A051301: 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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Presentation Objectives

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

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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

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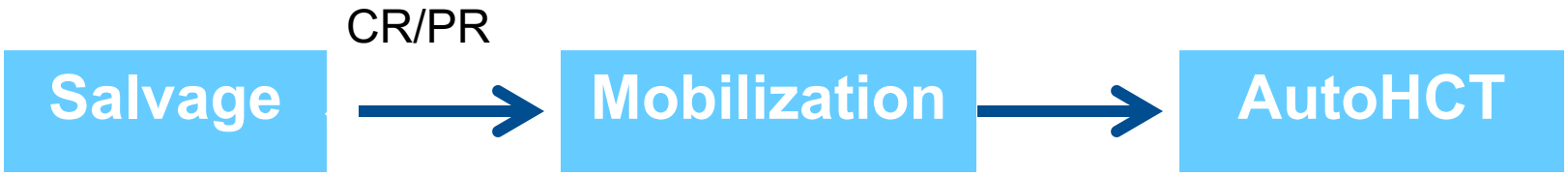
Treatment at relapse/progression

- 2nd 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)



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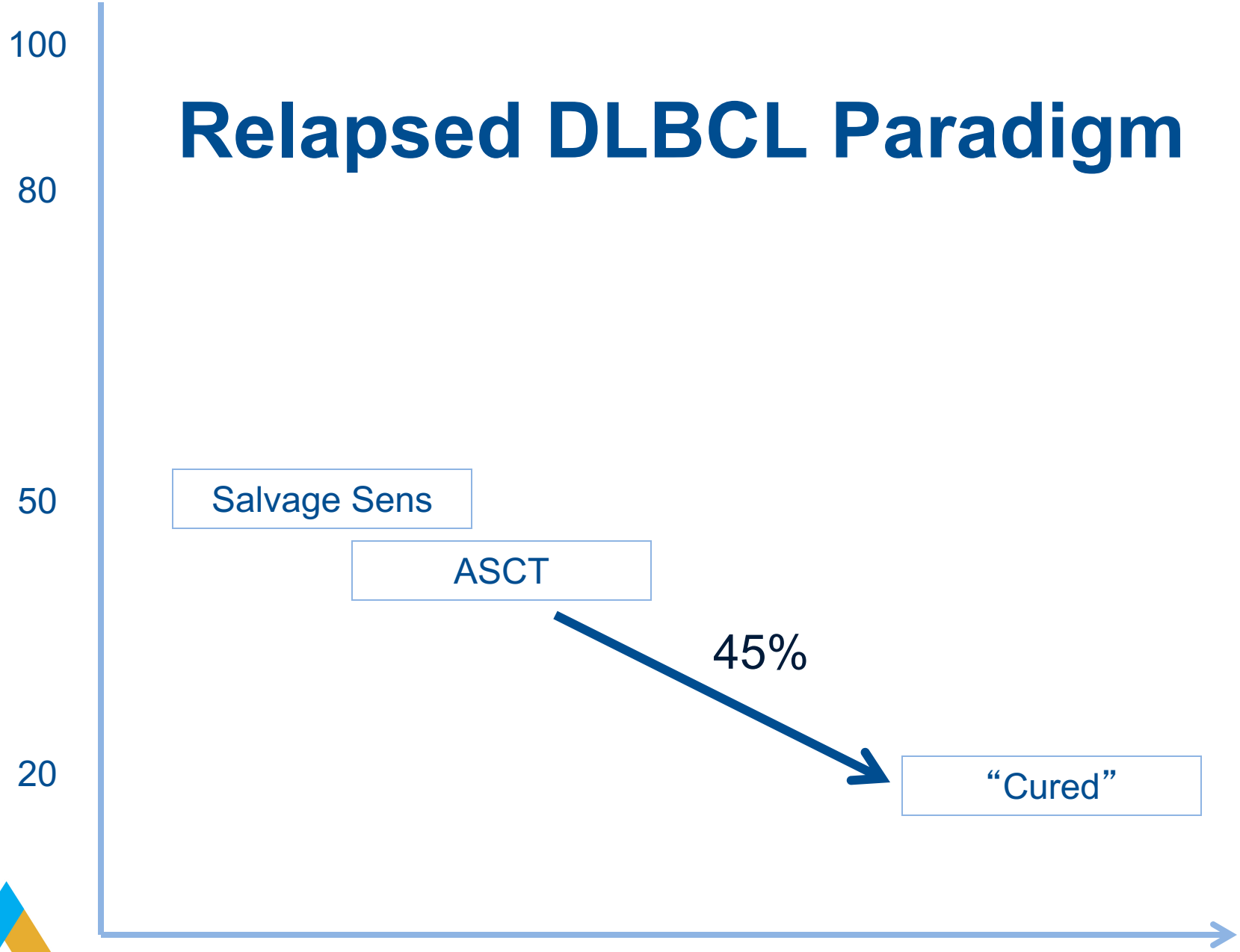
Relapsed DLBCL Paradigm



