrolein and to other urotoxic metabolites. In multiple human xenograft or rodent tumor model studies, mesna in combination with ifosfamide (at dose ratios of up to 20-fold as single or multiple courses) failed to demonstrate interference with antitumor efficacy.

After an 800 mg dose the half lives for mesna and dimesna are 0.36 hours and 1.17 hours, respectively. Approximately 32% and 33% of the administered dose was eliminated in the urine in 24 hours as mesna and dimesna, respectively. The majority of the dose recovered was eliminated within 4 hours.

Toxicity[1]:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Nausea, vomiting, stomach pain, fatigue, headache	Facial flushing, fever, pain in arms, legs, and joints, rash, transient hypotension, tachycardia, dizziness, anxiety, confusion, periorbital swelling, anaphylaxis, coughing
Prompt: Within 2-3 weeks, prior to the next course		Diarrhea	
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of mesna have not been noted in animals fed 10 times the recommended human doses. There are however no adequate and well-controlled studies in pregnant women. It is not known if mesna or dimesna is excreted into human milk		

[1]All currently available products in the U.S. are preserved with benzyl alcohol. Benzyl Alcohol has been associated with death in pre-term infants weighing less than 2500 g and receiving 99-405 mg/kg/day. Benzyl alcohol is normally oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. In pre-term infants, however, this metabolic pathway may not be well developed. Onset of toxic illness in these infants occurred between several days and a few weeks of age with a characteristic clinical picture that included metabolic acidosis progressing to respiratory distress and gasping respirations. Many infants also had central-nervous-system dysfunction, including convulsions and intracranial hemorrhage; hypotension leading to cardiovascular collapse was a late finding usually preceding death. [For comparison in the ICE regimen of 3000 mg/m²/day of ifosfamide and a daily mesna dose of 60% of the ifosfamide dose = to 1800 mg/m²/day; a child would be expected to receive 18 mL/m²/day of mesna (concentration of 100 mg/mL and 10.4 mg/mL of benzyl alcohol) 187.2 mg/m²/day of benzyl alcohol or 6.24 mg/kg/day.]

Formulation and Stability:
Mesna for injection is available as 100 mg/mL in 10 mL multidose vials which contain 0.25 mg/mL edetate disodium and sodium hydroxide for pH adjustment. Mesna Injection multidose vials also contain 10.4 mg/mL of benzyl alcohol as a preservative. Store product at controlled room temperature 15º-25°C (68º-77ºF). Mesna is not light-sensitive, but is oxidized to dimesna when exposed to oxygen. Mesna as benzyl alcohol-preserved vials may be stored and used for 8 days.

Guidelines for Administration: See Treatment, Dose Modifications, and Supportive Care sections of the protocol.

For IV administration, dilute mesna to 20 mg/mL with dextrose or saline containing solutions. Mesna may be mixed with ifosfamide or cyclophosphamide. After dilution for administration, mesna is physically and chemically stable for 24 hours at 25ºC (77ºF). Mesna may cause false positive test for urinary ketones.

Supplier: Commercially available from various manufacturers. See package insert for further information.

CANADIAN SITES
Preservative-free Mesna is commercially available in Canada from Baxter Corporation (Urometixan®); supplied as a 100mg/mL solution which contains edentate disodium and sodium hydroxide for pH adjustment, 4 mL and 10 mL single-use ampoules. It is also available from Baxter and Fresenius Kabi Canada in multi-dose vials containing antibacterial preservatives.

6.13 METHOTREXATE - IV only (02/29/12)
(MTX, amethopterin) NSC #000740

Source and Pharmacology:
A folate analogue which reversibly inhibits dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. Inhibition of tetrahydrofolate formation limits the availability of one carbon fragments necessary for the synthesis of purines and the conversion of deoxyuridylate to thymidylate in the synthesis of DNA and cell reproduction. The polyglutamated metabolites of MTX also contribute to the cytotoxic effect of MTX on DNA repair and/or strand breaks. MTX cytotoxicity is highly dependent on the absolute drug concentration and the duration of drug exposure. MTX is actively transported across cell membranes. At serum methotrexate concentrations exceeding 0.1 µmol/mL, passive diffusion becomes a major means of intracellular transport of MTX. The drug is widely distributed throughout the body with the highest concentration in the kidney, liver, spleen, gallbladder and skin. Plasma concentrations following high dose IV MTX decline in a biphasic manner with an initial half-life of 1.5-3.5 hours, and a terminal half life of 8-15 hours. About 50% is bound to protein. MTX is excreted primarily by the kidneys via glomerular filtration and active secretion into the proximal tubules. Renal clearance usually equals or exceeds creatinine clearance. Small amounts are excreted in the feces. There is significant entero-hepatic circulation of MTX. The distribution of MTX into third-space fluid collections, such as pleural effusions and ascitic fluid, can substantially alter MTX pharmacokinetics. The slow release of accumulated MTX from these third spaces over time prolongs the terminal half-life of the drug, leading to potentially increased clinical toxicity.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Transaminase elevations	Nausea, vomiting, anorexia	Anaphylaxis, chills, fever, dizziness, malaise, drowsiness, blurred vision, acral erythema, urticaria, pruritis, toxic epidermal necrolysis, Stevens-Johnson Syndrome, tumor lysis syndrome, seizures[1], photosensitivity
Prompt: Within 2-3 weeks, prior to the next course		Myelosuppression, stomatitis, gingivitis, photosensitivity, fatigue	Alopecia, folliculitis, acne, renal toxicity (ATN, increased creatinine/BUN, hematuria), enteritis, GI ulceration and bleeding, acute neurotoxicity[1] (headache, drowsiness, aphasia, paresis, blurred vision, transient blindness, dysarthria, hemiparesis, decreased reflexes) diarrhea, conjunctivitis
Delayed: Any time later during therapy, excluding the above conditions		Learning disability[1] (L)	Pneumonitis, pulmonary fibrosis (L), hepatic fibrosis (L), osteonecrosis (L), leukoencephalopathy[1] (L), pericarditis, pericardial effusions, hyperpigmentation of the nails
Late: Any time after the completion of therapy			Progressive CNS deterioration[1]
Unknown Frequency and Timing:	Methotrexate crosses the placenta. Fetal toxicities and teratogenic effects of methotrexate have been noted in humans. The toxicities include: congenital defects, chromosomal abnormalities, severe newborn myelosuppression, low birth weight, abortion, and fetal death. Methotrexate is excreted into breast milk in low concentrations.		

[1] *May be enhanced by HDMTX and/or cranial irradiation. (L) Toxicity may also occur later.*

Formulation and Stability:
Methotrexate for Injection is available as a lyophilized powder for injection in 1000 mg vials. The powder for injection contains approximately 7 mEq sodium in the 1000 mg vial. Methotrexate for Injection is also available as a 25 mg/mL solution in 2, 4, 8, 10, and 40 mL preservative free vials and 2 and 10 mL vials with preservative. The 2, 4, 8, 10, and 40 mL solutions contain approximately 0.43, 0.86, 1.72, 2.15, and 8.6 mEq sodium per vial, respectively. The preserved vials contain 0.9% benzyl alcohol as a preservative**.**

Sterile methotrexate powder or solution is stable at 20º-25ºC (68º-77ºF); excursions permitted to 15º-30ºC (59º- 86 Fº). Protect from light.

Guidelines for Administration: See Treatment and Dose Modifications sections of protocol. Leucovorin rescue may be necessary with certain doses of methotrexate.
For IV use: Powder for injection: Dilute 1000 mg vial with 19.4 mL of preservative free SWFI, D5W or NS to a 50 mg/mL concentration. The powder for injection may be further diluted in NS or dextrose containing solutions to a concentration of ≤ 25mg/mL for IV use.

