A randomized phase III study of Ibrutinib during and following autologous stem cell transplantation versus placebo in patients with relapsed or refractory Diffuse Large B-Cell Lymphoma of the Activated-B-Cell Subtype

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May 12, 2017
Presentation Objectives

- Describe DLBCL and treatment of relapse/progression
- Understand the mechanics of AutoHCT
- Discuss A051301 study logistics
- Answer questions about data management
DLBCL

- DLBCL is the most common lymphoma in adults, comprising ~40% of NHL cases.
- Aggressive malignancy with over 50% cure rate with modern front-line therapy (e.g. R-CHOP, DA-EPOCH-R, etc.)
- Patients who do not respond to 1st therapy or progress thereafter, can be cured with an approach that includes stem cell transplant.
Treatment at relapse/progression

- 2\textsuperscript{nd} line ("salvage") therapy:
  - Given x 2-4 cycles
  - Includes a stem cell collection step
  - E.g. R-ICE, R-DHAP, R-GemOx, etc.

- Mobilization for stem cell collection
  - Apheresis (HPC-A) or Bone Marrow Harvest (HPC-M)

- Stem cell Transplantation (AutoHCT)
Relapsed DLBCL Paradigm

- Salvage Sens
- ASCT

45% "Cured"

NCIC-CTG Ly.12 → CORAL → CTN 0401
Relapsed DLBCL Paradigm

- Salvage Sens
- ASCT
- "Cured"

NCIC-CTG Ly.12  CORAL  CTN 0401
DLBCL-Gene Expression Profiling

Alizadeh, Nature 2000; Wright, PNAS, 2002; Rosenwald, NEJM 2002; Lenz, NEJM 2008; Alizadeh/Lossos; NEJM 2009
Targeting of B-Cell Receptor Signaling

From: Nat Rev Immunol 2:945
Ibrutinib

- A Bruton’s Tyrosine Kinase (Btk) inhibitor that interferes with B-Cell receptor signaling.
- Activity against ABC-type DLBCL cell lines \(^1\)
- Phase I and II data in heavily pretreated patients with DLBCL showed 40% RR in ABC subtype (8% CR, 32% PR, N=25), only 5% in GCB. \(^2\), \(^3\)
- Well tolerated with 13% ≥ gr 3 AEs. \(^2\), \(^3\)
  - Most common related gr 3: hyponatremia, fatigue, GI
  - Heme: <8% gr3,4 neutropenia, anemia, or thrombocytopenia

Ibrutinib - Immunology

- A potent irreversible inhibitor of ITK that together with RLK drives TCR signalling
- Ibrutinib can suppress Th-2 activation.¹
- A Th-1 predominant response can have beneficial effects for cancer immunity.²,³
  - Generation of inflammatory cytokines
  - Stimulation of APCs/cross-priming?
  - CTL generation and persistence

A051301: Hypothesis

- Addition of ibrutinib to autoHCT regimen will synergistically improve response to treatment
- Additional consolidation with single agent ibrutinib will eliminate residual disease following autoHCT and prevent relapse
Study Objectives

**Primary objective**
- 24 month Progression-Free Survival

**Secondary objective(s)**
- Overall Survival
- Progression-Free Survival
- Post-Auto Response Rates
- Hematopoietic Recovery
- Safety/tolerability of Ibrutinib
- Secondary Malignancies
- Immune Reconstitution
Study Schema

Registration
Relapsed/Refractory DLBCL-ABC
Salvage ≥PR

Randomization
Stratify by time to relapse, conditioning regimen

Arm A
AutoHCT: CBV or BEAM + Ibrutinib 560 mg
Ibrutinib x 12 cycles
Follow Up

Arm B
AutoHCT: CBV or BEAM + Placebo
Placebo x 12 cycles
Follow Up
Pre-Registration

- Necessary for central path review and establishment of DLBCL subtype
  - Only ABC subtype is eligible (~50%)
- TAT ~ 3-4 weeks
- Tissue submission requirements in section 6.2 of protocol
Pre-Registration

Relapsed DLBCL Patient Consent
Prior/during/after “salvage”

