



## Information for Patients with Aggressive Lymphomas



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### Welcome & Introductions

Dr. Roschewski's slides are available for  
download at [www.LLS.org/programs](http://www.LLS.org/programs),  
under the program listing.

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### Information for Patients with Aggressive Lymphomas

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### Disclosures

**Mark Roschewski, MD**, has no affiliations with commercial interests to disclose.

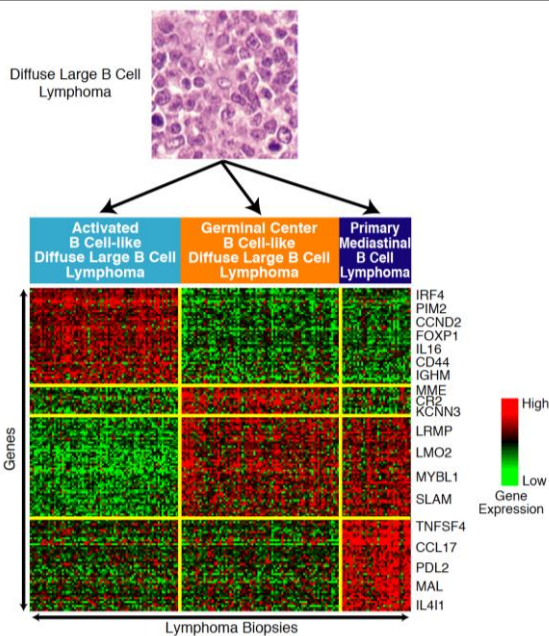
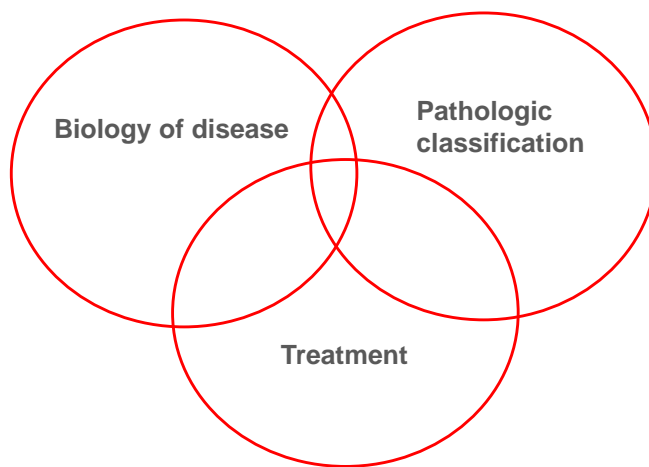
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### Agenda

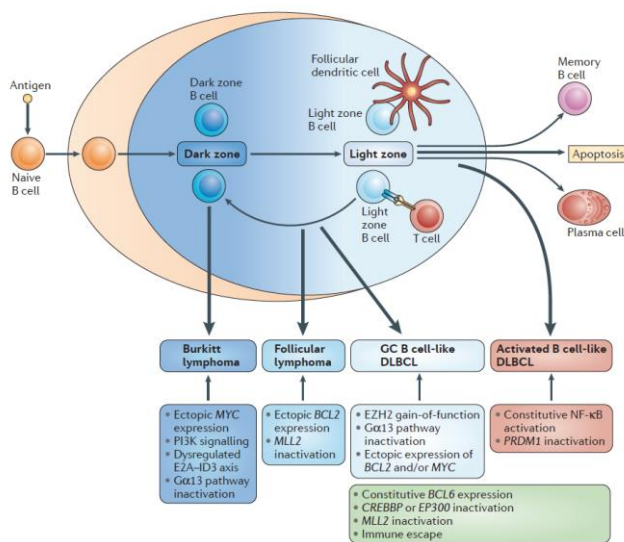
- ◆ Understand the current approach to DLBCL and BL
- ◆ Discuss strategies to overcome chemotherapy resistance
- ◆ Describe “precision medicine” approaches to aggressive NHL
- ◆ Introduce the role of circulating tumor DNA to monitor therapy

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## Challenge of precision medicine