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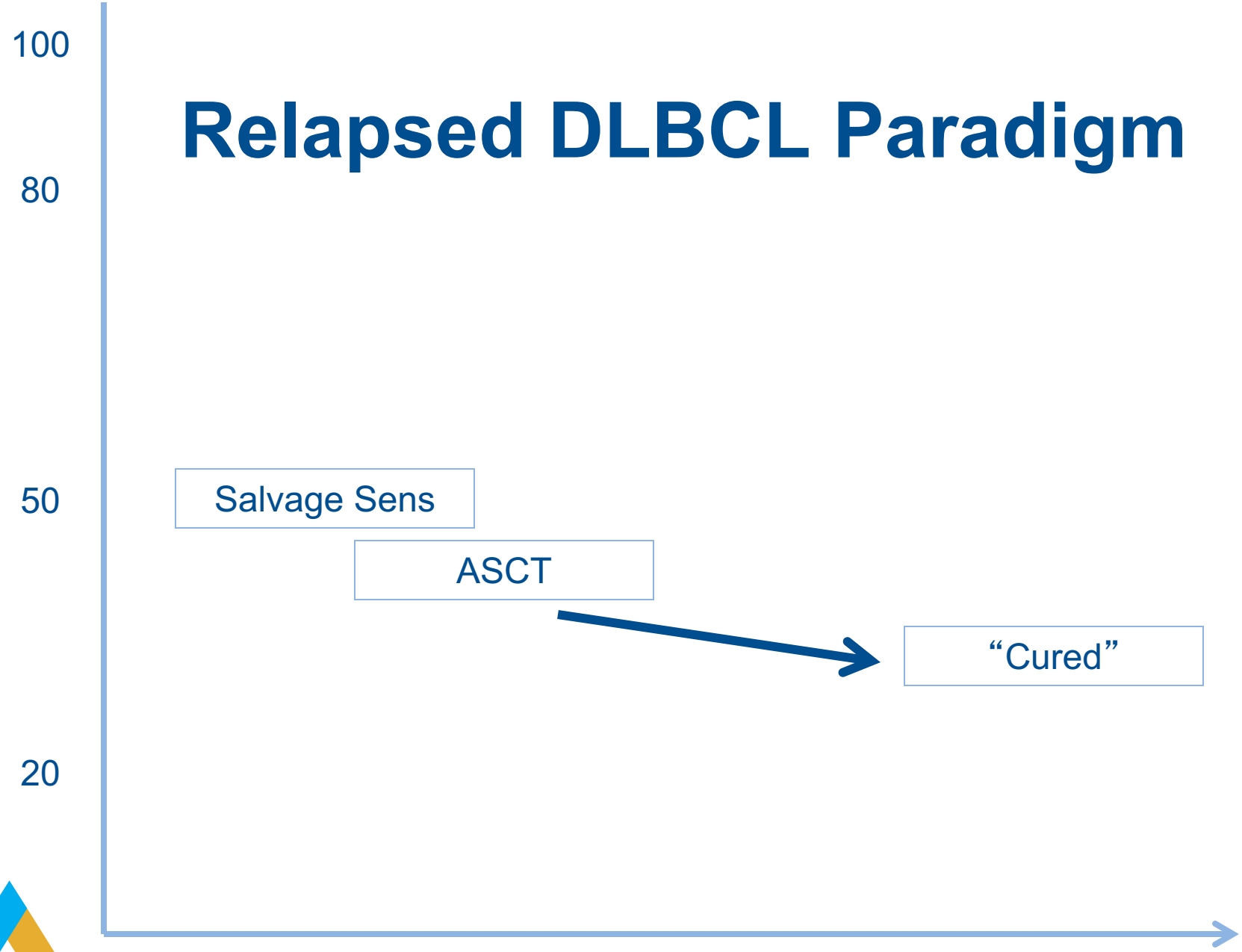
Relapsed DLBCL Paradigm