“Salvage” Therapy
Any therapy allowed
Ibrutinib OK

Response Assessment
Per institution preference

Stem Cell Collection

Wash U CLIA Lab
Excision or Core from diagnosis or relapse

Central Path Review

Frederick Lab
Subtype Assignment

Wash U Biorepository
Correlatives and Banking

REGISTRATION
Eligibility: Additional Disease Criteria

- Age 18 years and older
- Progressed or refractory to 1\textsuperscript{st} line therapy
- No more than 3 prior therapies for large cell
- Prior ibrutinib is allowed as long as no disease progression
- No active CNS lymphoma (> 91 days)
- Chemosensitive disease by local criteria (PET/CT preferred)
- Approved to proceed to autoHCT by transplant center committee
Eligibility: Organ Function

- **Cardiac**
  - NYHA Class I or less
  - If 60 or older, LVEF measured $\geq 40\%$ (TTE/MUGA)

- **Pulmonary Eligibility**
  - DLCO, FEV1, FVC $\geq 40\%$ of predicted (corrected for hemoglobin)

- **Hepatic**
  - Total Bilirubin $\leq 1.5 \times \text{ULN}$. AST and ALT $\leq 3 \times \text{ULN}$
  - No Child-Pugh class B or C impairment

- **Renal**
  - Creat $\leq 2.0 \text{mg/dL}$ OR Crcl $\geq 40 \text{mL/min}$
Eligibility: Ibrutinib specific

- No coagulopathy or bleeding diathesis
  - PT/INR and PTT (aPTT) < 1.5 x ULN
- No major surgery ≤ 7 days and no minor surgery ≤ 3 days prior to registration
- No strong CYP3A inhibitors or strong CYP3A inducers (see Appendix II).
- No steroids (> 20 mg of prednisone/day)
- No warfarin or vit K antagonists
- No recent stroke or hemorrhage
Eligibility: Infectious

- No ACTIVE hepatitis B or C infection by PCR. HBcAb +, HBsAg+, HCVAb+
- HIV is ALLOWED
  - No prior history of AIDS defining conditions
  - Use of HIV protease inhibitors is not allowed
  - Zidovudine is not allowed
  - Once daily combination pills containing a booster such as cobicistat are not allowed
  - Patients with multi-drug resistant HIV are not eligible
## Procedures Cheat Sheet

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<td><strong>PRE-REGISTRATION</strong></td>
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<td><strong>Salvage &amp; Mobilization</strong></td>
<td><strong>AUTO-HCT</strong></td>
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Treatment Plan
Cycle 1: autoHCT

- Starts with first day of conditioning
- Ends day +29 (~36 days)
- BEAM or CBV conditioning, center choice
- Ibrutinib or placebo 560 mg daily, days -6 to -1
- Stem cell infusion HPC-A or HPC-M on day 0
- Weekly follow up until day +29
- See section 8.1 for ancillary/con meds
- For dose modifications see section 8.2.1
Treatment Plan
Cycle 2: Continuation

- Ibrutinib vs. placebo 560 mg PO qd x 28 days
- Start between day +30 and +60 of AutoHCT
- **Day 1 visit at study site. To start:**
  - ANC ≥ 1000/μL, platelets ≥ 30,000/μL
  - No active bleeding
  - Serum creatinine ≤ 2.0 mg/dL
  - AST, ALT ≤ 2x ULN; Total bilirubin ≤ 1.5x ULN
- **Day 15 follow up visit can be done locally**
- See section 8.1 for ancillary/con med temps
- Dose modifications, section 8.2.2
Treatment Plan
Cycles 3-13: Continuation

- Ibrutinib vs. placebo 560 mg PO qd x 28 days
- Day 1 visits:
  - Study Center: Cycles 3, 7, 10, and 13
  - Locally: Cycles 4, 5, 6, 8, 9, 11, and 12
- See section 8.1 for ancillary/con meds
- Dose modifications, section 8.2.2
- Two 7-day drug holidays for reasons other than toxicity allowed
Follow Up

- Clinical: 18, 24, 30, 36, 42, 48, 54, 60 mos

- Imaging
  - Baseline PET/CT during salvage/before registration
  - Response assessment PET/CT at 3 +/- 1 months
  - Monitoring at 6, 12, 18, and 24 months (+/- 1 month)