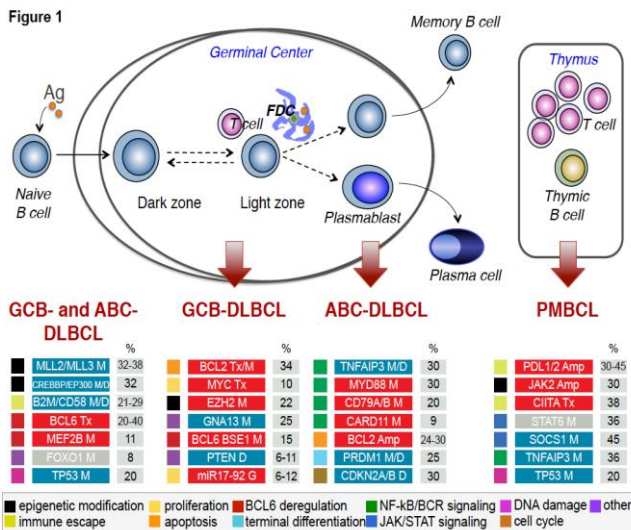


## B-cell biology and B-cell lymphomas



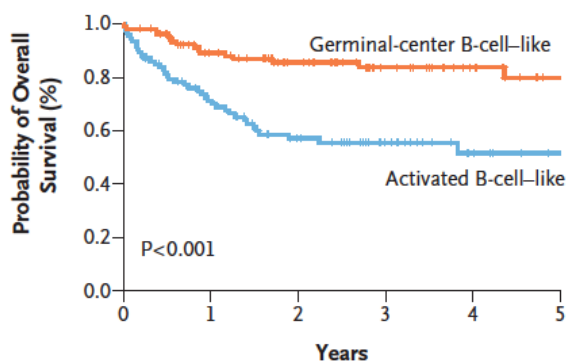
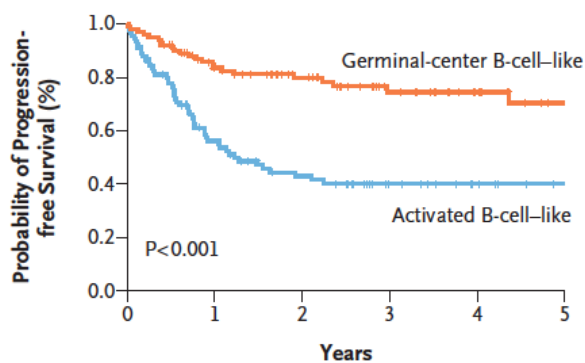
Basso et al. *Nat Rev Immunol.* 2015 Mar;15(3):172-84

## Genomic landscape of DLBCL(s)



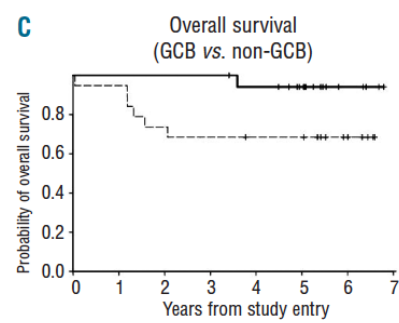
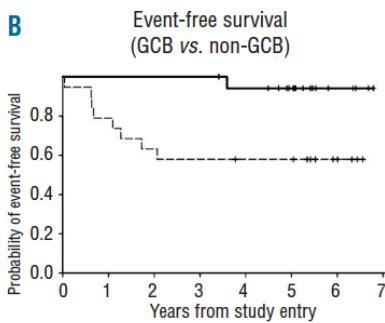
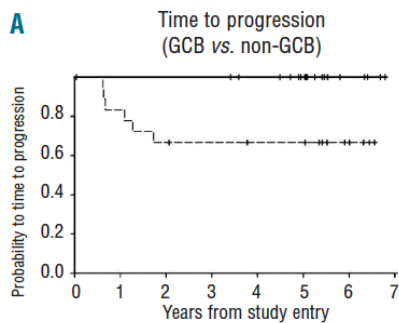
Pasqualucci et al. *Semin Hematol* 2015 Apr;52(2):67-76

