

# MRD in Clinical Trials (NAIG)

Neil Kay

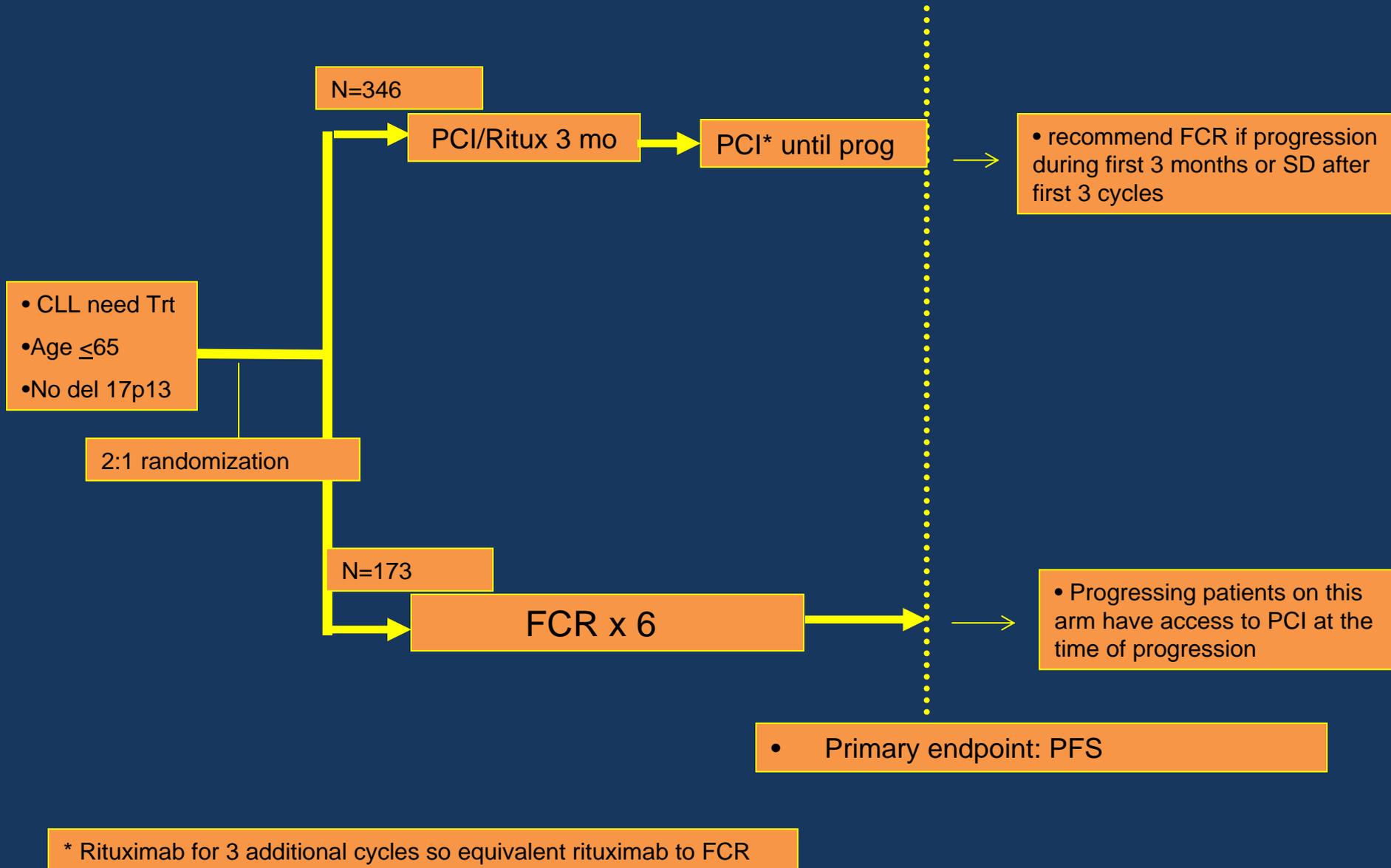
John Byrd

Jennifer Woyach

E1912 Randomized Phase III Study of PCI-32765  
based therapy versus standard fludarabine,  
cyclophosphamide, and rituximab (FCR)  
chemoimmunotherapy in untreated younger  
patients with CLL

- Tait Shanafelt, M.D.
- Neil Kay, M.D.
- Martin Tallman, M.D.

# Phase III Trial Design



# Status

- CTEP approved revised phase 3 design August 2012
- Leukemia Steering Committee approved revised phase 3 design Sept 2012
- Revised protocol resubmitted to CTEP
- Hoping to activate early spring 2013
- Extensive correlative studies
  - RO1 was submitted -Feb 2013

# Objectives

## Primary Objectives

–The primary objective for the trial is to evaluate the ability of PCI-32765-based induction therapy (**Non-CIT**) to prolong progression free survival (PFS) compared to standard FCR chemoimmunotherapy (**CIT**) for younger patients ( $\leq 65$ ) with CLL.