Do not use the preserved solution for high dose methotrexate administration due to risk of benzyl alcohol toxicity. Methotrexate dilutions are chemically stable for at least 7 days at room temperature but contain no preservative and should be used within 24 hours. Diluted solutions especially those containing bicarbonate exposed to direct sunlight for periods exceeding 4 hours should be protected from light.

High dose Methotrexate requires alkalinization of the urine, adequate hydration and leucovorin rescue. Avoid probenecid, penicillins, cephalosporins, aspirin, proton pump inhibitors, and NSAIDS as renal excretion of MTX is inhibited by these agents.

Supplier: Commercially available from various manufacturers. See package insert for further information

6.14 PEGFILGRASTIM (02/10/16)

(pegylated filgrastim, PEG filgrastim, SD/01, Neulasta®) NSC #725961

Source and Pharmacology:
Pegfilgrastim is the pegylated form of recombinant methionyl human G-CSF (filgrastim). Pegfilgrastim is produced by covalently binding a 20-kilodalton (kD) monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim. The molecular weight of pegfilgrastim is 39 kD. G-CSF is a lineage specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens).

After subcutaneous injection the elimination half-life of pegfilgrastim ranges from 15 to 80 hours and the time to peak concentration ranges from 24 to 72 hours. Serum levels are sustained in most patients during the neutropenic period postchemotherapy, and begin to decline after the start of neutrophil recovery, consistent with neutrophil-dependent elimination. After subcutaneous administration at 100 mcg/kg in 37 pediatric patients with sarcoma, the terminal elimination half-life was 30.1 (+/- 38.2) hours in patients 0 to 5 years-old, 20.2 (+/- 11.3) hours in patients 6 to 11 years-old, and 21.2 (+/- 16) hours in children 12 to 21 years-old.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Local irritation at the injection site (pain, induration, and local erythema), headache	Low grade fever, allergic reactions (anaphylaxis, angioedema, or urticaria), generalized erythema and flushing,
Prompt: Within 2-3 weeks, prior to the next course	Mild to moderate medullary bone pain	Increased: alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia	Splenomegaly, splenic rupture, sickle cell crises in patients with sickle cell disease (SCD), excessive leukocytosis, Sweet's syndrome (acute febrile neutrophilic dermatosis)
Delayed: Anytime later during therapy			ARDS
Unknown frequency and timing:	Fetal toxicities and teratogenic effects of pegfilgrastim in humans are unknown. Conflicting data exist in animal studies. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:
Supplied as a preservative-free solution containing 6 mg (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dose syringe with 27 g, ½ inch needle with an UltraSafe® Needle Guard. The needle cover of the prefilled syringe contains drug natural rubber (a derivative of latex). Store refrigerated at 2º-8ºC (36º-46ºF) and in the carton to protect from light. Prior to injection, pegfilgrastim may be allowed to reach room temperature protected from light for a maximum of 48 hours. Avoid freezing.

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

Pegfilgrastim should not be administered in the period between 2 weeks before and 24 hours after chemotherapy. Do not shake. The manufacturer does not recommend use of the 6-milligram (mg) fixed-dose formulation of pegfilgrastim in infants, children, or adolescents under 45 kilograms.

Supplier: Commercially available. See package insert for further information.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

7.1 Required Clinical, Laboratory and Disease Evaluations

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. If PET scan shows uptake at a site that was not imaged by CT or MRI scanning, a CT or MRI scan of this site is recommended. **Obtain other studies prior to start of cycle unless otherwise indicated.**

STUDIES TO BE OBTAINED	Baseline	Prophase, Cycle 1 & 2	End of Cycle 2	Cycles 3,4,5 & 6	End of Cycle 4	End of Therapy (End of Cycle 6)
History	X	X		X		X
Physical Exam (Ht, Wt, BSA, Vital Signs)	X	Weekly		X		X
Pregnancy Test[1]; Uric Acid, LDH	X					
Performance Status	X	X		X		X
CBC, differential, platelets	X	Weekly		Prior to each cycle, then weekly		X
Electrolytes including Ca++, PO_4, Mg++	X	Weekly		X		X
Cr, Bilirubin, AST (SGOT), ALT (SGPT)	X	X		X		X
Total protein, Albumin	X					X
Urinalysis	X	X		X		
Bone Marrow Aspirate/Biopsy (Bilateral)	X		X[2]			
CSF	X					
Echocardiogram and EKG	X			X[3]		X
CXR (PA + Lateral)	X		X[5]		X[5]	X
CT or MRI (primary site and neck/chest/abd/pelvis)	X		X[5]		X[5]	X
Bone Scan (For patients with bone primary disease only)	X		X[5]		X[5]	X
FDG-PET Scan (highly recommended - not mandatory)	X		X[5]		X[5]	X[4]
Blood for MRD	**X**	**X[6]**				

[1] Women of childbearing potential require a negative pregnancy test prior to starting treatment; males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method during protocol therapy and for at least 30 days after the last dose of chemotherapy. Abstinence is an acceptable method of birth control.

[2] After Cycle 2, if positive at diagnosis.

[3] Echocardiogram prior to Cycle 4 and 6.

[4] If most recent PET was positive.

[5] All sites of disease should be evaluated after Cycle 2 and cycle 6. If not in CR or CRU after Cycle 2, obtain after Cycle 4

[6] **MRD COLLECTED AT 3 TIMES POINTS: BASELINE PRIOR TO THERAPY, DAY 6 AT END OF PROPHASE BEFORE CYCLE 1 AND AT END OF CYCLE 1. PLEASE SEE SECTION 13 FOR DETAILS ON SPECIMEN SHIPPING.**

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

7.2 Follow-up

The following studies are required until the patient is off study as defined in Section 8.2.

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

7.2.1 Follow-up Table

STUDIES TO BE OBTAINED	Every 3 Months up to 12 Months (Months 3, 6, 9, 12)	Every 6 Months up to 24 Months (Months 18, 24)	Annually up to 60 Months (Months 36, 48, 60)
History	X	X	X
Physical Exam with vital signs	X	X	X
CBC, differential, platelets[1]	X	X	X
Creatinine, ALT (SGPT), bilirubin[1]	X	X	X
Electrolytes including Ca^{++}, PO_4, Mg^{++2}	X	X	X
Echocardiogram and EKG[2]	X[2]		
CT or MRI (primary site and neck/chest/abd/pelvis)[3]	X[3]	X[3]	
Bone Scan (for bone primaries only)[3]	X[3]	X[3]	

[1] Repeated as clinically indicated
[2] Obtain at month 12
[3] Disease evaluation should be at months 3, 6, 12, and 18 and as clinically indicated

Obtain other studies as needed for good patient care and as per COG Late Effects Guidelines.

See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org/

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease: The diagnosis of relapse or progression should be proven by biopsy and histology.
b) Relapse: Relapse will be defined as a recurrence of disease at any site. The diagnosis of relapse or progression should be proven by biopsy and histology.
c) Refusal of further protocol therapy by patient/parent/guardian.
d) Completion of protocol therapy.
e) Physician determines it is in patient's best interest.
f) Development of a second malignancy.
g) Repeat eligibility studies (if required) are outside the parameters required for eligibility.
h) Study is terminated by Sponsor.
i) Pregnancy.
j) Adverse Event requiring removal from protocol therapy (See Section 5.0).

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent is withdrawn.

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG study with tumor therapeutic intent (e.g., at recurrence).
d) Withdrawal of consent for any further data submission.
e) The fifth anniversary of the date the patient was enrolled on this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size and Study Duration

Enrollment of newly diagnosed patients with ALCL to ANHL0131 averaged about 30 patients per year. With the ANHL12P1 expanded eligibility criteria, namely stage II patients to be consistent with ALCL99, COG expects to enroll about 41 patients per year. As detailed below, enrollment up to 140 patients will be required (to enroll 128 eligible patients, evaluable for the primary adverse events outcome) and we expect that this enrollment will be accomplished in about 3.5 years.