## Outcomes by molecular subtype after R-CHOP



Lenz et al. *N Eng J Med* 2008; 359:2313-232

## Outcomes by molecular subtype after DA-EPOCH-R

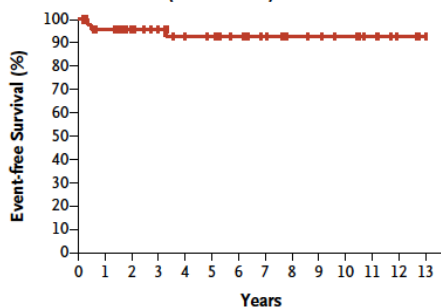


Wilson et al. *Haematologica* May 2012 97: 758-765

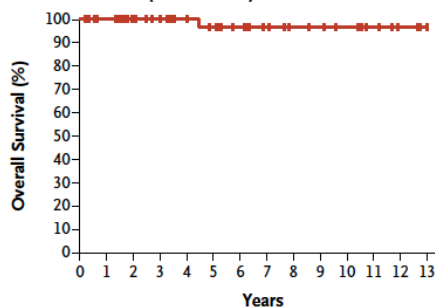
## ORIGINAL ARTICLE

## Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma

A Event-free Survival (NCI Patients)



B Overall Survival (NCI Patients)

Dunleavy et al. *N Eng J Med* 2013 Apr 11;368(15):1408-16

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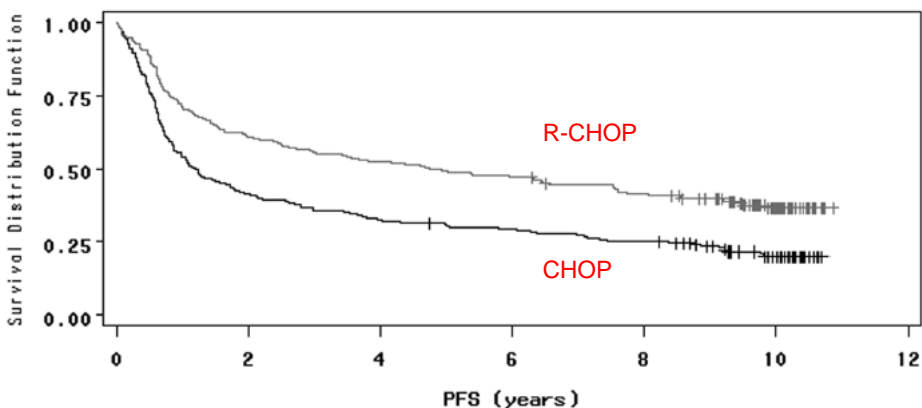
### *Frontline treatment of DLBCL*



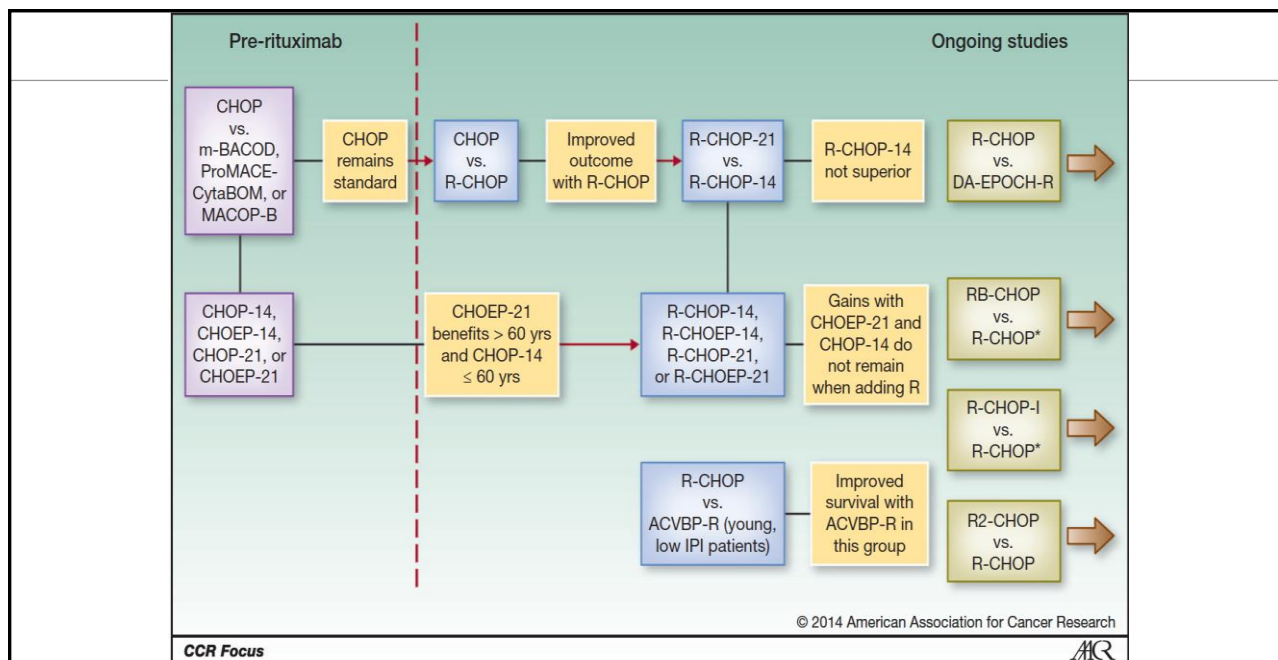
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## Rituximab improves overall survival