# Objectives

## Secondary Objectives

–Eradication of MRD following chemotherapy and CIT is an independent predictor of PFS and OS <sup>1</sup>

- **Determine if the minimal residual disease (MRD) status as assessed by flow cytometry at different time points during and after treatment is an effective surrogate marker for prolonged PFS and overall survival.**

# MRD Studies In E1912

- Establish the ability of post-treatment MRD status to predict clinical outcome after treatment of CLL with CIT and non-CIT approaches.
- *Hypothesis:* MRD status either immediately after CIT or studied over time in non-CIT will be associated with both PFS and OS.
  - To identify a robust and timely surrogate endpoint for OS and PFS, we will prospectively measure MRD at multiple time-points and evaluate how well it predicts clinical outcome for both CIT and non-CIT approaches.

<u>MRD assessment time-points</u>	<u>3 mo</u>	<u>12 mo</u>	<u>24 mo</u>	<u>36 mo</u>
CIT	X	X	X	X
Non-CIT	X	X	X	X

# MRD Studies

- Expected Outcomes :
  - We anticipate that MRD status at the time of the 12 month response evaluation will correlate with PFS (and ultimately OS) in patients treated with conventional CIT.
  - We also anticipate MRD status will correlate with PFS and OS for patients treated with non-CIT,
    - But we expect the optimal timing of MRD assessment will need to occur at a later time point (e.g. 24 or 36 months) than that used for conventional chemotherapy.

# MRD Studies

- Hypothesis 1 **Conventional CIT**:
  - The conventional CIT arm will have the highest proportion of MRD negative patients at the time of the 12 month response evaluation.
  - MRD status at the time of the 12 month response evaluation will be an accurate predictor of PFS (and ultimately OS) for the conventional CIT arm but will be less useful for the non-CIT arm.
  
- Hypothesis 2 **Non CIT**:
  - The proportion of patients in the non-CIT arm who achieve an MRD negative disease state will be higher at the 24 and 36 month time-points than at the 12 month time-point.
  - MRD status at these later time-points will be a better predictor of PFS (and ultimately OS) for the non-CIT approach than assessment at 12 months.

# ALLIANCE A041202

**A Randomized Phase III Study of Bendamustine Plus Rituximab Versus Ibrutinib Plus Rituximab Versus Ibrutinib Alone in Untreated Older Patients ( $\geq 65$  years of age) with Chronic Lymphocytic Leukemia (CLL)**

**Study Chair**

Jennifer Woyach

**Leukemia Correlative Study Co- Chair**

John Byrd

# ALLIANCE A041202

Untreated patients age  $\geq 65$  who meet IWCLL criteria for CLL treatment

Randomize

Bendamustine 90 mg/m<sup>2</sup> days 1&2 of each 28 day cycle +  
Rituximab 375 mg/m<sup>2</sup> day 0 cycle 1, then 500 mg/m<sup>2</sup> day 1 of cycles 2-6

Ibrutinib 420 mg daily until disease progression

Ibrutinib 420 mg daily until disease progression +  
Rituximab 375 mg/m<sup>2</sup> weekly for 4 weeks starting cycle 2 day 1, then day 1 of cycles 3-6

Documented progression

# ALLIANCE A041202

## **Primary Objective**

- 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

# ALLIANCE A041202

## Secondary Objective

- 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 arm
- MRD to be evaluated at 9 months and at 2 years

# Status of Alliance Protocol

- To be activated in 3-4 months

# MRD Assay (E1912)

# MRD

- Developed a single tube, 6-color (CD45, CD19, CD20, CD5, kappa and lambda immunoglobulin light chains) flow cytometry panel for assessing MRD in CLL patients.
  - The standard single-tube, 6-color antibody panel includes:
    - CD45, CD19, CD20, CD5, and kappa and lambda immunoglobulin light chains
  - This assay was developed at Mayo Clinic
    - validated by comparing it to a previous standard 4-color assay in 562 specimens (unpublished data).

# MRD Assay

- 500,000 events were collected in all cases and analyzed on a Becton-Dickinson Canto II flow cytometer.
- Positive events were based on :
  - Identification of lymphoid cells by light scatter followed by gating on CD19-positive B-cells
  - Then dual expression of CD20(lo)/CD5 cells
  - Evaluation for kappa/lambda monoclonality.

# MRD Assay

- Level of MRD was assessed by %-MRD calculated as  $(\text{CLL events}) / (\text{total live, non-aggregated WBCs}) * 100$ .
- Validation studies confirmed a high level of sensitivity with this 6-color assay and the ability to consistently detect MRD events to the 0.005% level (25/500,000 events)
  - below that of the historic standard using the 3 parallel or 4-color approach

