A041202 CRP Breakout Session

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Alliance Fall Group Meeting

November 5, 2015

Agenda

- Introductions
- Overview of CLL
- Overview of A041202 Clinical Trial (Woyach)
  - Topic 1
  - Topic 2
  - Topic 3
  - Patient enrollment process (Woyach/Sublett)
- Data Submission
  - Reading Reports(Woyach)
  - Tour of Rave (Wilson)
  - Uploading Supporting Documentation (Wilson)
  - Frequently Seen Reporting Errors (Wilson)

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Agenda continued

- Update #03 Review of Major Changes (Sublett)
- Review of Frequently Asked Questions (Woyach/ Sublett)
- Open Q&A (Woyach/Sublett/Wilson)

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Study Team Introductions

- Jennifer Woyach, MD, Study Chair
- Sumithra Mandrekar, PhD, Primary Statistician
- Amy Stark, Secondary Statistician
- Samantha Sublett, Protocol Coordinator
- Luke Wilson, Data Manager
- Kristina Laumann, Statistical Programmer Analyst

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Overview of CLL

- CLL Diagnosis
- CLL Staging
- CLL Indications for Therapy

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Chronic Lymphocytic Leukemia (CLL) Diagnosis

- One of the most common types of leukemia in adults
  - 15,000 cases per year
- Variable clinical course
  - Asymptomatic or not (anemia, infections, lymphadenopathy)
- Main characteristics
  - Clonal expansion of mature B-lymphocytes
  - CD19+/CD5+/CD23+/CD43+/$CD20^{Low}$
  - Disrupted apoptosis
  - Aberrant activation of survival pathways (i.e. B-cell receptor, NF_KB
- Diagnosis
  - Absolute malignant lymphocyte count >5,000 uL in the peripheral blood

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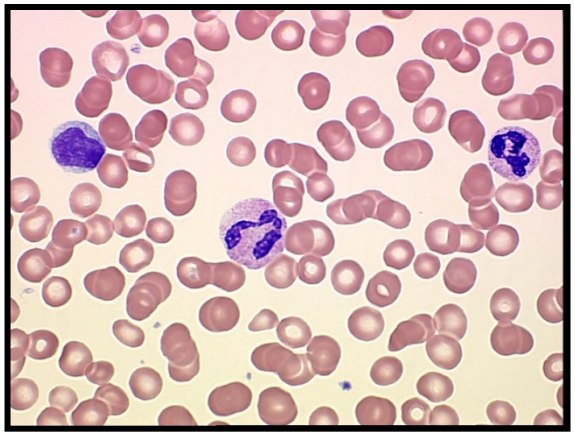
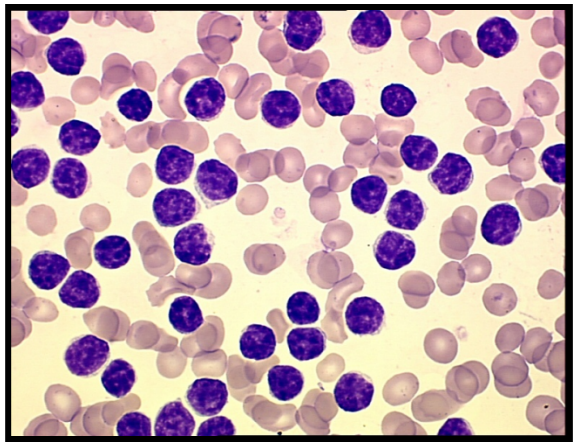
Chronic Lymphocytic Leukemia (CLL) Diagnosis

Normal peripheral blood smear



CLL peripheral blood smear



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CLL Staging

Table 2. Rai and modified Rai classification system*

Stage (Rai)	Description	Risk status (Modified Rai)	Median survival (years)†
0	Lymphocytosis, with lymphoid cells >30% in the blood and/or bone marrow	Low	11.7
I	Stage 0 with enlarged node(s)	Intermediate	8.3
II	Stage 0–1 with splenomegaly, hepatomegaly, or both	Intermediate	5.8
III	Stage 0–II with hemoglobin <110 g/L	High	1.7
IV	Stage 0–III with platelets <100 x 10^9/L	High	1.7

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CLL Indications for Therapy

- Evidence of marrow failure as manifested by the development or worsening of anemia or thrombocytopenia (not attributable to autoimmune hemolytic anemia or thrombocytopenia)
- Massive (≥6 cm below the costal margin), progressive or symptomatic splenomegaly
- Massive nodes (≥10 cm) or progressive or symptomatic lymphadenopathy
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy

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CLL Indications for Therapy
continued

