CALGB-50303

Phase III Randomized Study of R-CHOP V. Dose-Adjusted EPOCH-R With Molecular Profiling in Untreated De Novo Diffuse Large B-Cell Lymphomas

ClinicalTrial.gov Identifier: NCT00118209

Study Background

Trial Description

This randomized phase III trial studies rituximab when given together with two different combination chemotherapy regimens to compare how well they work in treating patients with diffuse large B-cell non-Hodgkin's lymphoma. Monoclonal antibodies, such as rituximab, may block cancer growth in different ways by targeting certain cells. Drugs used in chemotherapy work in different ways to stop the growth of cancer cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. Giving rituximab together with combination chemotherapy may kill more cancer cells. It is not yet known which combination chemotherapy regimen is more effective when given with rituximab in treating diffuse large B-cell non-Hodgkin's lymphoma. PURPOSE: This randomized phase III trial is studying rituximab when given together with two different combination chemotherapy regimens to compare how well they work in treating patients with diffuse large B-cell lymphoma.

Arms:

Arm A - R-CHOP: (Active Comparator): Patients receive the following treatment:

- Rituximab 375 mg/m^2 IV infusion on Day 1 prior to CHOP chemotherapy
- Cyclophosphamide 750 mg/m^2 IV on Day 1
- Doxorubicin 50 mg/m^2 IV on Day 1
- Vincristine 1.4 mg/m^2 IV (2 mg cap) on Day 1
- Prednisone 40 mg/m^2/day PO on Days 1-5
- Filgrastim or pegfilgrastim as defined in the protocol. Required ancillary medications are administered during all cycles as defined in the protocol. Cycles will be repeated every 21 days for 6 treatment cycles. Restaging will occur after Cycles 4 and 6.

Arm B - DA-EPOCH-R: (Experimental): Patients receive the following treatment: Cycle 1 Doses:

- Rituximab 375 mg/m^2 IV infusion on Day 1 prior to EPOCH chemotherapy
- Doxorubicin 10 mg/m^2/day CIVI on Days 1-4
- Etoposide 50 mg/m^2/day CIVI on Days 1-4
- Vincristine 0.4 mg/m^2/day (no cap) CIVI on Days 1-4 (total 1.6 mg/m2 over 96 hours)
- Cyclophosphamide 750 mg/m^2 IV on Day 5 (following completion of 96 hour infusions)
- Prednisone 60 mg/m^2 PO BID on Days 1-5
- Administer filgrastim 480 mcg subcutaneous daily from Day 6 until ANC > 5000 after the nadir (nadir usually between Days 10-12) or for 10 days (Days 6-15) if the ANC is not being monitored, during every cycle.

Doses for subsequent cycles will be determined by the absolute neutrophil (ANC) or platelet nadir from the previous cycle. Required ancillary medications are administered during all cycles as defined in the protocol. Cycles will be repeated every 21 days for a maximum of 6 cycles. Restaging will occur after Cycles 4 and 6.

Objectives:

PRIMARY OBJECTIVES:

I. To compare the event-free survival of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone (R-CHOP) versus dose-adjusted (DA-) etoposide, prednisone, vincristine sulfate, doxorubicin hydrochloride, cyclophosphamide, and rituximab (EPOCH-R) chemotherapy in untreated cluster of differentiation (CD)20 positive (+) diffuse large B-cell lymphomas.

II. To develop a molecular predictor of outcome of R-CHOP and DA-EPOCH-R chemotherapy using molecular profiling.

SECONDARY OBJECTIVES:

I. To compare the response rates, overall survival and toxicity of R-CHOP versus DA-EPOCH-R.

II. To define the pharmacogenomics of untreated diffuse large B-cell lymphoma (DLBCL) and correlate clinical parameters (toxicity, response, survival outcomes and laboratory results) with molecular profiling.

III. To assess the use of molecular profiling for pathological diagnosis.

IV. To identify new therapeutic targets using molecular profiling.

V. To perform a comprehensive analysis of somatic alterations to the tumor genome and to understand which genomic alterations are somatically acquired by the tumor and which are encoded in the germ line of the patient.

VI. To identify biomarkers of response to chemotherapy by fludeoxyglucose F 18 (FDG)-positron emission tomography (PET)/computed tomography (CT) imaging that are predictive of histopathologic remissions and survival in patients with stage I (mediastinal), II, III, or IV untreated DLBCL.

VII. To evaluate the use of semiquantitative measurements of FDG uptake in defining FDG-PET/CT based biomarkers of response to chemotherapy in patients with DLBCL.

VIII. To determine whether FDG-PET/CT measurements of tumor response after the second cycle of chemotherapy can predict clinical response.

