A041202

A RANDOMIZED PHASE III STUDY OF BENDAMUSTINE PLUS RITUXIMAB VERSUS IBRUTINIB PLUS RITUXIMAB VERSUS IBRUTINIB ALONE IN UNTREATED OLDER PATIENTS (≥ 65 YEARS OF AGE) WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

ClinicalTrial.gov Identifier: NCT01886872

Study Background

Trial Description

RATIONALE: The excellent response rates and durable remissions seen thus far with ibrutinib, especially in comparison to modest outcomes and significant toxicity with standard therapy in this age group, justify the movement to phase III study as initial therapy for older patients with CLL. PURPOSE: To perform a phase III trial of bendamustine plus rituximab versus ibrutinib versus ibrutinib plus rituximab to determine whether ibrutinib containing regimens are superior to standard therapy and also to determine whether combination therapy with ibrutinib plus rituximab is superior to ibrutinib alone.

Arms:

Arm 1: Bendamustine/Rituximab (BR)

Arm 2: Ibrutinib (I)

Arm 3: Ibrutinib/Rituximab (IR)

Objectives:

- To determine whether progression free survival (PFS) is superior after therapy with bendamustine in combination with rituximab, ibrutinib alone, or ibrutinib in combination with rituximab in patients age 65 or older with previously untreated CLL
- To determine 2-year PFS in each of the three treatment arms
- To determine which treatment arm produces superior overall survival (OS)
- To determine the complete response (CR) rate, complete and nodular partial response (CR/nPR) rate, and overall response (PR+nPR+CR) rate (ORR) among the three treatment arms and compare these arms
- To determine the impact of MRD-negative disease at time of CR documentation and at 2 years on PFS and OS in each of the treatment arms
- To determine duration of response after each of the three treatments and compare these treatment arms
- To determine toxicity and tolerability of the three treatment regimens

- To determine response and PFS of patients initially on the bendamustine in combination with rituximab arm who cross over to ibrutinib

OUTLINE: This is a randomized phase III trial designed to evaluate whether or not two different ibrutinib based therapeutic regimens improve progression-free survival (PFS) over standard of care (bendamustine + rituximab) in previously untreated, older (age ≥ 65 years) CLL patients who are symptomatic and require therapy by the IWCLL guidelines. This study will not be blinded. Randomization will be stratified on Rai stage (intermediate vs. high) and presence of high risk FISH abnormalities (del(11q22.3) or del(17p13.1) vs. not). In addition, we will also stratify on ZAP-70 methylation status (methylated vs. not, using a 20% methylation cut point), which is hypothesized to be strongly associated with clinical outcomes in CLL.

Patients are followed up to 10 years from study entry.

STUDY ACCRUAL: A total of 547 patients were accrued for this study.

Study Milestones:

Primary Completion Date: December 2018

Publication Information:

Analysis Type: Primary

Pubmed ID: 30501481

Citation: N Engl J Med. 2018 Dec 1. doi: 10.1056/NEJMoa1812836.

Associated Datasets:

NCT01886872-D1-Dataset.csv (Analysis),

NCT01886872-D2-Dataset.csv (AE),

NCT01886872-D3-Dataset.csv (PreRegistration),

NCT01886872-D4-Dataset.csv (Deaths)

NCT01886872-D5-Dataset.csv (bsl_qol)

Dataset Information:

Dataset Name: NCT01886872-D5-Dataset.csv (bsl_qol)

Description: Dataset NCT01886872-D5-Dataset.csv (bsl_qol) is one of 5 datasets associated with PubMed ID 30501481. This dataset contains information that will allow you to reproduce the baseline QOL analysis (table S3) in the supplemental materials.

Unless otherwise indicated, missing values indicate a value that was not collected or could not be calculated.

NCT01886872-D5-Dataset.csv (bsl_qol) Data Dictionary:

LABEL	NAME	elements	comments
Number of Falls in last 6 months	numfalls1	% with 0 falls, % with 1+ falls	Number of times a fall occurred in the last 6 months
Percent Unintentional Weight Loss in last 6 months	weightchange5_1	% with <= 5% weight loss, % with > 5% weight loss	(Unintentional weight lost in last 6 months / baseline body weight) X 100
Blessed Orientation Memory Concentration Test (BOMC)	bomcgt11_1	% with < 11, % with >= 11	Cognitive assessment, score 11 or greater may reveal signs of cognitive impairment (0-28 scale)
De-identified Patient ID	patref		
Karnofsky Performance Status (Physician-reported)	KPS		Global scale used quantify patient function from “normal” to “dead”, as determined by the physician (0-100 scale)
Timed “Up and Go” (TUG)	TMUPGO		Time it takes for individual to stand up, walk 10 feet, return to chair and sit back down

Treatment Arm	ARM	1= Arm 1 (BR), 2= Arm 2 (I), 3= Arm 3 (IR)	
BMI	bmi		Weight (kg) / Height (m)^2
Karnofsky Performance Status (Self-reported)	kpspt		Global scale used quantify patient function from “normal” to “severely disabled”, as determined by the patient (30-100)
Activities of Daily Living (Medical Outcomes Study [MOS] subscale)	datot1		Measures limitations in physical function activities, ranging from bathing and dressing to running (0-14 scale)
Instrumental Activities of Daily Living (Older American Resources and Services)	pascore		Measures ability to complete activities required to maintain independence, ranging from making telephone calls to money management (0-100 scale)
Physician Health Scale (OARS subscale)	hqscore		Assesses the presence or absence of 14 comorbid conditions and effect of the illness on daily activities. (Number of Comorbidities)
Mental Health Inventory	sascore		Evaluates the level of depression and anxiety experienced in the last month (0-100 scale)
MOS Social Activity Survey	ssscore		Measures the level of physical or emotional interference experienced with social activities (0-100 scale)
MOS Social Support:Tangible subscale	tangiblescore		Evaluates the self-reported availability of

			tangible/physical social support (0-100 scale)
MOS Social Support:Emotional/Informational subscale	emotionalscore		Evaluates the self-reported availability of emotional/informational social support (0-100 scale)