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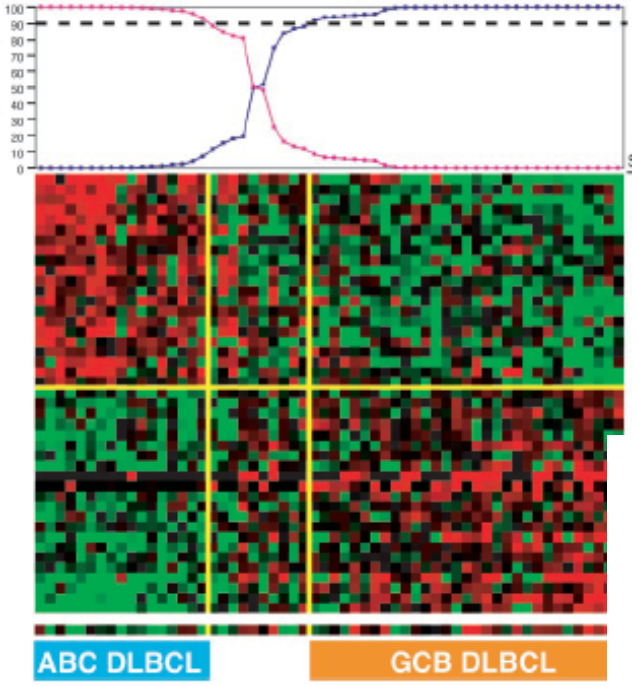
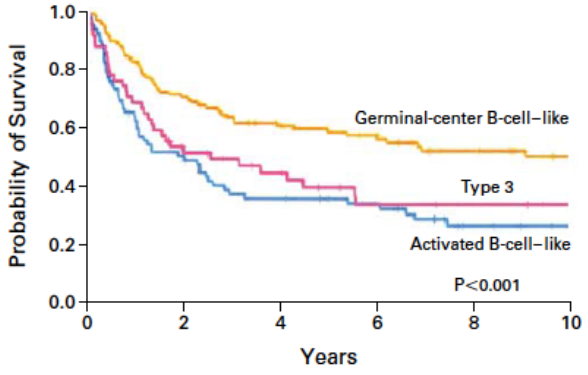
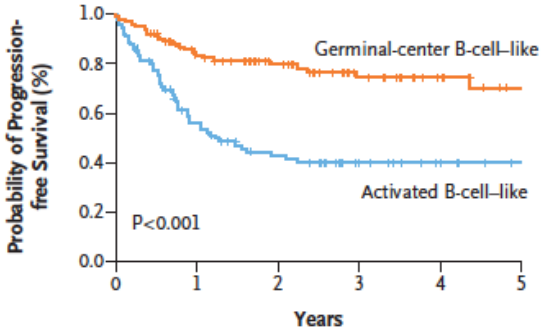
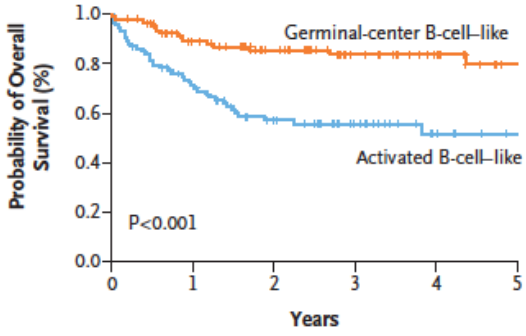
DLBCL-Gene Expression Profiling









Alizadeh, Nature 2000; Wright, PNAS, 2002;
Rosenwald, NEJM 2002; Lenz, NEJM 2008;
Alizadeh/Lossos; NEJM 2009