9.2 Study Design

This study is designed to evaluate the feasibility of the addition of brentuximab vedotin or crizotinib to standard chemotherapy (ALCL99).

Patients will be randomized 1:1 to ALCL99 chemotherapy plus either brentuximab vedotin or crizotinib. Total enrollment will be up to 140 patients (70 per randomized treatment to assure the enrollment of 64 eligible patients on each of the 2 regimens. Should enrollment to one of the treatment regimens be closed (see below) prior to reaching 64 eligible patients, enrollment to the remaining regimen will continue to a total sample size that will assure 64 eligible patients.

9.2.1 Primary study endpoint:

The primary study endpoints will be the occurrence of Grade 3+ non-hematologic adverse events and event-free survival defined as the time from study entry until progressive disease, relapse, or death. All patients receiving any protocol treatment will contribute to the primary analysis.

Patient rates of certain Grade 3+ non-hematologic toxicities for each regimen (pre-phase plus 6 cycles of alternating A/B courses) will be compared to those seen on ALCL99. Information about the ALCL99 adverse event experience is primarily available.[30] The authors report patient level incidence rates for infection (21%); stomatitis (42%), and liver toxicity (defined as hyperbilirubinemia or AST/ALT elevation) (38%).

For the first 10 patients of each arm, the study chair will review reported toxicities on a weekly basis through the COG system. The study committee will have conference calls at least every month reviewing all the adverse experience data, with focus on targeted toxicities. The study chair will review reported toxicities on a weekly basis and all deaths, and patients removed from study due to toxicity will be reported to the DSMC for review, as well. Because the patients will be monitored continuously by the study chair, the study committee, and the DSMC, the study will not be stopped after the first 10 patients of each arm to evaluate for toxicity.

Because of concern regarding pulmonary toxicity with brentuximab vedotin and liver toxicity with crizotinib, these toxicities will be monitored. A 5% rate of Grade 3+ pulmonary toxicity with brentuximab vedotin and a 5% rate of Grade 4+ liver toxicity with crizotinib are considered acceptable, but a true rate of 15% for either of these would be unacceptable. Thus interim analysis of these rates will be performed using an alpha-spending function approach using an O'Brien-Fleming monitoring boundary (truncated at 3 standard deviations) beginning at about 33% of the expected information (21 patients per treatment).

With 64 eligible subjects, if only one analysis were to be done once all patients had completed treatment, the rule applied would be to declare the adverse event experience acceptable if six (6) or fewer patients experienced the targeted grade 3+ or grade 4+ adverse event and unacceptable if seven (7) or more experienced this adverse event. Using exact binomial probabilities, the probability of declaring the adverse event rate unacceptable when the true rate is 5% is 4% (0.0403), whereas the probability of declaring the adverse event rate unacceptable when the true rate is 15% is 86% (0.8635).

However, these rates of adverse event will be monitored during the conduct of the study. The actual rules for declaring the adverse event rate unacceptable will depend on when the monitoring takes place. The table below presents the boundaries should the interim monitoring be done at exactly 33%, 56%, 77% and 100% of the expected information with the overall alpha expended equal to or less than 0.05.

Percent of total information	Sample size for regimen	Rule to reject adverse event rate of 5%	Nominal alpha for comparison
33%	21	6+ with adverse event	0.00044
56%	36	6+ with adverse event	0.00834
77%	49	7+ with adverse event	0.01058
100%	64	7+ with adverse event	0.04030

Total alpha is less than 0.05 because the individual tests to be performed are with the exact binomial distribution and these rules generate nominal alphas less than the O'Brien-Fleming boundary which produces an overall alpha of 0.05. Application of a similar rule (an alpha-spending function approach using an O'Brien-Fleming monitoring boundary truncated at 3 standard deviations beginning at about 33% of the expected information with subsequent interim looks) will have the same property.

ALCL99 had 4 treatment related deaths (1%) during treatment. Therefore, we will suspend enrollment to any arm of the study if more than 1 patient dies to review the circumstances of the deaths. A recommendation to re-open enrollment might be made if causes other than therapy were thought to be the primary cause of death

Due to the apparent increased risk of thromboembolic events and the requirement for prophylactic anticoagulation in Arm CZ, as of Amendment 6A additional stopping rules have been added. The trial will be stopped if any of the following occur in patients enrolled after Amendment 6A:

- Two CVL-associated thrombotic events
- Any one event of
  - Thromboembolic event requiring surgical intervention, or
  - Pulmonary embolism
- Two bleeding events, defined as Grade 2 or higher hemorrhage events as classified in CTCAE. Grade 2 or higher events correspond to bleeding events which require intervention and consist of major bleeding and clinically relevant minor bleeding. Please see Section 11.10 for reporting details.

Evidence of improvement in event-free survival outcome compared to that expected outcome with ALCL99 therapy: There is anecdotal evidence that these agents are effective in CD30+/ALK+ disease. Long-term event-free survival (EFS) for ANHL12P1 patients is expected to be 70%. We will compare the EFS outcome for each regimen to a fixed exponential cure model with a "cure" rate of 70%, and the 30% who fail failing as exponential with lambda equal to 1.5 (95% of failures occurring in the first 2 years). Testing at a 10% level of statistical significance (1-sided), there will be 90% power to detect an increase in long-term EFS from 70% to 84% (relative risk: 0.50:1.00). The EFS for each of the treatment regimens will be compared to the fixed standard using a 1-sample log-rank test. No formal comparison of EFS between the two randomized treatments is planned.

Futility monitoring plan
The alternative hypothesis is that, compared with standard therapy, the risk of an event will be reduced by 50%; that is, the event-free survival (EFS) under the alternative is expected to be:

$$S(t) = [0.7 + 0.3 \cdot \exp(-1.5t)]^{1/2}$$

Let K be the number of failures observed in the available follow-up and R be the sum of the cumulative hazards associated with $S(t)$ to time t_i, where t_i is the follow-up for patient i. Then, under the alternative, $T = K–R$ is approximately normal and may be used for interim monitoring. Under the alternative hypothesis, we expect to observe a total of about 10 failures among the 64 eligible patients randomized to each treatment. Formal interim monitoring for futility will be done twice for each regimen (at about 5 and 10 observed events). Should the test comparing the event-free survival outcome to $S(t)$ have an associated 1-sided p-value less than 0.05 for either treatment group at either interim analysis (indicating poorer EFS), the Data and Safety Monitoring Committee may consider suspending enrollment, because the observed outcome is inconsistent with the expected improvement in EFS with the addition of crizotinib or brentuximab vedotin to standard treatment.

In the event that enrollment of one regimen is suspended (because of unacceptable toxicity or because EFS appears worse that that seen with ALCL99 therapy, enrollment of patients will continue and patients will be non-randomly assigned to the other treatment regimen.

Because 95% of failures are expected to be observed in the first two years of follow-up, the minimal required follow-up for the EFS analyses will be 2 years from the enrollment of the last patient.

9.2.2 Secondary study endpoints:
Prognostic significance of minimal residual disease (MRD): MRD evaluations will be performed at 3 time points (diagnosis, end of prophase (Day 6), and end of Cycle 1 (first Course A). Data from Damm-Welk et al. suggests that about half of the patients with ALK-positive ALCL will have tumor cells detected at diagnosis by PCR in bone marrow or peripheral blood, and that the failure rate for those with tumor cells detected by PCR in bone marrow or peripheral blood is much higher than that for patients who are PCR negative.[29] For instance, 3 of 25 patients whose peripheral blood was negative for NPM-ALK by PCR at diagnosis relapsed (5-year event-free survival: 80%) versus 10 of 27 patients whose peripheral blood was positive for NPM-ALK by PCR at diagnosis (5-year event-free survival: 46%). The expected long-term event-free survival for all patients receiving ALCL99 therapy is 70%. Assuming a total sample size of 128 eligible patients and an equal number of patients with and without peripheral blood MRD at diagnosis, if 25 events is assumed to be the total expected information (allowing for the possibility that the ANHL12P1 EFS outcome may be improved), then there will be 80% power (testing at the 5% level of statistical significance, 1-sided) to detect a relative risk of 2.7:1.0 (corresponding approximately to an event-free survival of 82% for MRD negative and 58% for MRD positive patients) consistent with the results of Damm-Welk et al. These comparisons will be made using the log-rank test.

