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-D1-Dataset.csv (Analysis)

Description: This dataset is a collection of data used for analysis of primary and secondary objectives. Contains one observation per patient enrolled to A041202. It does not contain Adverse Event data nor patients that were screened and pre-registered to A041202 but never enrolled.

Tables S4 and S5:

In generating Tables S4 and S5, only patients with complete data on all variables considered for modeling were included. 467 of 547 patients had non-missing data on treatment arm (arm_numeric), age (age), sex (female), Rai stage (highrai_strat), performance status (ps), wbc (log2wbc), beta-2m (highb2m), LDH (highldh), splenomegaly (spleen), Zap-70 methylation (zap70meths20_strat), high-risk FISH (highriskfish_strat), complex karyotype (complex3), TP53 mutations (tp53mut), and Dohner's hierarchical classification (dohner). Specifically, complex karyotype was missing on 48 patients (547-48=499), an additional 30 were missing TP53 mutations (499-30=469), an additional patient had unknown Zap-70 methylation (469-1=468), and an additional patient was missing central cytogenetics for Dohner's hierarchical classification (468-1=467).

NCT01886872-D1-Dataset.csv (Analysis) Data Dictionary:

LABEL	NAME	elements	comments
Age (years)	age	Continuous	Age of patient at time of study entry.
Randomized Arm	arm_numeric	Arm 1 (BR) Arm 2 (I) Arm 3 (IR)	Randomization arm of patient in numeric format.
Number BR Cycles	arm1_num_cycles	Continuous	Number of BR cycles received for Arm 1 patients. Blank for patients randomized to Arms 2 or 3 or if patient never

			began treatment.
Best Response Assessed CT or PE	assess	Yes No	If patient never had a CT or physical examination assessment, then assess was derived to No. Else, assess was derived to Yes.
Best Response by CT	best_CT	Yes No	If best_response was derived from a cycle when a CT was performed, then best_CT is derived to Yes. Else, best_CT is derived to No.
Best Response	best_response	CR CCR nPR PR SD PD Not Evaluated	Best objective status reported during cycles when a CT was performed (CR, CCR, nPR, PRL, SD, PD, or Not Evaluated). If a CT was never performed, then best objective status reported during cycles when a physical exam was performed. If neither CT nor physical exam were performed, then derived to 'Not Evaluated'.
Beta-2 Microglobulin Serum at Baseline (mg/L)	beta2cat	Normal High	Lab at baseline derived: If B2M value at baseline is greater than the reference range upper limit for B2M, then beta2cat = High

			If B2M value at baseline is less than or equal to reference range upper limit for B2M, then beta2cat = Normal
Censored For Alternative Treatment	censorAlt	Yes No	If the patient received non-protocol treatment for CLL **and was censored for PFS**, then censorAlt is derived to Yes. Else censorAlt is derived to No. Note: reasons why a patient may have received non-protocol treatment but not have been censored for PFS: 1. Progression occurred prior to non-protocol treatment 2. Patient received non-protocol Treatment after withdrawal of clinical or ALL consent. **See PFS Stat rules footnote for details on determining PFS events.
Censored Prior To An Event	censorEvent	Yes No	Derived to Yes if the patient was censored for withdrawn consent and/or alternative treatment prior to an EVENT. Else it is derived to No. **See PFS Stat rules footnote for details on determining PFS

			events.
Censored For Withdrawal All Consent	censorWA	Yes No	If the patient withdrew ALL consent **and was censored for PFS due to withdrawn consent**, then censorWA is derived to Yes. Else, censorWA is derived to No. Note: reasons why a patient may have withdrawn ALL consent but not have been censored for PFS due to withdrawn consent: 1. Progression occurred prior to withdrawal of consent 2. Patient received non-protocol Treatment prior or equal to withdrawal of ALL consent. **See PFS Stat rules footnote for details on determining PFS events.
Censored For Withdrawal Clinical Consent	censorWC	Yes No	If the patient withdrew clinical consent **and was censored for PFS due to withdrawn clinical consent,** then censorWC is derived to Yes. Else, it is derived to No. Note: reasons why a patient may have withdrawn clinical consent but not have

			been censored for PFS due to withdrawn clinical consent: 1. Progression occurred prior to withdrawal of consent 2. Patient received non-protocol Treatment prior or equal to withdrawal of clinical consent. 3. Patient withdrew ALL consent prior to or equal to withdrawal of clinical consent. **See PFS Stat rules footnote for details on determining PFS events.
Central FISH 13q14.3 Results	central_del13q	Normal Abnormal	Central FISH results for 13q14.3(D13S319); 0-1 copy Values are Normal and Abnormal Missing if results not available
Central FISH 12cen Results	central_tri12	Normal Abnormal	Central FISH results for 12cen(D12Z3); 3 copies Values are Normal and Abnormal Missing if results not available
Central FISH 11q22.3 Results	central_11q	Normal Abnormal	Central FISH results for 11q22.3(ATM); 1 copy Values are Normal and