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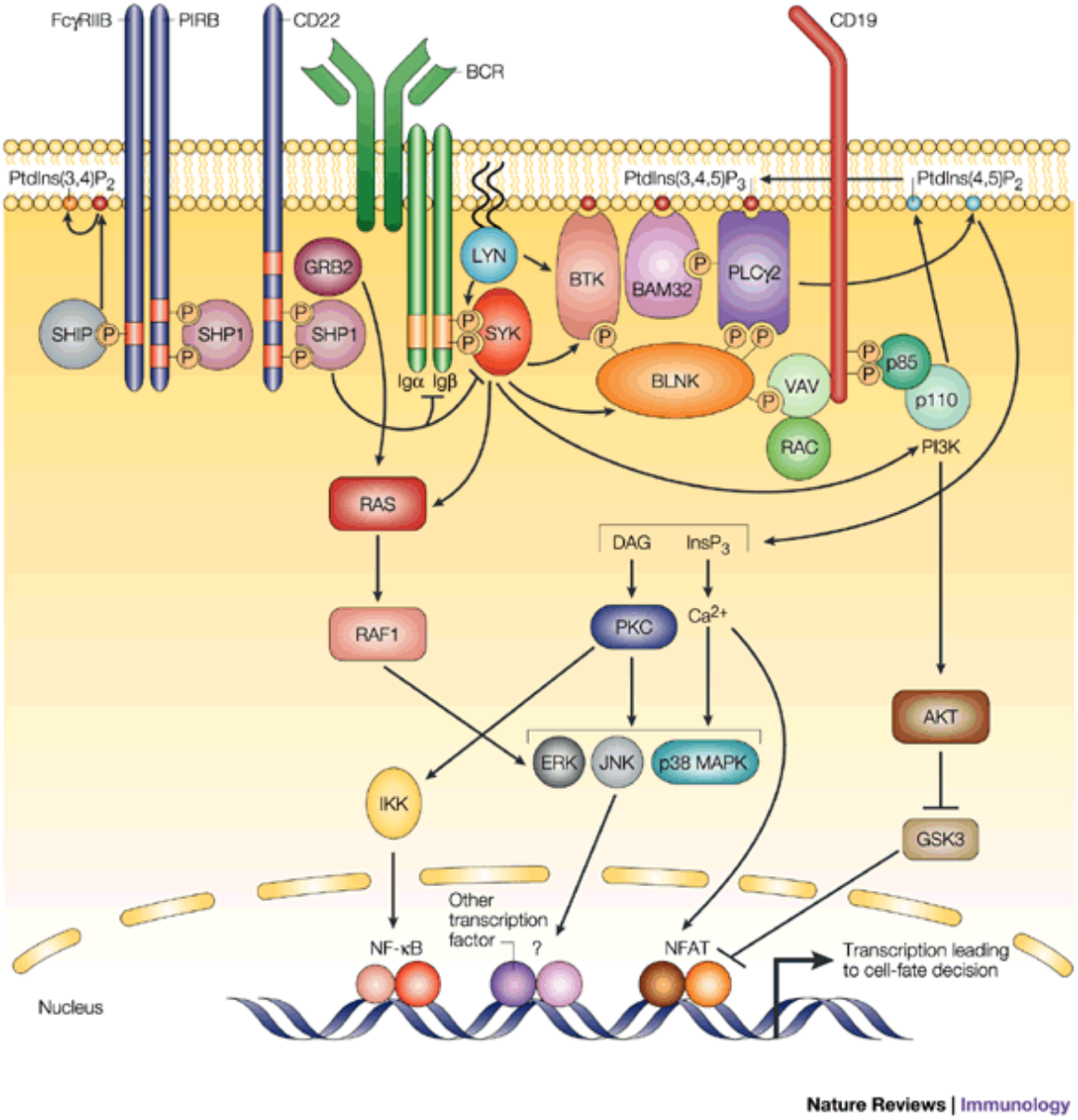
Targeting of B-Cell Receptor Signaling



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

1: Davis et al, Nature 2010 2: Advani et al, JCO 2012 3: Wilson et al, ASH 2012

Ibrutinib - Immunology

- A potent irreversible inhibitor of ITK that together with RLK drives TCR signalling
- Iburitnib 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

1: Dubovsky et al, Blood 2013 2: Knutson et al, CII 2005 3:Disis, JCO 2010

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

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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