- Constitutional symptoms, which include any of the following:
  - Unintentional weight loss of 10% or more within 6 months
  - Significant fatigue
  - Fevers >100.5 degrees F for 2 weeks or more without evidence of infection
  - Night sweats >1 month without evidence of infection

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Overview of A041202

- Study Rationale
- Study Objectives
- Study Schema
- Patient Enrollment Process and Suggestions

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Study Rationale

- Ibrutinib has improved survival for patients with relapsed/refractory CLL. This study will determine whether PFS with ibrutinib or ibrutinib + rituximab is superior to SOC chemotherapy for older patients with previously untreated CLL

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Study Objectives

- Primary Objective
  - Progression Free Survival (PFS)
- Secondary Objectives
  - Overall Survival (OS)
  - Complete response (CR) rate, complete and nodular partial response (CR/nPR) rate, and overall response (PR+nPR +CR) rate (ORR)
  - Impact of MRD negative disease on PFS and OS
  - Duration of response
  - Toxicity and tolerability

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Study Objectives continued

- Secondary Objectives Cont.
  - Response and PFS of cross-over patients receiving bendamustine + rituximab to ibrutinib
  - Correlative laboratory studies
  - Geriatric assessment
  - Assessment of FCGR3A and C1QA polymorphisms and relation to outcomes

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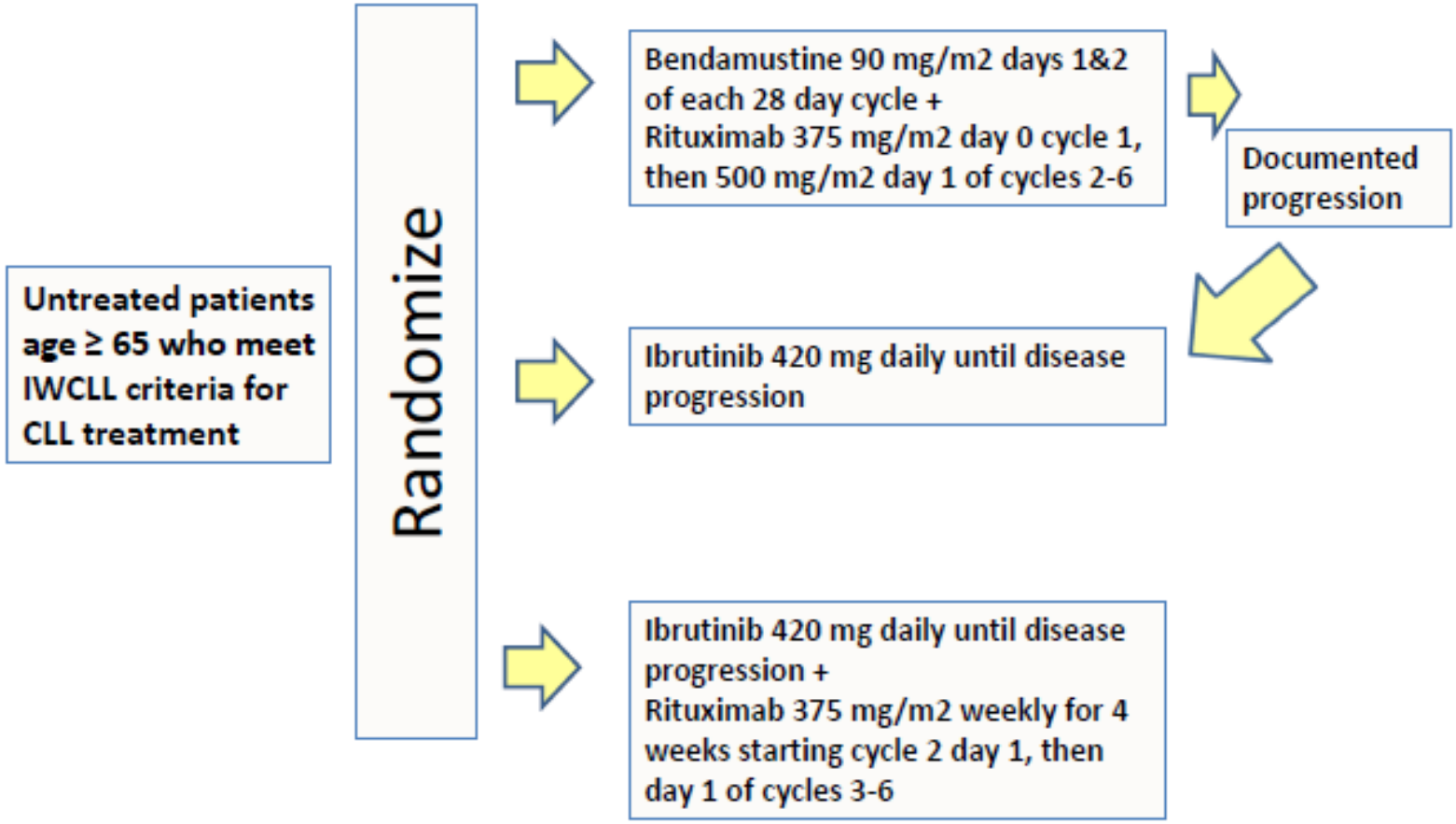
Study Schema



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Patient Enrollment Process & Best Practices

- See Handout
- Any issues you have at our own site? Please bring them up during the open Q&A!