IX. To establish a standardized protocol for FDG-PET/CT image acquisition.

X. To determine additional FDG-PET/CT parameters (e.g., the ratio of tumor maximum standard uptake value [SUV max] to liver SUV mean; SUVs corrected for body surface area and lean body mass; nuclear medicine physician's assessment) and evaluate their utility in refining FDG-PET/CT based biomarkers of response to therapy.

XI. To evaluate inter-institutional reproducibility of FDG-PET/CT measurements for this indication.

OUTLINE: Patients are randomized to 1 of 2 treatment arms.

Study Milestones:

Start date: May 2005

Primary Completion Date: October 2017

Publication Information:

Analysis Type: Primary

Pubmed ID: 30939090

Citation: Bartlett NL, Wilson WH, Jung S, Hsi ED, Maurer MJ, Pederson LD, Polley MC, Pitcher BN, Cheson BD, Kahl BS, Friedberg JW, Staudt LM, Wagner-Johnston ND, Blum KA, Abramson JS, Reddy NM, Winter JN, Chang JE, Gopal AK, Chadburn A, Mathew S, Fisher RI, Richards KL, Schoder H, Zelenetz AD, Leonard JP. Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. Journal of Clinical Oncology. 2019.

Associated Datasets:

NCT00118209-D1-Dataset.csv (master),

NCT00118209-D2-Dataset.csv (adverse_events),

Dataset Information:

Dataset Name: NCT00118209-D1-Dataset.csv (master)

Description: Dataset NCT00118209-D1-Dataset.csv (master) is one of 2 datasets associated with PubMed ID 30939090. This dataset contains information that will allow you to reproduce the baseline characteristics table, primary and secondary analyses.

Data can be used to approximate published study findings, but exact reproduction of previous manuscripts may not be possible in some cases (e.g., when data must be modified for de-identification purposes or have undergone further data cleaning).

Blank values indicate data not applicable or missing, except where otherwise noted.

NCT00118209-D1-Dataset.csv (master) Data Dictionary:

LABEL	NAME	ELEMENTS	COMMENTS
Patient ID	patid		Contains patient ID
Eligible	eligible	Yes, No	Patients eligible for analysis have values of "Yes".
Central Pathology Exclusion?	path_exc	No, Yes	Patients will have a value of "Yes" if they were excluded due to central pathology review. Missing implies no central pathology was done.
Ineligibility Reason	inelig_rsn		Reason for Ineligibility. Missing for eligible patients.
Diagnosis	diagnosis	Primary mediastinal large B-cell lymphoma, Diffuse large B-cell lymphoma (DLBCL), NOS, High-grade B-cell lymphoma, NOS, Follicular lymphoma - Grade 1-2, DLBCL and FL - Grade 3A, Marginal zone B-cell lymphoma nodal type (+/-	Contains the patient's diagnosis by WHO criteria.

		monocytoid B cells), T-cell/histiocyte-rich large B-cell lymphoma, EBV+ DLBCL, NOS, Intravascular large B-cell lymphoma, DLBCL and FL - Grade 3B, B-cell neoplasm - unclassifiable (non-WHO wastebasket), Diffuse follicle center lymphoma, Lymphomatoid granulomatosis, Primary cutaneous follicle center lymphoma	
Diagnosis Group	mediastinal	Primary Mediastinal, Not Primary Mediastinal	Diagnosis grouping.
Treatment Received	rx	DA-EPOCH-R, R-CHOP	Holds the treatment the patient received.
Time from Diagnosis to Registration (days)	dx_to_reg		
Time from Diagnosis to First Dose (days)	dx_to_tx		
Ethnicity	ethnic_id	Non-Hispanic, Unknown, Hispanic or Latino	Contains patient ethnicity.
Race	race_id	White, Unknown, Black or African American, American Indian or Alaska Native, Asian, More than one race, Native Hawaiian or Pacific Islander	Contains patient race.
Performance Score	ps	0, 1, 2	ECOG performance score. Missing indicates the data was not collected.
Age (years)	ptage		Contains the patient age at registration.

Extranodal Disease (>=1 site)	exnoddz	Not extranodal, Extranodal Disease	"Extranodal Disease" implies the patient had at least 1 extranodal site involved. Missing indicates the data was not collected.
Extranodal Disease Group	exnode_ipi	0-1, 2+	Number of extranodal disease sites grouped. Missing indicates the data was not collected.
Prior radiation therapy	radther	No, Yes	Indicator if patient received radiotherapy prior to study. Missing indicates the data was not collected.
Radiation specify	radtherspec	T5-T6 VERTEBRAL BODY AREA, PROSTATE CA, BREAST CANCER, FOR PROSTATE CANCER, LIMITED FIELD RT TO ORBIT, 1800GY R ISCHIAM/1500cGY, L MAXILLARY SINUS 5 Gy, 4 DOSE PALLIATIVE, T9-11 SPINE	Type of prior radiation. Missing indicates the data was not collected.
Short course of glucocorticoids?	glucocorticoids	No, Missing, Yes	Indicator if patient received glucocorticoids (steroids).
Stage	stage	Stage II de novo CD20+ DLBCL, Stage IV de novo CD20+ DLBCL, Stage III de novo CD20+ DLBCL, Stage I primary mediastinal (thymic) DLBCL	Ann Arbor Stage. Missing indicates data was not collected.