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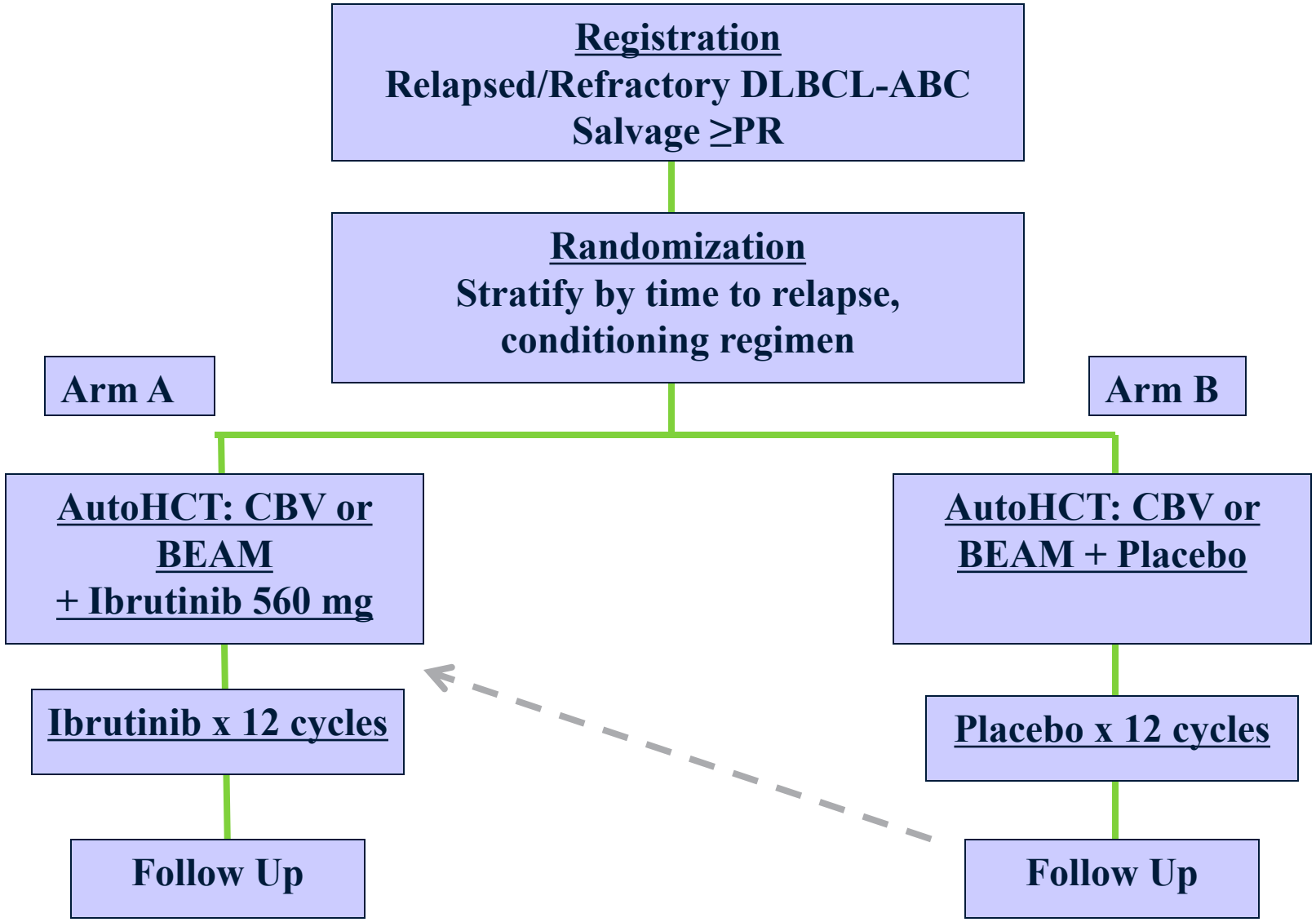
Study Schema



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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