			Abnormal Missing if results not available
Central FISH 17p13.1 Results	central_17p	Normal Abnormal	Central FISH results for 17p13.1(TP53); 1 copy Values are Normal and Abnormal Missing if results not available
Karyotype Complexity >=3 Abnormalities	Complex3	Present Absent	Complex karyotype. Values are Present and Absent. If not available, then value is missing.
Serum Creatinine at Baseline (mg/dL)	creatcat	Normal High	Lab at baseline derived: If Serum Creatinine value at baseline is greater than reference range upper limit for Serum Creatinine, then creatcat = High If Serum Creatinine value at baseline is less than or equal to reference range upper limit for Serum Creatinine, then creatcat = Normal

Arm1 Current Tx Phase	current_tx	Observation Crossover Tx Off Tx Not Applicable	Derivation to answer question: What phase of treatment are Arm 1 patients currently in? Note: For Arm 2 and 3 patients, current_tx is derived to Not applicable. NOTE: Discrepancy found in manuscript. 87 patients were in observation at the time of data freeze, not 88.
First Crossover Cycle	Cycle_co	Continuous	First cycle of crossover treatment received for Arm 1 patients. Note: Missing for Arm 1 patients that did not cross over and for Arm 2 and 3 patients.
Central FISH Derived Dohner Classification	Dohner	Del(17p) Del(11q) Trisomy 12 None Del(13q)	Derived from Central FISH Results Form: 1. If central_17p = 'Abnormal', then Dohner = Del(17p). 2. Else if central_11q = 'Abnormal', then Dohner = Del(11q). 3. Else if central_tri12= 'Abnormal', then Dohner = Trisomy 12. 4. Else if central_del13q = 'Abnormal', then Dohner = Del(13q). 5. Else if central_17p,

			central_11q , central_tri12, and central_del13q are all reported and not equal to 'Abnormal', then dohner = None. NOTE: 5 patients were missing specimens, value is missing.
Eligible	Elig	Yes No	Eligibility of patient Yes if deemed eligible No if deemed ineligible
OffTx Reason	ENDATRSN	Treatment Completed Per Protocol Patient Withdrawal/Refusal After Beginning Protocol Therapy Adverse Events/Side Effects/Complications Disease Progression, Relapse During Active Treatment (Intervention) Alternative Therapy Patient Off-Treatment (Intervention) For Other Complicating	Reason patient went off protocol treatment. NOTE: If patient is still on treatment, then ENDATRSN=0.

		Disease Death On Study Other Disease Progression Before Active Treatment (Intervention) Patient Withdrawal/Refusal Prior To Beginning Protocol Therapy (Intervention) 0	
Estimated Creatinine Clearance at Baseline (mL/min)	Estcrtclr	Continuous	Lab at baseline Missing if lab not available.
Patient Had Assessment	evalresp	Yes No	If patient had an assessment on the Measurements form (assessment date is reported and cycle is greater than 0), than evalresp is derived to 'Yes'. If progression or death is reported, than evalresp is derived to 'Yes'. Else, it is derived to 'No'. Note: If a patient's only assessment was after withdrawing consent or non-protocol therapy, then evalresp is derived to 'No'.

Presence of del(11q22) or del(17p13), Local Results	Fishdel	Yes No	Local results captured by registration system.
Follow-up Status	fu_stat	Alive Dead	Patient status at last follow-up.
Baseline Hemoglobin (g/dL)	lab_hgb	Continuous	Lab value at baseline Missing if lab not available.
Baseline Platelets (10^9{Cells}/L)	lab_plt	Continuous	Lab value at baseline
Baseline WBC (10^9{Cells}/L	lab_wbc	Continuous	Lab value at baseline
LDH at Baseline (U/L)	ldhcat	Normal High	Lab at baseline derived: If lab value is greater than reference range upper limit for LDH, then ldhcat = High. If lab value is less than or equal to reference range upper limit for LDH, then ldhcat = Normal.
Skin Malignancies	malig1	Yes No	Derived to 'Yes' if the patient had a malignancy (excluding non-melanoma skin and Richter's). Note: does not include malignancies that occurred post crossover for Arm 1 patients. If patient did not have a