9.3 Methods of Analysis

All patients will be included in the analyses provided they are eligible and evaluable for the particular endpoint (EFS, toxicity, etc.). The EFS for each of the treatment regimens will be compared to the fixed standard using Woolson's 1-sample log-rank test.[31] No formal comparison of EFS between the two randomized treatments is planned. MRD evaluations will be performed at 3 time points (diagnosis, end of prophase (Day 6), and end of Cycle 1) and groups analyzed using the log-rank test. Toxicities will be summarized by individual toxicity counts and incidence rate separated by arm and course.

9.4 Evaluability for Toxicity

All patients will be evaluable for toxicity and included in the toxicity tables and summaries.

9.5 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	7	13	20
Not Hispanic or Latino	47	73	120
Ethnic Category: Total of all subjects	54	86	140*
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	5	4	10
Black or African American	7	16	23
Native Hawaiian or other Pacific Islander	0	0	0
White	42	66	107
Racial Category: Total of all subjects	54	86	140*

* These totals must agree

This distribution was derived from **ANHL0131**, *A Phase III Trial of Treatment of Advanced-Stage Anaplastic Large Cell Lymphoma (ALCL) with Standard APO (Doxorubicin, Prednisone, Vincristine) versus Consolidation with a Regimen Including Vinblastine*

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (i.e., v4.02 and all subsequent iterations prior to version 5.0).

10.2 Response Criteria Overview

Response will be evaluated in this study using guidelines and response criteria that have been revised from previous protocols (ANHL0131 and ALCL99) and the recent work of the International Lymphoma Working Group's revised recommendations for malignant lymphoma.

Establishing strict response criteria for ALCL is complicated by the fact that a large number of patients possess extranodal disease which by its nature is more difficult to measure. In addition, establishing strict CT size criteria for presumptive lymphomatous nodal enlargement is complicated by a number of factors, including substantial size overlap between benign reactive lymphoid hyperplasia and malignant lymphadenopathy, interobserver measurement variability, obliquity of node orientation to the scan plane, multiplicity of criteria for size measurement (volumetric vs. bidimensional vs. unidimensional; short axis vs. long axis), variability of normal nodal size with body region and age. For children and younger adolescents, there are no established size limits for normal lymph nodes. Furthermore, in children reactive hyperplasia is common in the cervical, axillary, mesenteric, and inguinal regions, and may be associated with nodes up to 1.5-2 cm in diameter. In other anatomic regions, including the supraclavicular, retroperitoneal, iliac, mediastinal, and hilar regions, normal nodes are typically less than 1-1.5 cm. Despite these limitations, certain features suggest lymphomatous involvement, such as contiguous nodal clustering or matting, and nodal FDG avidity.

With these caveats in mind, the nodal size criterion used by previous lymphoma protocols will be used. For visceral organs (such as liver, spleen, kidney, lung) any focal mass lesion large enough to characterize is considered due to lymphomatous involvement unless the imaging characteristics indicate an alternative nature (e.g., cyst, hemangioma, abscess, etc.). Lesions too small to characterize are considered indeterminate unless follow-up studies allow characterization or tissue sampling is performed.

A measurable lesion by CT or MRI is a lesion that can be accurately measured in 2 orthogonal dimensions. For extranodal sites, this typically involves lesions of at least 1 cm diameter. Lymph nodes are considered abnormal if the long axis is ≥ 1.5 cm, regardless of the short axis. Lymph nodes with a long axis measuring between 1.1-1.5 cm are only considered abnormal if their short axis is ≥ 1.0 cm.

All measurable lesions should be measured in the axial plane on CT. All measurable lesions, representative of all involved organs, will be measured as target lesions at baseline and followed for response. Target lesions will be selected on the basis of size (i.e., largest lesions) and suitability for accurate repeated measurements by imaging or clinical exam. Lesions will be recorded with size expressed as the PPD (product of perpendicular diameters). The PPD is obtained by multiplying the longest diameter of the lesion by the maximal diameter perpendicular to the longest diameter in axial plane, and serves as a surrogate measurement of tumor volume, assuming the mass has a spherical or ellipsoid shape. The SPPD, or sum of the products of the perpendicular diameters, is obtained by adding the products of the perpendicular diameters of measured lesions. FDG-PET imaging will be performed as per clinical routine, adhering to the imaging guidelines.

Non-measurable assessable lesions include permeative bone lesions, malignant ascites, malignant pleural/pericardial effusions, pulmonary or cutaneous lymphangitic spread, and lesions too small to accurately measure in 2 dimensions by CT. All non-target and non-measurable assessable lesions should be recorded at baseline and noted on follow-up.

10.3 Response Criteria for Patients with ALCL

10.3.1 Complete Response (CR)

Disappearance of all evidence of disease from all sites. This will be determined by physical exam and imaging. All lymph nodes and nodal masses must have regressed on CT to normal size (< 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Bone marrow aspirate/biopsy must be normal if initially positive and any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. PET scans must be negative if initially positive.

10.3.2 Complete Response Unconfirmed (CRu)

A residual lymph node mass > 1.5 cm in greatest transverse diameter that has regressed by > 75% in sum of the products of the greatest perpendicular diameters (SPPD) or returned to normal size (< 1.5 cm in greatest diameter) will be considered CRu. Any residual lesions in organs that have decreased by >75% and with a negative PET scan will be considered CRu. When disease affects the liver, spleen or kidneys it may be the case that residual abnormalities are seen following treatment. These generally measure < 1 cm diameter. Patients with only residual positive bone lesions on PET and/or bone scans will be considered in CRu. Patients with bone involvement may have positive lesions on PET or bone scan for some time; therefore, these patients will be considered in CRu if the other residual lesions have disappeared, or if the residual lymph node mass or masses > 1.5 cm in greatest transverse diameter have regressed by > 75% in sum of the products of the greatest perpendicular diameters (SPPD).

10.3.3 Partial Response (PR)

≥ 50% decrease in the SPPD of the lesions. No new lesions.

10.3.4 No Response (Stable Disease)

Failure to qualify for a PR. No new lesions.

10.3.5 Progressive disease (PD)
≥ 25% increase in the size of any lesions or appearance of new lesions.

Caveat: The presence of a residual mass should not be considered as a failure in the majority of the cases if it is less than 25-30% of the initial tumor volume and should not imply any modifications of the treatment. In the ALCL99 series, many patients had a residual mass at the end of the treatment and were followed without evidence of progression

10.3.6 Duration of Response

10.3.6.1 Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

10.3.6.2 Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *Grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label*.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial*.

***In this study both brentuximab vedotin and crizotinib are considered investigational agents and should have adverse events reported as investigational agents.**

When a study includes both investigational and commercial agents, these rules apply:

- *Concurrent administration*: When an investigational agent is used in combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent and a commercial agent on the same study arm, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events which occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

11.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations which are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.4 Special Situations for Expedited Reporting

11.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting tables in this protocol.

11.4.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI IND/IDE since these are considered to be serious AEs

11.4.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as Grade 5 "*Disease progression*" in the system organ class (SOC) "*General disorders and administration site conditions*". Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.4.4 Secondary Malignancy

A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (eg, treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) must also be reported via the routine reporting mechanisms outlined in this protocol.

11.4.5 Second Malignancy

A ***second malignancy*** is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

11.4.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.4.6.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the ***Pregnancy, puerperium and perinatal conditions*** SOC.