Cure rate ~60%



Coiffier et al. *Blood* 2010 Sep 23;116(12):2040-5



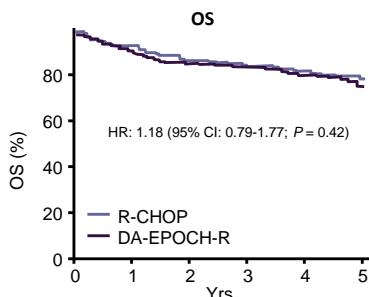
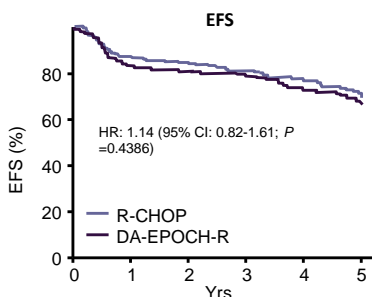
© 2014 American Association for Cancer Research

CCR Focus



Dunleavy, Roschewski, Wilson *Clin Cancer Res* 2014

## CALGB 50303: R-CHOP vs. DA-EPOCH-R



Arm	N	Events, n	3 Yrs (95% CI)	5 Yrs (95% CI)
R-CHOP	233	64	0.81 (0.75-0.85)	0.69 (0.62-0.75)
DA-EPOCH-R	232	70	0.79 (0.73-0.84)	0.66 (0.59-0.72)

Arm	N	Events, n	3 Yrs (95% CI)	5 Yrs (95% CI)
R-CHOP	233	44	0.85 (0.80-0.89)	0.80 (0.74-0.85)
DA-EPOCH-R	232	50	0.85 (0.79-0.89)	0.76 (0.70-0.71)

\*Median follow-up 5 yrs  
Wilson WH, et al. ASH 2016. Abstract 469.



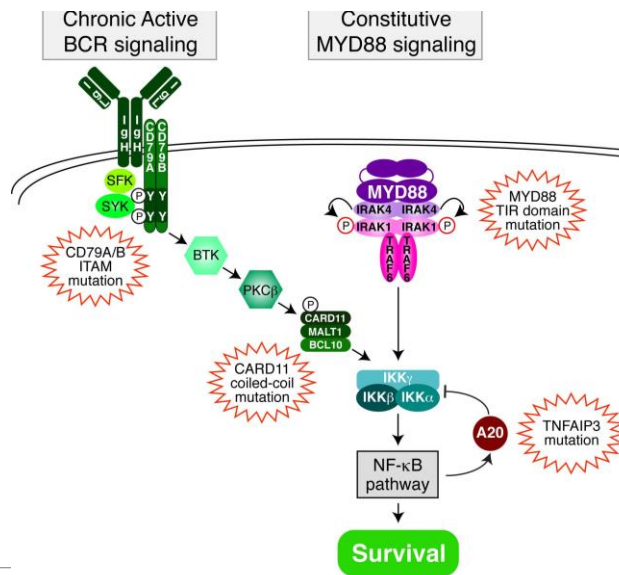
Wilson WH, et al. ASH 2016. Abstract 469.