			malignancy, malig1 is 'No'.
Time on Treatment (Months)	maxTxMos	Continuous	(Maximum treatment date – Date on study) / 30.44
MRD Negative Status at C9D1	mrdneg	Yes No	Derived from bone marrow samples labelled as C9D1 and drawn between 6-12 months since date on study, prior to any crossover. If (CD19+/CD5+/CD43+/ CD79b- %) < 0.01, not missing, and samples is good material (viability >= 60) , then mrdneg= Yes Else mrdneg=No .
Zap70 Methylation Status, Central Results	Mtylcpg3	<20% >= 20%	Central results captured by registration system. Missing if results not available.
Overall Survival (months)	osmos	Continuous	(Date of most recent contact or death date – Enrollment date)/30.44 Note: if patient was censored for survival, then osmos is (Date of censor – Enrollment date)/30.44
Overall Survival Status	osstat	Censored	Derived for all registered patients.

		Event	If patient's survival status is alive and/or the patient is censored for survival, then osstat = Censored. If the patient's survival status is dead and the patient is not censored, then osstat= Event.
Patient Reference	patref	Continuous	Unique Patient Identifier
PFS Months	pfsmos	Continuous	Months from enrollment until an event occurs (if pfsstat=Event) or until date of censor (if pfsstat=Censored). **See PFS rules below for details.
Progression Free Survival	pfsstat	Censored Event	**See PFS rules below for details
Progression Status	pg_stat	NO PROGRESSION PROGRESSION	Progression Status
ECOG Performance Status	Ps	0 1 2	Performance status at baseline
RAI Stage	Raicat	Intermediate (Stage I/II) High (Stage III/IV)	RAI stage of patient captured by registration system.
Transformation Richters	richter1	Yes No	If patient reported Richters then derived to 'Yes'. Else derived to

			'No'. Note: Excludes Richter's reported after crossover for Arm 1 patients.
Rituximab held	rituxheld	1=Yes	If rituximab was reduced or omitted at ANY cycle, then rituxheld = 1. Else, rituxheld is missing.
Treatment delayed	rxdelay	Yes	If an agent at ANY cycle is marked as delayed, then rxdelay = Yes Else, rxdelay is missing
Treatment omitted	rxomit	Yes	If an agent at ANY cycle is marked as omitted, then rxdomit = Yes. Else, rxomit is missing
Treatment reduced	rxreduc	Yes	If an agent at ANY cycle is marked as treatment modified, then rxreduc = Yes. Else rxreduc is missing NOTE: Discrepancy found in manuscript. For arm 3, dose was reduced in 13% of patients, not 14%.
Gender	sex	Female Male	Gender of patient captured by registration system.
Skin Malignancies	skin1	Yes	Derived to 'Yes' if the patient had a skin

		No	malignancy (excluding melanoma). Note: does not include malignancies that occurred post crossover for Arm 1 patients. If patient did not have a skin malignancy, then skin1 is derived to 'No'.
Splenomegaly at baseline	Splenomg	Yes No	Reported at baseline.
TP53 Mutated	Tp53mut	Present Absent	Derived from peripheral blood samples. If the gene name was TP53 and allele frequency >=0.10 then tp53mut=1 Present. Else if the gene name was TP53 and allele frequency was <0.10, then tp53mut=Absent. If not tested for TP53, then TP53mut is missing.
Time until off treatment (months)	Txmos	Continuous	(Date off treatment – Date on study) / 30.44
IGHV mutation	vh98mut	IGHV mutated IGHV unmutated	Derived from peripheral blood samples. Missing if sample not available.

**PFSSTAT and PFSDATE derived using the following rules:

1) A patient had an event (PFSSTAT=1) at time of progression or death (whichever comes first). All other patients were censored (PFSSTAT=0).
2) If a patient progressed, then pfsmos was calculated using the patient's progression date. Else, if the patient died, then pfsmos was calculated using the patient's death date.
3) PFSMOS for censored patients was calculated using the patient's most recent date of clinical assessment. If the patient never had a clinical assessment, then pfsmos was determined by taking the maximum date of the following: date off-treatment, most recent date that the patient received treatment (or most recent date alive for patients in Observation), and registration date.
4) If the patient had alternative treatment or withdrew all consent prior to an event, then the patient was censored (PFSSTAT=0). PFSMOS was calculated to the maximum date found in #3 above that was prior to or equal to the date of withdrawn consent/alternative therapy.
5) If the patient withdrew clinical consent (but not all consent) prior to a progression, then the patient was censored (PFSSTAT=0). PFSDATE was derived to the maximum date found in #3 above that is prior to or equal to the date of withdrawn clinical consent. Note: the patient could still have a death event after withdrawal of clinical consent.