- BM Biopsy
  - Repeat at 3 months ONLY if positive at baseline

- Pulmonary Function Tests
  - Baseline required
  - Repeat at 3 months
Follow Up, cont

- Quantitative Immunoglobulins (IgG, IgM, IgA)
  - Monitor for hypogammaglobulinemia
  - at baseline and at 3, 6, 9, 12, 18, and 24 months

- T-cell Subsets (CD3+, CD4+, CD8+)
  - Evaluate immune reconstitution
  - at baseline and at 3, 6, 9, 12, 18, and 24 months
Progression

- History & Physical
- Routine Lab assessment
- PT/CT imaging, central review
- Tissue collection
  - See section 6.2.3 for substudy A051301-ST1
- Unblinding allowed for Crossover
Crossover

- Eligibility
  - ANC $\geq 1000/\mu L$, platelets $\geq 30,000/\mu L$
  - Creat $\leq 2.0$ mg/dL OR CrCl $\geq 40$ mL/min
  - AST, ALT $\leq 2 \times$ ULN, Total bilirubin $\leq 1.5 \times$ ULN
- Up to 12 cycles allowed
- Ibrutinib 560 mg PO qd x 28 days
- Monthly follow up (locally OK)
- Imaging every 3 months
- Measure response rate, 2\textsuperscript{nd} PFS, OS
Statistics & Accrual

• Primary Endpoint: 24 month PFS
• Assumptions
  Prolong 24-month PFS from 50% to 67%
  5% attrition rate
  $\alpha=0.05$, power=0.80
• Accrual and Follow-Up
  N=296 at ~75 pts/year (4 years)
  24 months of additional follow-up
• BMT/CTN estimate
  732 DLBCL ASCT/year at top 50 US sites
  If ~50% ABC, 366 patients potentially eligible annually
Safety and Interim Analyses

• **Safety in combination with conditioning**
  - Run-In cohort of 6 patients on active agent and monitored for first cycle before formal enrollment begins
  - 6 Registrations to date

• **Interim Analyses**
  Early termination for futility or superiority
  Interim analyses will be conducted when 140 and 210 patients have at least 24 months F/U
AE Reporting

- **Cycle 1: AutoHCT**
  - Only grade $\geq 2$ related or $\geq 3$ are captured
  - Only unexpected with auto are reported
- **Cycles 2-13: continuation**
  - Only related or $\geq 3$ are captured
- **AEs of special interest**
- **Section 9** for details
Correlatives

- Imagining Correlative Science
  - Role of FDG-PET in predicting outcomes following AutoHCT in relapsed/refractory DLBCL
  - Central Radiology Submission, section 6.3
- Substudy A051301-PP1
  - Evaluate the Pharmacogenetics of High-dose Chemotherapy and Treatment Efficacy in Relapsed/Refractory DLBCL
  - Peripheral blood submission at registration
  - Section 6.2
Correlatives, cont.

- Substudy A051301-ST1
  - Assess activating mutations in the BCR pathway and response to ibrutinib
  - Assess phenotypic associations with IHC markers (particularly MYC protein expression level) and presence of BCR mutations
  - Tissue submission at pre-registration, registration and progression, section 6.2
CRFs Question & Answers

- **On Study**
  - Prior Surgery- document only surgeries related to this tumor (i.e. biopsies, complications)
  - Prior Radiation- document only radiation therapy related to NHL
CRFs Question & Answers

- *Pulmonary Function tests*
  - Required fields are: DLCO, FEV1, FVC.
  - FEF 25-75 and TLC are all measured but optional.

- *Cardiac Function*
  - If cardiac disease is present, NYHA grade > 1 is an exclusion
CRFs Question & Answers

Response Assessment

- Patients enter study in response ("CR" or "PR")
  - 3 month PET: response to auto (Lugano or Deauville)
  - Subsequent scans: progression on maintenance (CT-based criteria)

- **Target Lesion Measurement**
  - Capture type of scan used in assessment
  - Spleen size matters for CT-based progression
Questions?