## *Targeted therapy for ABC*

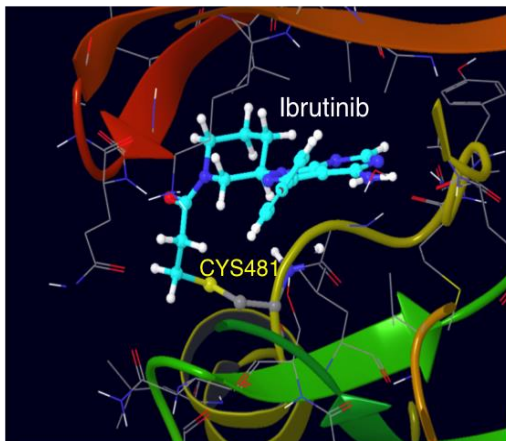




## Oncogenic activation of NF- $\kappa$ B in ABC DLBCL

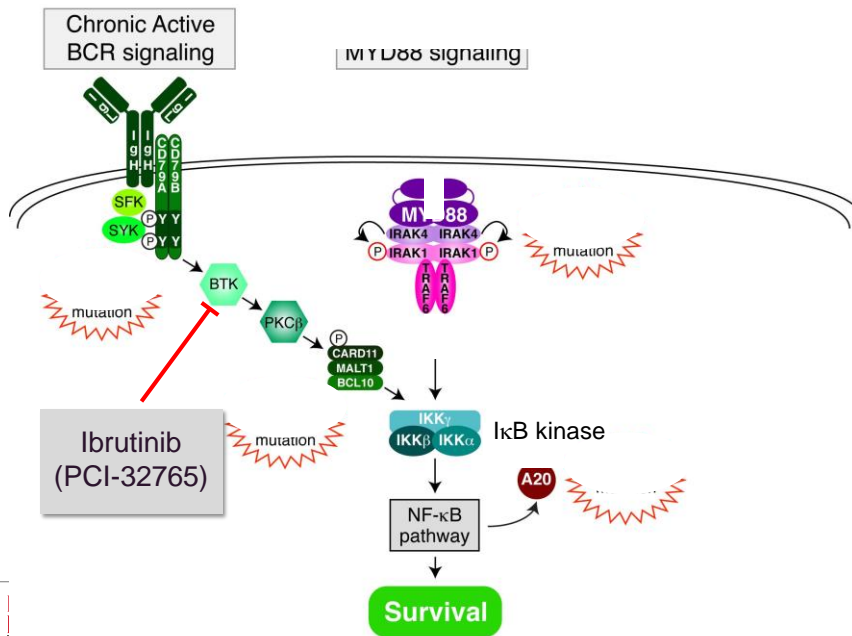


## Ibrutinib: first in-class inhibitor of BTK

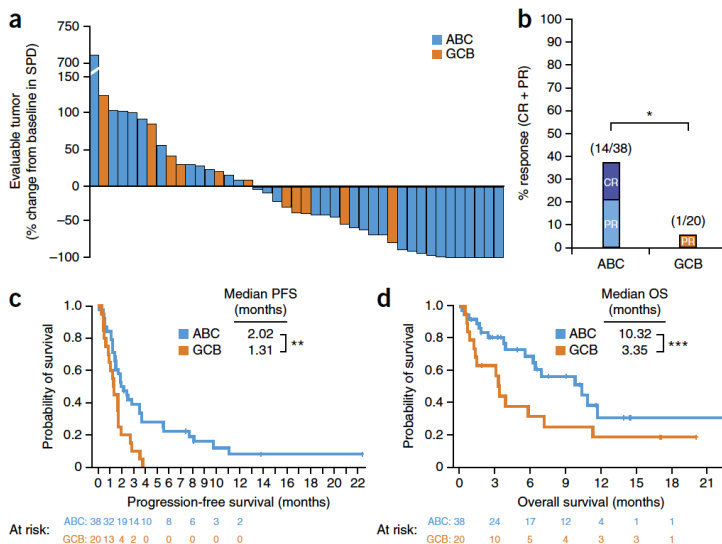


- ◆ Forms covalent bond with cysteine-481 in BTK
- ◆ High BTK specificity
- ◆ IC<sub>50</sub> = 0.5 nM
- ◆ Daily oral dosing produces 24-hr BTK inhibition
- ◆ Blocks NF- $\kappa$ B activation in DLBCL cell lines<sup>1,2</sup>