There is a possibility that the sperm of male patients treated on studies involving possible teratogenic agents may have been damaged. For this reason, **pregnancy in partners of men on study needs be reported and followed in the same manner as a patient pregnancy**.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.4.6.2 **Pregnancy Loss (Fetal Death)**

Pregnancy loss is defined in CTCAE as "*Death in utero*." Any Pregnancy loss should be be reported expeditiously, as **Grade 4 "*Pregnancy loss*" under the "*Pregnancy, puerperium and perinatal conditions*" SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4.6.3 **Death Neonatal**

Neonatal death, defined in CTCAE as *"Newborn death occurring during the first 28 days after birth*", should be reported expeditiously as **Grade 4, "*Death neonatal*" under the "*General disorders and administration*" SOC, when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.5 Reporting Requirements for Specialized AEs

11.5.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.5.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent cycle. If the grade becomes more severe the AE must be reported again with the new grade.

EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent cycle.

11.5.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle of therapy and then reoccurs in a later cycle.

ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle must be reported by the routine procedures.

EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

11.6 Exceptions to Expedited Reporting

11.6.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL).

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.6.2 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting Table A for this protocol.

11.7 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.8 General Instructions for Expedited Reporting via CTEP-AERS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at: https://eapps-ctep.nci.nih.gov/ctepaers.

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to 301-897-7497.

In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**
- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.
- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Any medical documentation supporting an expedited report (eg, H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to brentuximab vedotin and critzotinib** to: **301-230-0159** (back-up: 301-897-7404).

Also: Fax supporting documentation **for AEs related to brentuximab vedotin AND crizotinib** to COG for **all** IND studies (fax # 310-640-9193 attention: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.9 Reporting Table for Phase 1 and Early Phase 2 Studies

Table A: Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date:May 5, 2011

11.10 **Protocol Specific Additional Instructions and Reporting Exceptions**

Additional Reporting Instructions

- **Targeted toxicities such as pulmonary toxicity with brentuximab vedotin and liver toxicity with crizotinib will be monitored closely on this study.**
- **Grade 2 or higher thromboembolic events require expedited reporting. All catheter-related thrombosis should be reported as thromboembolic events and not vascular access complications. This should be done for consistency to ensure that all events are graded similarly.**
- **Grade 2 or higher hemorrhage (bleeding) events require expedited reporting. Please note that CTCAE uses the location of the hemorrhage to define the event (e.g. gastric hemorrhage, colonic hemorrhage, oral hemorrhage, etc.).**

Reporting Exceptions

- **Grades 1-4 myelosuppression (anemia, neutropenia, thrombocytopenia; lymphopenia) do not require expedited reporting.**
- **Grades 1-2 AST/ALT elevations do not require expedited reporting, and Grade 3 AST/ALT elevations do not require expedited reporting if they recover to ≤ Grade 1 (< 2.5 X ULN) or baseline within 7 days of study drug interruption.**
- **Grade 3 febrile neutropenia does not require expedited reporting.**
- **Grade 3 infection does not require expedited reporting.**
- **Grade 3 nausea and vomiting of < 3 days duration does not require expedited reporting**
- **Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation does not require expedited reporting.**

11.11 **Reporting of Adverse Events for commercial agents – CTEP-AERS abbreviated pathway**

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study.

Commercial reporting requirements are provided in Table B.

COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.

Table B
Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study. CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy with a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS
[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.			

11.12 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all toxicities reported via CTEP-AERS and all Grade 3 and higher Adverse Events (except what is listed in Section 11.10), and all Grade 1-2 Adverse Events which result in dose modifications (See Section 5.0).

12.0 STUDY REPORTING AND MONITORING

The Case Report Forms and the submission schedule are posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

12.2 Data Safety and Monitoring Committee

To protect the interests of patients and the scientific integrity for all clinical trial research by the Children's Oncology Group, the COG Data and Safety Monitoring Committee (DSMC) reviews reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair's report. The DSMC may recommend the study be modified or terminated based on these analyses.

Toxicity monitoring is also the responsibility of the study committee and any unexpected frequency of serious events on the trial are to be brought to the attention of the DSMC. The

study statistician is responsible for the monitoring of the interim results and is expected to request DSMC review of any protocol issues s/he feels require special review. Any COG member may bring specific study concerns to the attention of the DSMC.

As explained earlier in Section 9.2, for the first 10 patients of each arm, the study chair will review reported toxicities on a weekly basis through the COG system. The study committee will have conference calls at least every month reviewing all the adverse event data, with focus on targeted toxicities. The study chair will review reported toxicities, all deaths, and patients removed from study for due to toxicity on weekly basis and will be reported to the DSMC for review, as well.

The DSMC approves major study modifications proposed by the study committee prior to implementation (eg, termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, etc.). The DSMC determines whether and to whom outcome results may be released prior to the release of study results at the time specified in the protocol document.

12.3 CRADA/CTA

NCI/DCTD Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA), a Cooperative Research and Development Agreement (CRADA) or a Clinical Supply Agreement, hereinafter referred to as Collaborative Agreement:

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:
Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13.0 PATHOLOGY GUIDELINES AND SPECIAL STUDIES

13.1 Pathology Guidelines

13.1.1 Pathology Goals

1. Provide accurate diagnosis and classification of pediatric anaplastic large cell lymphoma included in this treatment protocol. The diagnosis to be based on both morphological and immunophenotypic criteria.
2. Employ the World Health Organization Lymphoma Classification to facilitate concordance in diagnosis.
3. Evaluate pediatric ALCL included in this protocol for pathologic features that may impact prognosis.

13.1.2 Requirements for Handling Tissue or Cytology Specimens at Primary Institutions

Tissue should, whenever possible, be obtained fresh and delivered immediately to the Pathology laboratory for optimal handling and distribution (fixation, snap freezing, cytogenetics, etc.)

Representative tissue sections should be submitted for fixation including one block with 10% Formalin and, if possible, a second block of tissue with a different fixative routinely used by the local pathologist.

13.1.3 Immunophenotyping Recommendations for Primary Institutions

For initial determination of cell lineage (T or null) the methodology and criteria for immunophenotypic analysis defined by the submitting institution will be accepted. Recognized methods include paraffin section, immunohistochemistry, frozen section immunohistochemistry, and cytospin immunocytochemistry.

Recommended antibodies

- Two anti-B antibodies (CD79A, and CD20)
- Two anti-T antibodies (CD3 and CD43 or CD3 and CD45RO)
- CD30
- CD15
- EMA
- ALK-1
- LMP-1 and/or EBER

13.1.4 Morphology

The following are recognized morphological variants of anaplastic large cell lymphoma

- Common type
- Small cell variant
- Lymphohistiocytic variant
- Giant cell variant
- Mixed variant: association in the same lymph node biopsy specimen of features of more than one morphological variant (i.e. common type plus small cell variant, common type plus lymphohistiocytic, small cell variant plus lymphohistiocytic variant etc.)
- Unclassifiable: because of small biopsy specimens or peculiar morphological features (i.e. sarcomatous features, signet cells etc.).

13.1.5 Bone Marrow

Because of frequent occult bone marrow involvement, immunohistochemical studies using anti-CD30 and anti-ALK antibodies should be performed even if the bone marrow appears to be uninvolved on conventional examination. Note that ALK1 antibody does not always give reliable staining on fixed and decalcified trephine bone marrow biopsy.

13.1.6 Study Pathologists

For any questions regarding the pathology protocol or assistance with immunophenotyping studies, contact the pathologists listed below. Difficult cases may also be reviewed in consultation prior to enrollment with one of the pathologists listed below.