LDH	ldh_ipi	Normal, Elevated	Indicator of elevated LDH. Missing indicates data was not collected.
IPI	ipi	0, 2, 3, 1, 4, 5	Raw IPI score. Missing indicates data was not collected.
IPI Risk Group	ipig	Low, Low-Intermediate, High-Intermediate, High	Missing indicates data was not collected.
IPI Risk Group	ipig2	0 to 2, 3 to 5	Grouped IPI. Missing indicates data was not collected.
Gender	sex_id	Male, Female	Missing indicates data was not collected.
CNS Indication: >1 EN and elevated LDH	cns_ind	1	Indicator if patient is at risk for CNS relapse. 1 implies Yes. Derived from raw data collected on the number of extranodal sites, rather than variable exnode_ipi.
Time from Randomization to First Dose Date (days)	rand_to_tx		Zero indicates the patient was randomized and treated on the same day. Negative values are due to data entry error.
DA-EPOCH-R: Maximum Dose Level	max_dose_inc_miss	1, 2, 4, 3, 5, 6, 7	Maximum dose level for patients in DA-EPOCH-R arm. Ignores cycles with missing dosing data.
Received Methotrexate	mtx	No, Yes	Missing indicates data was not collected.
Received Pegfilgrastim	peg	No, Yes	Missing indicates data was not collected.
Received	fil	Yes, No	Missing indicates

Filgrastim			data was not collected.
Received growth factor	gcsf	Yes, No	Missing indicates data was not collected.
Off Treatment Reason	endrsn	Treatment completed per protocol, Other, Patient withdrawal/ refusal after beginning protocol therapy, Alternative therapy, Adverse Event/Side Effects/Complications, Disease progression, relapse during TX, Patient withdrawal/ refusal prior to beginning protocol therapy, Death on study	Missing indicates data was not collected.
Off Treatment Reason-specify	endrsn_spec	30% REDUCTION, NON COMPLIANT, INELIG-FOLL, NOT DLBCL, CYTOGENETIC RESISTANCE, DIED PRIOR TO STARTING TX, INFXTN RISK D/T SURG, INELIGIBLE PRIOR TO TX ST, PT UNABLE TO KEEP APPTS, MD DISCRETION, PATIENT NON COMPLIANT, PATIENT NON-COMPLIANT	Off treatment comments.
Has the patient achieved a response?	resp	Yes, No	Missing indicates data was not collected.
Best response	bestresp	CRu, CR, PR, SD, PD	Best response

			experienced. Missing indicates data was not collected.
Best Response Group	bestrespg	CR/CRu, PR, SD, PD	Grouped best response. Missing indicates data was not collected.
Double Expressed	de	Yes, No	Indicator if patient had double expressed DLBCL. Missing indicates data was not collected.
MYC FISH status	myc_fish_pos	Normal, Positive	Indicator if patient was positive for MYC biomarker. Missing indicates data was not collected.
BCL2 Status (DH)	bcl2_dh_pos	Normal, Positive	Indicator if patient was positive for BCL-2 biomarker. Missing indicates data was not collected.
BCL6 status (DH)	bcl6_pos	Normal, Positive	Indicator if patient was positive for BCL-6 biomarker. Missing indicates data was not collected.
Double Hit	dh	No, Yes	Indicator if patient had double hit DLBCL. Missing indicates data was not collected.
Progression Status	pg_stat	Censor, Event	Event implies progression, censor implies no progression.
Time to Progression	pg_time		Negative values are due to data entry

(days)			error.
CNS Relapse	cns_relapse	No, Yes	Indicator if patient experienced a CNS relapse. Missing indicates data was not collected.
PFS Status	efs_stat	Censor, Event	Event =progression or death. Censor=Alive and progression-free.
PFS Time (days)	efs_time		
Follow-up Status	fu_stat	Censor, Event	Event=Death. Censor=Alive.
Overall Survival (days)	fu_time		Time to death or last follow-up.
Primary cause of death	pricauseofdeath	Due to this disease, Due to other cause, Unknown, Due to protocol treatment	Only entered for those who died.
Cause of Death, specify	describecod		Comments for Cause of Death.
Late Cardiac AE	late_cardiac_ae	Yes, No	"Yes" indicates the patient began the post-treatment follow up phase and experienced a cardiac AE.
Type of Late Cardiac AE	late_cardiac_type		Literal type of late cardiac event reported. Only entered for those who experienced late cardiac AE (where late_cardiac_ae = Yes).