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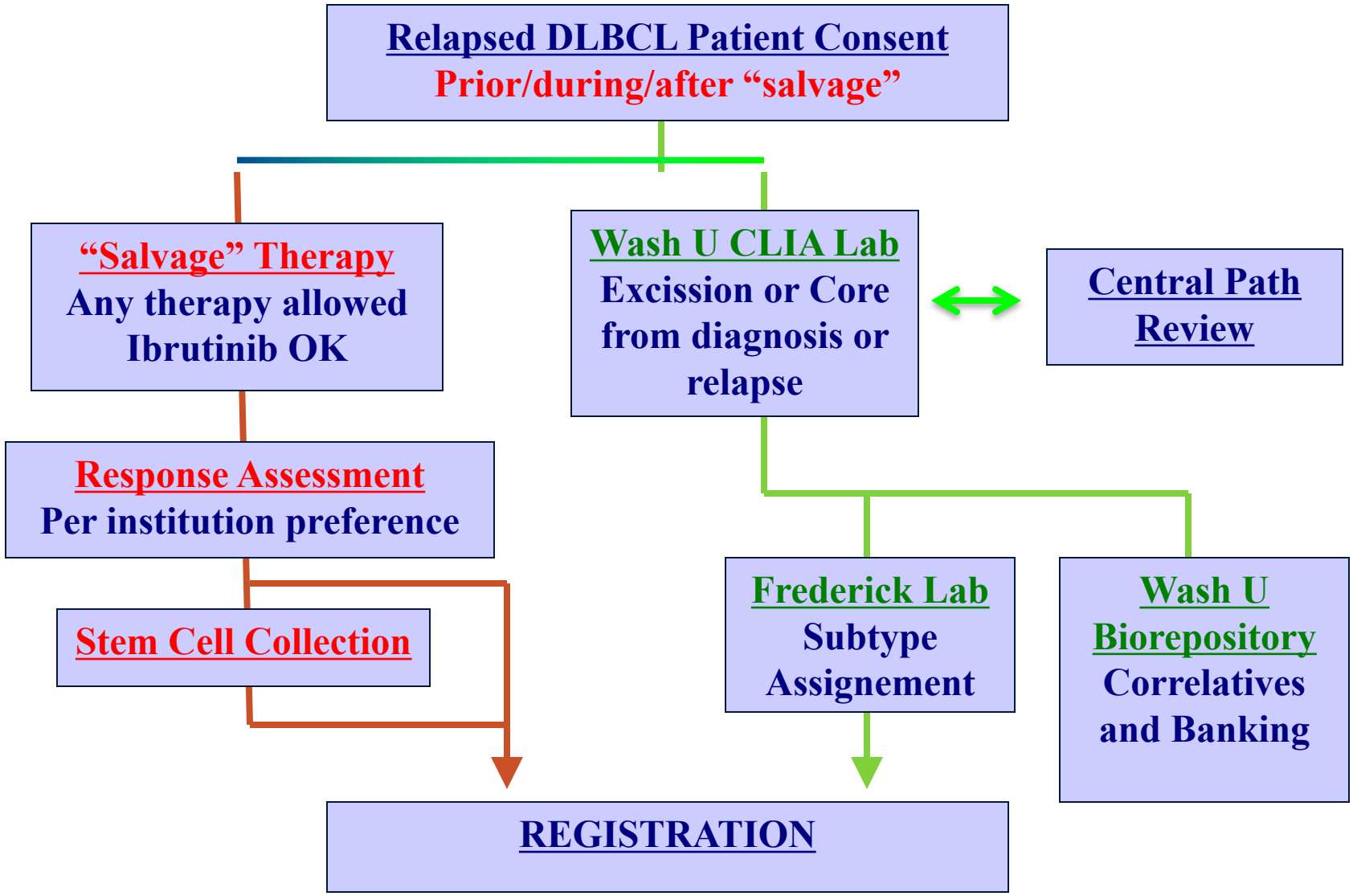
Pre-Registration



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Eligibility: Additional Disease Criteria

- Age 18 years and older
- Progressed or refractory to 1st 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

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Eligibility: Organ Function

- Cardiac
  - NYHA Class I or less
  - If 60 or older, LVEF measured ≥ 40% (TTE/MUGA)
- Pulmonary Eligibility
  - DLCO, FEV1, FVC ≥ 40% of predicted (corrected for hemoglobin)
- Hepatic
  - Total Bilirubin ≤ 1.5 x ULN. AST and ALT ≤ 3 x ULN
  - No Child-Pugh class B or C impairment
- Renal
  - Creat ≤ 2.0 mg/dL OR Crcl ≥ 40 mL/min

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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

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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

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Procedures Cheat Sheet

	≤12 weeks	≤ 6 weeks	≤ 3 weeks	≤ 2 weeks		≤ 3 weeks	
PRE-REGISTRATION					REGISTRATION		
Salvage & Mobilization							AUTO-HCT
	PFTs						
	BM Biopsy						
		PET/CT					
			Visit & all Labs				
				HCG			
						Fatigue Assessment	

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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

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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 meds
- Dose modifications, section 8.2.2

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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

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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

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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

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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

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Crossover

- Eligibility
  - ANC ≥ 1000/μL, platelets ≥ 30,000/μL
  - Creat ≤ 2.0 mg/dL OR CrCl ≥ 40 mL/min
  - AST, ALT ≤ 2 x ULN, Total bilirubin ≤ 1.5 x 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, 2nd PFS, OS**

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Statistics & Accrual

- Primary Endpoint: 24 month **PFS**
- Assumptions
  - Prolong 24-month PFS from 50% to 67%
    5% attrition rate
  - α=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

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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

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AE Reporting

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

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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
  - Peipheral blood submission at registration
  - Section 6.2

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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

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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

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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

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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

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Questions?

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