Megan S. Lim, MD, PhD
Director of Hematopathology
Room 514/515
Stellar-Chance Laboratories
422 Curie Boulevard
Philadelphia, PA 19104
Phone: (215) 898-2925
E-mail: Megan.Lim@uphs.upenn.edu

Robert E. Hutchison, MD
SUNY Upstate Medical University
Pathology
750 East Adams Street
Syracuse, NY 13210
Phone: (315) 464-6771
Fax: (315) 464-7322
E-mail: hutchisb@upstate.edu

Rodney Miles, M.D., Ph.D.
University of Utah Health Sciences Center/ARUP Laboratories
Hematopathology Mail G02-100
500 Chipeta Way
Salt Lake City, UT 84108
Phone: (801) 584-5240
Fax: (801) 584-5124
E-mail: Rodney.Miles@path.utah.edu

13.2 Specimens to Submit For Central Pathology Review

13.2.1 List of Specimen Types

Materials to be submitted for retrospective pathology review are not required but strongly encouraged. If possible, please submit the following materials to the COG Biopathology Center (BPC):

1. Paraffin blocks from tumor biopsy at original diagnosis and relapse (if applicable). If blocks are unavailable submit 30 unstained from one representative block and 2 H&E slides from each available block. For surgical biopsy specimens 10% buffered formalin is the preferred fixative. Please submit unbaked slides that air dried at room temperature for the unstained slides on silane coated slides (i.e. Fisher Superfrost Plus).

2. One stained bone marrow aspirate smear (Romanowsky) and an H&E stained section and 6 unstained sections from the bone marrow clot and biopsy blocks.

3. Representative peripheral blood smear (Romanowsky stain) containing lymphoma cells when peripheral blood involvement is suspected.

4. All corresponding pathology and ancillary testing (i.e. flow cytometry, cytogenetics) reports should be submitted.

5. COG Generic Specimen Transmittal Form along with the Pathology Data Collection Form (Institutional Pathology Form).

13.2.2 Pathology Reports

A copy of all pathology reports on each case must be submitted. These are required. This should include:

- Final reports of diagnostic biopsies, bone marrow specimens, and cerebrospinal fluid specimens including all immunophenotyping reports of diagnostic biopsy, bone marrow specimens and cerebrospinal fluid specimens (if available) also include copies of flow cytometry histograms (if available);

- Results of any genotypic studies (i.e. gene rearrangement or fluorescent in-situ hybridization studies); and

- Results of any cytogenetic (karyotypic) analysis.

13.2.3 Pathology Data Collection Forms (Institutional Pathology Form)

A separate pathology data collection form (Institutional Pathology Form) must be completed and submitted along with the above materials. Also, indicate the primary institution pathology diagnosis utilizing the WHO[32] on the data collection form.

13.2.4 Submission of Pathology Review Materials

Label all review materials with the patient's COG patient ID number and the surgical pathology identification number and block number from the corresponding pathology report. Send a completed COG Generic Specimen Transmittal Form with the pathology review materials by U.S. mail or using your institution's courier account. All material submitted for central pathology review should be sent to:

Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, WA 1340
Columbus, OH 43205
Phone: (614) 722-2894
FAX: (614) 722-2897

13.3 Special Tissue Banking

13.3.1 Tissue Banking

If sufficient tissue is available, representative fresh tissue should be snap frozen for biology studies. It is recommended that a minimum of a 5x5x3 mm section of tumor tissue be placed in foil and snap frozen in the vapor phase of liquid nitrogen. Tissue should be stored at -70 to -80 degrees Centigrade until shipment. Label the foil with the patient's BPC number and place the tissue in a zip lock bag labeled with the patient's BPC number, specimen type and collection date.

Specimen procurement kits for submission of frozen tumor tissue are provided upon request. To obtain a kit, click on the 'Biopathology Center Application' link on either the Protocol or the CRA Home Page of the COG web site. On the Biopathology Center Applications page, select the BPC Kit Management link to enter the Kit Management application.

Ship the tissue on dry ice and include a transmittal form and the corresponding pathology report in the shipment. Specimens must be shipped Monday through Thursday for Tuesday through Friday delivery. Obtain a FedEx shipping label via the BPC Kit Management application.

Ship to: Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, WA 1340
Columbus, OH 43205
Phone: (614) 722-2865
FAX: (614) 722-2897

13.4 Peripheral Blood Studies for MDD/MRD (Required)

MDD/MRD studies will be performed in children with ALCL. **These correlative studies are required and the study chair must be notified if these samples are not available.** RT-PCR will be performed on total RNA extracted from serial peripheral blood specimens, for detection of the t (2;5) NPM/ALK fusion transcript. Results will not be returned to the treating physician.

Peripheral blood (15 mL) should be collected in EDTA (purple top) tubes. Use as many collection tubes as needed in order to collect the required volume. Record the exact time and date that the sample is drawn. Samples should be shipped room temperature, the same day as drawn. If the samples cannot be shipped immediately (i.e. is collected in the evening and will be shipped out the next morning via FedEx), they should be stored in a refrigerator until shipment. **Note: Samples should be sent ASAP once drawn.**

Do not ship samples for delivery on a weekend or Holiday. Because Saturday/Sunday delivery is NOT available and the study requires fresh specimens, please collect MRD at appropriate times to allow for M-F delivery. There are 3 time points to collect blood.

i. Baseline: Collect on weekdays for M-F delivery.

ii. Day 6 (End of Prophase): Collect as close as possible to Day 6 for M-F delivery (if Day 6 is a Friday, please collect and send on Thursday for Friday delivery; if Day 6 is Saturday or Sunday collect on Sunday night or Monday am for Monday shipment).

iii. End of Cycle 1: Collect as close as possible to end of Cycle 1 (prior to starting Cycle 2). Sample should be sent for M-F delivery.

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the MDD/MRD specimen transmittal form, which must accompany the sample(s). Samples will be sent at room temperature.

13.4.1 Shipment of Peripheral Blood

- Label tube with patient's registration number, the study ID (ANHL12P1) and date and time it was drawn.
- Place tube(s) in water-tight envelope or container with absorbent material.
- Place the container in a Styrofoam box.
- Package sample as appropriate for biologic material.
- **Ship the sample on the same day it was obtained with FedEx priority overnight** using the COG FedEx account number available at: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf

Ship to: Dr. Megan S. Lim
Attention Dr. Delphine Rolland
Room 514/515
Stellar-Chance Laboratories
422 Curie Boulevard
Philadelphia, PA 19104
Phone: (215) 898-2925
E-mail: Megan.Lim@uphs.upenn.edu

Email Dr. Megan Lim (Megan.Lim@uphs.upenn.edu) and Delphine Rolland (drolland@mail.med.upenn.edu) prior to Federal Express shipment of BM or PB samples. Do not ship samples for delivery on a weekend or Holiday. **Samples should be sent ASAP once drawn.**

14.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

CT and MRI guidelines are available on the COG Member site at:
https://cogmembers.org/_files/reference/RefMaterial/DiagnosticImagingGuidelines_MRICT.pdf

For PET scan guidelines please refer to the NCI guidelines for the recommended set of procedures for the acquisition and analysis of 18F-FDG PET scans of patients participating in NCI-sponsored diagnostic and therapeutic clinical trials, which can be found at the following link: https://imaging.cancer.gov/programs_resources/reports_publications/publications/clinical_trials_guidelines.htm

15.0 SURGICAL GUIDELINES

15.1 Role of the Surgeon

The role of the surgeon in patients with anaplastic large cell lymphoma (ALCL) is to obtain tissue for diagnosis and occasionally to treat complications related to the disease. In all cases, ALCL is considered a "systemic" disease and thus therapy revolves around chemotherapy rather than methods to achieve local control such as surgery or radiotherapy. For all sites, tissue should be sent to the pathologist FRESH for histopathology, immunohistochemistry, and cytogenetics.

