# 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-D2-Dataset.csv (AE)

Description: There are multiple observations in this dataset for each patient's adverse events. For each patient, there is one observation per adverse event per cycle. All adverse events are included (treatment, observation, late, crossover).

Example:

| patref | cycle | toxicity | grade | rel_smed |
|---|---|---|---|---|
| 0123456 | 1 | nausea | 1 | 4 |
| 0123456 | 1 | vomiting | 3 | 3 |
| 0123456 | 2 | nausea | 2 | 2 |
| 0123456 | 2 | vomiting | 2 | 3 |
| 0123456 | 2 | pain | 3 | 3 |

Due to data cleaning efforts during analysis, data may contain slight discrepancies from that reported in the publication. For example, 66 deaths were collected on a patient status form and included in the manuscript and appear in the NCT01886872-D4-Dataset.csv (deaths). However, at the time of data freeze, 63 were entered as a grade 5 event.

For tables S7 and S8, we include the following information for determining what was included as infection, bleeding and secondary malignancies:

Infections: Events where toxcode=10003011, 10019799, 10021881, 10023216, 10027199, 10033078, 10040047, 10040872, 10046300, 10046571, 10048038, 10048762, 10055078, 10056519, 10061017, 10061229, 10062156, 10005047, 10014594

Bleeding: Events where toxcode=10015090, 10022763, 10030980

Secondary malignancies: Events where toxcode= 10029104, 10049737, 10028533

There was an error in the footnote for Table S7. The publication included *all* grades for the infection. It should read ’40 patients had multiple infections of any grade.’

## NCT01886872-D2-Dataset.csv (Adverse Events) Data Dictionary:

| LABEL | NAME | elements | comments |
|---|---|---|---|
| AE Phase | ae_phase | 1=AE Reported During Initial Treatment<br>2=Late AE<br>3=Crossover AEs | Time point of AE. Missing values indicate the patient was not evaluated for adverse events.<br>Late AEs are those that occur more than 30 days after last treatment.<br>Note: If patient never started treatment, ae_phase is missing.<br>Tables S7 and S8 include adverse events where ae_phase='AE Reported During Initial Treatment'<br>Table S6 includes adverse events where ae_phase = 'AE Reported During Initial Treatment' or 'Late AE' |
| First 6 Cycles | ae6 | Yes | If AE occurred within first 6 cycles of treatment (or within 30 days after first 6 cycles of treatment), then ae6='Yes'.<br>Otherwise ae6 is blank.<br>Note: Reasons why cycles 1-6 may be blank:<br>1. Event occurred after crossover for |

| | | | |
|---|---|---|---|
| | | | Arm 1 patients.<br>2. Event occurred after all treatment ended. |
| Arm | arm | 1= Arm 1 (BR)<br>2= Arm 2 (I)<br>3= Arm 3 (IR) | Randomized Arm<br>Missing if patient never began treatment |
| CTCAE#V4 | ctc_v4 | Y | Derived to "Y" to indicate CTCAE Version 4 is used for this study<br>Missing if patient never began treatment |
| Cycle | cycle | | Cycle number from AE form<br>Missing if patient never began treatment |
| Grade | grade | 0, 1, 2, 3, 4, 5 | Severity of the adverse event according to CTC guidelines.<br>Missing if patient never began treatment |
| Hematologic Adverse Event | hemeFlag | 1 = Hematologic AE<br>2 = Not a hematologic AE | Flag to indicate if an event is designated as a hematologic event or not.<br>Missing if patient never began treatment |
| Patient Reference | patref | | Unique Patient Identifier |
| Relationship Study Meds | rel_smed | NOT RELATED<br>UNLIKELY | Relationship/attribution to study medication. |

| | | | |
|---|---|---|---|
| | | POSSIBLE<br>PROBABLE<br>DEFINITE | May be missing if:<br>1. Grade is 0<br>2. Patient never began treatment<br>3. Attribution not reported by site |
| SOC | soc | *See SOC table for list of values | General System Organ Class from CTCAE/MeDra associated with the given adverse event.<br>Missing if patient never began treatment<br>The events reported for 'Injury, poisoning and procedure complications' in Table S8 are those that meet all 3 criteria below:<br>1. soc=' Inj, pois and proced complic'<br>2. ae_phase=1<br>3. Grade > 2 |
| Toxicity Code | toxcode | | MedDra code assigned to the given adverse event using CTCAE version 4.0<br>Missing if patient never began treatment |
| Toxicity | toxicity | | CTCAE v4.0 Term<br>Note: For MedDRA codes that were recategorized, the new (recategorized) term.<br>Missing if patient never began treatment |

| | | | |
|---|---|---|---|
| Toxicity Specification | tox_sp | | If toxicity is a term with 'Other, specify', then tox_sp is the text specification entered by the site.<br><br>Otherwise, tox_sp is blank. |