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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-D4-Dataset.csv (Deaths)

Description: This dataset contains one observation for each patient death. The cause of death was characterized by the Study Chair by taking into account the following: Grade 5 adverse events, contributing adverse events, cause of death reported, and correspondence between the study team and site.

NCT01886872-D4-Dataset.csv (Deaths) Data Dictionary:

LABEL	NAME	elements	comments
Arm	arm	1= Arm 1 (BR) 2= Arm 2 (I) 3= Arm 3 (IR)	Randomized Arm
Cause of Death	cod	CLL/Richter's CVA Co-Morbidities Death, NOS Dementia Encephalopathy Infection Multi-organ failure Myocardial infarction Secondary Cancer Sepsis Subdural/intracranial hemorrhage Suicide Surgical Complication Unexplained/unwitnessed death	Cause of death as summarized by the Study Chair.
Months until Death	cod_mos	Continuous	Months from study enrollment until

			patient death.
Patient Reference	patref	Continuous	Unique Patient Identifier