APPENDIX I: STAGING

Stage	Criteria for extent of disease
I	A single tumour (extranodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen
II	A single tumor (extranodal) with regional node involvement Two or more nodal areas on the same side of the diaphragm Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm A primary gastointestinal tumor usually in the ileocaeacal area with or without involvement of associated mesenteric nodes only, grossly completely resected
III	Two single tumors (extranodal) on opposite sides of the diaphragm Two or more nodal areas above and below the diaphragm All primary intra-thoracic tumours (mediastinal, pleural, thymic) All extensive primary intra-abdominal disease All paraspinal or epidural tumours regardless of other tumor site(s)
IV	Any of the above with initial CNS and/or bone marrow involvement

Skin involvement
Skin involvement should always be confirmed by biopsy. Skin infiltration by continuous tumor growth arising by extension from a contiguous lymph node or soft tissue tumor is not considered as primary skin involvement.

Mediastinal involvement
Mediastinal involvement should be confirmed by X-ray or CT-scan. If the histopathological diagnosis can be performed by biopsy of other organs such as peripheral lymph nodes, a biopsy is not necessary for obvious lesions that may jeopardize the patient.

Lung involvement
Lung involvement should be confirmed by X-ray or CT-scan. If the histopathological diagnosis can be performed by biopsy of other organs such as peripheral lymph nodes, a lung biopsy not necessary for obvious lesions that may jeopardize the patient

Bone Marrow
The presence of any lymphoma cells in a bone marrow aspirate or biopsy represents involvement of the marrow by lymphoma. Use of CD30 and/or ALK immunostaining is suggested as it is very helpful in demonstrating bone marrow involvement as involvement is often morphologically subtle.

CNS involvement is considered if:
1. Tumor cells are present in CNS or
2. Cranial nerve palsy is present unexplained by a local extracerebral lesion or
3. Cerebral or spinal tumor is diagnosed by CT or MRI

APPENDIX II: PERFORMANCE STATUS CRITERIA

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10

ECOG(Zubrod)		Karnofsky Patients 17 and older		Lansky* Patients age 1-16	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort, some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Required occasional assistance and frequent medical care.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX III: CTEP REGISTRATION PROCEDURES

CTEP INVESTIGATOR REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Requirements for ANHL12P1 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Data Submission / Data Reporting

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role,

the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

APPENDIX IV: COMMON SUBSTRATES, INHIBITORS AND INDUCERS OF CYP3A4

This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently-updated medical references.

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Weak Inhibitors	Inducers
alfentanil[4,5]	atazanavir	aprepitant	alprazolam	armodafinil
amiodarone[4]	boceprevir	conivaptan	amiodarone	barbiturates
aprepitant[5]	clarithromycin	crizotinib	amlodipine	bosentan
atorvastatin[5]	cobicistat	diltiazem	atorvastatin	carbamazepine
benzodiazepines	darunavir	dronedarone	bicalutamide	deferasirox
bortezomib	delavirdine	erythromycin	cilostazol	echinacea
brentuximab	grapefruit[3]	fluconazole	cimetidine	efavirenz
budesonide[5]	grapefruit juice[3]	fosamprenavir	ciprofloxacin	etravirine
buspirone[5]	indinavir	grapefruit[3]	cyclosporine	fosphenytoin
calcium channel blockers	itraconazole	grapefruit juice[3]	fosaprepitant	glucocorticoids[2]
cisapride	ketoconazole	imatinib	fluvoxamine	modafinil
citalopram/escitalopram	lopinavir/ritonavir	mifepristone	isoniazid	nafcillin
conivaptan[5]	nefazodone	nilotinib	nicardipine	nevirapine
glucocorticoids[2]	nelfinavir	verapamil	propofol	oxcarbazepine
crizotinib	posaconazole		quinidine	phenobarbital
cyclosporine[4]	ritonavir		ranolazine	phenytoin
cyclophosphamide	saquinavir			pioglitazone
dapsone	telaprevir			primidone
darifenacin[5]	telithromycin			rifabutin
darunavir[5]	voriconazole			rifampin
dasatinib[5]				rifapentin
dihydroergotamine				ritonavir
docetaxel				St. John's wort
doxorubicin				topiramate
dronedarone[5]				
eletriptan[5]				
ergotamine[5]				
eplerenone[5]				
erlotinib				
esomeprazole				
estrogens				
etoposide				
everolimus[5]				
felodipine[5]				
fentanyl[4]				
fosaprepitant[5]				
gefitinib				
haloperidol				
HIV antiretrovirals				
HMG Co-A inhibitors[5]				
ifosfamide				
imatinib				
indinavir[5]				

irinotecan itraconazole ketoconazole lansoprazole lapatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] modafinil montelukast nefazodone nilotinib nisoldipine[5] omeprazole ondansetron paclitaxel pazopanib quetiapine[5] quinidine[4] saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sunitinib tacrolimus[4,5] telaprevir tamoxifen temsirolimus teniposide tetracycline tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vinca alkaloids zolpidem				

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2] Dexamethasone is considered a weak CYP3A4 inducer.
[3] The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4] Narrow therapeutic range substrates
[5] Sensitive substrates

APPENDIX V: CRIZOTINIB DOSING TABLES

CRIZOTINIB: 165 mg/m^2 PO BID dose level

Dose Group	Body Surface Area (m^2)	Dose
A*		250 mg PO once daily
B	0.9 – 1.29	200 mg PO BID
C	1.3 – 1.44	250 mg PO QAM and 200 mg PO QPM
D	1.45 - ≥ 2.00	250 mg PO BID

* Dose Group A will only be utilized if Dose Group B needs dose modification to a lower dose level. All patients should be started using Dose Levels B, C, or D.

APPENDIX VI: POSSIBLE DRUG INTERACTIONS

The lists below do not include everything that may interact with crizotinib and/or chemotherapy. Study patients and/or their parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in the diet.

Brentuixmab Vedotin:

Drugs that may interact with brentuximab vedotin

• Antibiotics
  o Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antifungals
  o Itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  o Leflunomide, tofacitinib
• Anti-rejection medications
  o Cyclosporine, sirolimus, tacrolimus
• Antiretrovirals and antivirals
  o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir
• Anti-seizure medications
  o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
• Heart medications
  o Nicardipine, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  o Bosentan, deferasirox, dexamethasone, lomitapide, natalizumab, nefazodone

Food and supplements that may interact with brentuximab vedotin*
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Crizotinib:

Drugs that may interact with crizotinib
• Antibiotics o Ciprofloxacin, levofloxacin, moxifloxacin, clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin • Antidepressants and antipsychotics o Aripiprazole, buproprion, citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, quetiapine • Antifungals o Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications o Leflunomide, tofacitinib • Anti-rejection medications o Cyclosporine, sirolimus, tacrolimus • Antiretrovirals and antivirals o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir • Anti-seizure medications o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone • Heart medications o Amiodarone, amlodipine, dronedenarone, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Many other drugs, including the following: o Aprepitant, artemether/lumefantine, deferasirox, ivacaftor, lomitapide, mifepristone, natalizumab, nimodipine, praziquantel, warfarin
Food and supplements* that may interact with crizotinib
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Cyclophosphamide:

Drugs that may interact with cyclophosphamide
• Allopurinol • Chloramphenicol • Cyclosporine • Digoxin • Etanercept • Hydrochlorothiazide • Indomethacin • Nevirapine • Ondansetron • Pentostatin • Tamoxifen • Trastuzumab • Warfarin
Food and supplements that may interact with cyclophosphamide*
• St John's Wort • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Cytarabine:

Drugs that may interact with cytarabine
• Clozapine • Digoxin • Flucytosine • Leflunomide

Food and supplements that may interact with cytarabine*
• Echinacea

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Dexamethasone (Decadron):