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Data Submission

- Reading Reports & Data Interpretation
- Tour of Rave
- Uploading Supporting Documentation
- Data Submission Reminders and Best Practices

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Reading Reports & Data Interpretation

WBC	42.6	H	4.5-11.0 K/uL
ANC	8.15	H	1.80-7.70 K/uL
RBC	5.14		4.70-6.10 M/uL
HGB	15.6		14.0-18.0 g/dL
HCT	47.3		40.0-54.0 %
MCV	92.0		79.0-100.0 fL
MCH	30.4		26.0-34.0 pg
MCHC	33.0		30.0-36.0 g/dL
RDW	14.6	H	11.5-14.5 %
PLT	147		140-440 K/uL
NEU%	19.1	L	40.0-92.0 %
LYM%	77.6	H	5.0-50.0 %
MON%	2.4		2.0-14.0 %
EOS%	0.2		0.0-7.0 %
BASO%	0.4		0.0-1.5 %
Immature Gran%	0.3		%
Abs Lymph Count	33.00	H	1.00-4.80 K/uL
Abs Mono Count	1.02	H	0.00-1.00 K/uL
Abs Eos Count	0.10		0.00-0.45 K/uL
Abs Baso Count	0.16		0.00-0.20 K/uL
Abs Immat Gran	0.12		K/uL
Nuc RBC (AUTO)	0		/100

Multicolor flow cytometric analysis is performed on peripheral blood cells prepared by whole blood lysis. The gated population consists of small to intermediate-sized, hypogranular CD45 positive cells (lymphocytes) which comprise 81% of the total events. Approximately 91% of the gated population are positive for B-lymphocyte markers (CD19, CD20) and demonstrate CD5 and CD23 co-expression with kappa light chain restriction. There is no significant co-expression of CD38 by the B-lymphoid population. No expression of CD10 is identified. The remaining cells in the gated population are T-lymphocytes (CD3,CD5,CD7) with a CD4:CD8 ratio of 2.4.

- Calculating B cells: 91% of "gated population" (lymphocytes). .91x33
  - =33 K/uL
- Calculating CD4 and CD8 T cells: CD4:CD8 is 2.4, so:
  - 2.4x + x = total T cells
  - 3.4x= (.09x33)
  - 3.4x=2.97
  - X= .873
  - CD4 is (2.4x.873)= 2.09 K/uL
  - CD8 is .873 K/uL

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Another Format

MARKER	DESCRIPTION	LYM REG%	ABS/mm3
ABSOLUTE LYMPHOCYTE COUNT			1790
CD19+	B CELL	0.0	0
CD19+/CD20+	B CELL	0.0	0
SIG	SURFACE IG	0	
K/L	KAPPA/LAMBDA	0:0	
CD2+	T CELL	90.0	1611
CD3+	T CELL	76.9	1377
CD4+/CD3-	T CELL	3.9	
CD4+/CD3+	T HELPER	42.3	757
CD8+/CD3-	T CELL	13.6	
CD8+/CD3+	T SUPPRESSOR	29.3	524
HSRA	CD4/CD8	1.4	
CD5+/CD19-	T CELL	72.3	
CD5+/CD19+		0.0	
CD23+	B CELL SUBSET	0.0	
CD19+/CD10+		0.0	
CD10+	CALLA	0.0	
CD7+/CD2-	T CELL	5.2	
CD7+/CD2+	T CELL	73.7	
CD13+/HLA DR-	MONO/GRAN	0.0	
HLA DR+/CD13+		1.6	

- CLL cells are CD5+/ CD19+
- CD4 T cells are CD4+/ CD3+
  - 757 K/uL
- CD8 T cells are CD8+/ CD3+
  - 524 K/uL

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Data Submission

- Tour of Rave
- Uploading Supporting Documentation
- Frequently seen reporting errors (see handout)

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Update #03 Changes

- Eligibility
- Enrollment timelines and requirements
- Study Calendar
- Consent

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Questions?

- Review of FAQs (see handout)
- Open Q&A

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