Drugs that may interact with dexamethasone

• Antibiotics
  o Ciprofloxacin, levofloxacin, moxifloxacin, clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  o Aripiprazole, buproprion, citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, quetiapine
• Antifungals
  o Caspofungin, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  o Leflunomide, tofacitinib
• Anti-rejection medications
  o Cyclosporine, sirolimus, tacrolimus
• Antiretrovirals and antivirals
  o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
• Anti-seizure medications
  o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
• Heart medications
  o Amiodarone, amlodipine, dronedenarone, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Some oral contraceptives or birth control medications
• Many other drugs, including the following:
  o Aprepitant, artemether/lumefantine, aspirin, deferasirox, ibuprofen, ivacaftor, lomitapide, mifepristone, natalizumab, nimodipine, praziquantel, warfarin

Food and supplements that may interact with dexamethasone*
• Echinacea • St John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Doxorubicin:

Drugs that may interact with doxorubicin
• Some antiepileptics (carbamazepine, oxcarbazepine, phenobarbital, phenytoin, fosphenytoin) • Some antiretrovirals (stavudine, zidovudine) • Other agents, such as clozapine, cyclosporine, verapamil, and warfarin

Food and supplements that may interact with doxorubicin*
• Echinacea • Glucosamine • St. John's Wort

- Grapefruit, grapefruit juice, Seville oranges, star fruit
- Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Etoposide:

Drugs that may interact with etoposide

- Antibiotics
  - Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
- Antidepressants and antipsychotics
  - Aripiprazole, clozapine, nefazodone
- Antifungals
  - Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
- Arthritis medications
  - Leflunomide, tofacitinib
- Anti-rejection medications
  - Cyclosporine, tacrolimus
- Antiretrovirals and antivirals
  - Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
- Anti-seizure medications
  - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
- Heart medications
  - Amiodarone, dronedenarone, verapamil
- Some chemotherapy (be sure to talk to your doctor about this)
- Many other drugs, including the following:
  - Aprepitant, atovaquone, bosentan, deferasirox, dexamethasone, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, sitaxentan

Food and supplements that may interact with etoposide*

- Echinacea
- Glucosamine
- St. John's Wort
- Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Hydrocortisone:

Drugs that may interact with hydrocortisone

• Arthritis medications
  o Leflunomide, tofacitinib
• Antiretrovirals and antivirals
  o Darunavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tenofovir, tipranivir
• Anti-seizure medications
  o Carbamazepine, phenobarbital, phenytoin, primidone
• Heart medications
  o Amiodarone, carvedilol, dronedarone, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Some oral contraceptives or birth control medications
• Many other drugs, including the following:
  o Aprepitant, aripiprazole, clarithromycin, cyclosporine, deferasirox, itraconazole, ivacaftor, ketoconazole, mifepristone, natalizumab, nefazodone, rifampin, tacrolimus, trazodone, warfarin

Food and supplements that may interact with hydrocortisone*
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Ifosfamide:

Drugs that may interact with ifosfamide

• Antibiotics
  o Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  o Citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, paliperidone, quetiapine, thioridizine, ziprasidone
• Antifungals
  o Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  o Leflunomide, tofacitinib
• Anti-rejection medications
  o Cyclosporine
• Antiretrovirals and antivirals
  o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
• Anti-seizure medications
  o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
• Heart medications
  o Amiodarone, dronedenarone, verapamil
• Stomach and reflux medications
  o Esomeprazole, omeprazole

- Some chemotherapy (be sure to talk to your doctor about this)
- Many other drugs, including the following:
  - Bosentan, sitaxentan, aprepitant, dexamethasone, lomitapide, mifepristone, natalizumab, pimozide

Food and supplements that may interact with ifosfamide*
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Leucovorin:

Drugs that may interact with leucovorin
• Some antiepileptics (fosphenytoin, phenobarbital, phenytoin, primidone)

Food and supplements that may interact with leucovorin*
• Folic acid

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Methotrexate (IV):

Drugs that may interact with methotrexate
• Some antibiotics (amoxicillin, Bactrim, chloramphenicol, ciprofloxacin, penicillin, piperacillin, tetracycline) • Some anti-inflammatory drugs (aspirin, acetaminophen, ibuprofen, naproxen, ketorolac) • Some heartburn medications (esomeprazole, lansoprazole, omeprazole, pantoprazole) • Several other specific agents, including the following: amiodarone, clozapine, cyclosporine, eltrombopag, leflunomide, phenytoin, pimecrolimus, probenecid, pyrimethamine, retinoids, theophylline, warfain

Food and supplements that may interact with methotrexate*
• Alcohol • Echinacea • Some vitamins, including those that contain folic acid or high doses of vitamin C

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

APPENDIX VII: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ANHL12P1
(for children from 7 through 12 years of age)

1 We have been talking with you about Anaplastic Large Cell Lymphoma (ALCL). ALCL is a type of cancer of the immune system. ALCL happens when a type of white blood cell that fights infection does not grow normally. After doing tests, we have found that you have this type of cancer.

2 We are asking you to take part in a research study because you have ALCL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about how to treat children with ALCL.

3 All children who are part of this study will get the standard treatment for ALCL. The standard treatment is with chemotherapy. Chemotherapy is medicine that kills cancer. In this study, one group of children will get an extra medicine called brentuximab vedotin and another group of children will get an extra medicine called crizotinib. The extra medicine you get will be decided by chance, like flipping a coin for “heads” or “tails.” Your doctor will tell you which group you are in. We do not know if treatment with either of the extra medicines will be better than usual treatment. That is why we are doing this study.

4 Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is getting rid of the cancer for as long as possible, and with fewer bad effects; but we don’t know for sure if there is any benefit of being part of this study.

5 Sometimes bad things can happen to people when they are in a research study. There is a risk that you will have more bad effects from adding either brentuximab vedotin or critzotnib to your usual medicines. We do not know this for sure which is why we are doing this study. Other things may happen to you that we don’t yet know about.

6 Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7 We are also going to collect extra blood three times during the study. We want to see if there are ways to tell how the cancer will respond to treatment. This sample would be taken when other regular blood tests are being performed.

8 We are also asking permission to save leftover tissue for future research to help us learn more about cancer and other diseases. This would be taken when a regular biopsy is being performed and will not involve an extra procedure. You can still take part in this study even if you don’t allow us to collect the extra tissue and/or save leftover samples for future research.

INFORMATION SHEET REGARDING RESEARCH STUDY ANHL12P1
(for teens from 13 through 17 years of age)

1 We have been talking with you about Anaplastic Large Cell Lymphoma (ALCL). ALCL is a type of cancer of the immune system. ALCL happens when a type of white blood cell that fights infection, called "lymphocytes" grows abnormally. After doing tests, we have found that you have this type of cancer.

2 We are asking you to take part in a research study because you have ALCL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about how to treat children and teens ALCL.

3 All children and teens who are part of this study will get the standard treatment for ALCL. The standard treatment is with chemotherapy. Chemotherapy is medicine that kills cancer. In this study, one group of children will get an extra medicine called brentuximab vedotin and another group of children will get an extra medicine called crizotinib. The extra medicine you get will be decided by chance, like flipping a coin for "heads" or "tails." Your doctor will tell you which group you are in. We do not know if treatment with either of the extra medicines will be better than usual treatment. That is why we are doing this study.

4 Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is getting rid of the cancer for as long as possible, and with fewer bad effects; but we don't know for sure if there is any benefit of being part of this study.

5 Sometimes bad things can happen to people when they are in a research study. There is a risk that you will have more bad effects from adding either brentuximab vedotin or crizotinib to your usual medicines. We do not know this for sure which is why we are doing this study. Other things may happen to you that we don't yet know about.

6 Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7 We are also going to collect extra blood three times during the study. We want to see if there are ways to tell how the cancer will respond to treatment. This sample would be taken when other regular blood tests are being performed.

8 We are also asking permission to save leftover tissue for future research to help us learn more about cancer and other diseases. This would be taken when a regular biopsy is being performed and will not involve an extra procedure. You can still take part in this study even if you don't allow us to collect the extra tissue and/or save leftover samples for future research.

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