## Blocking chronic active B-cell receptor signaling with through BTK

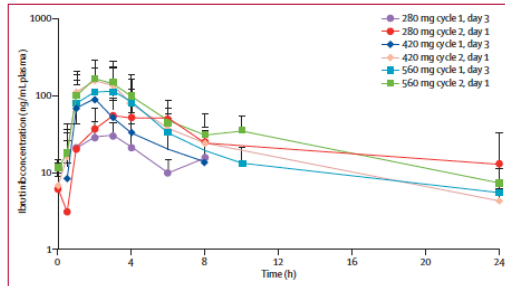


## Ibrutinib selective for ABC DLBCL



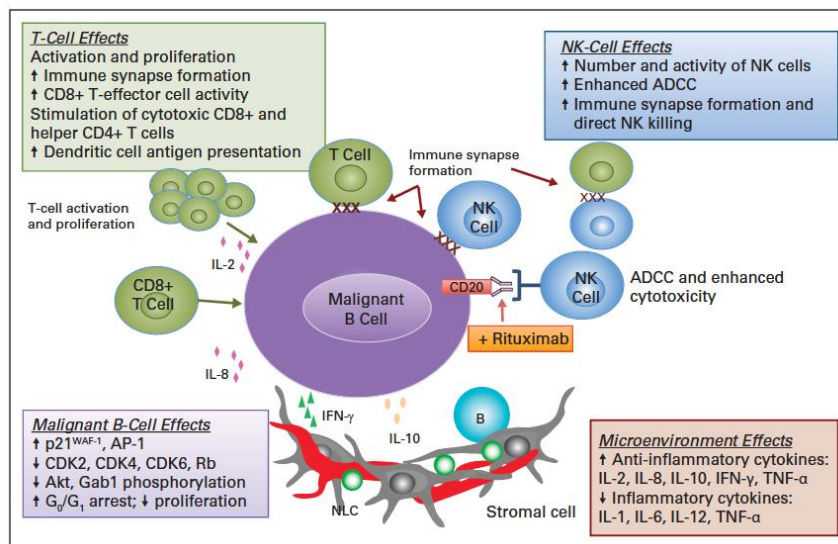
## Ibrutinib adds no toxicities to R-CHOP

Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naive patients with CD20-positive B-cell non-Hodgkin lymphoma: a non-randomised, phase 1b study

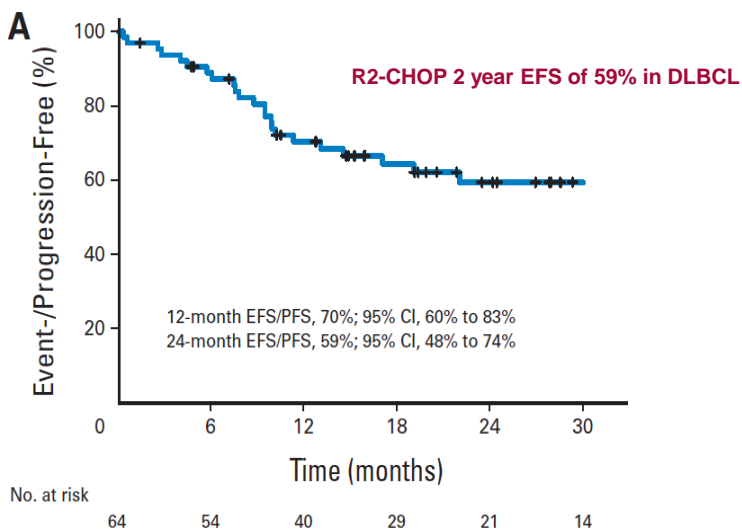


Ibrutinib safe to add to R-CHOP at 560mg  
Phase III study R-CHOP +/- ibrutinib accrued

## Lenalidomide active in ABC DLBCL



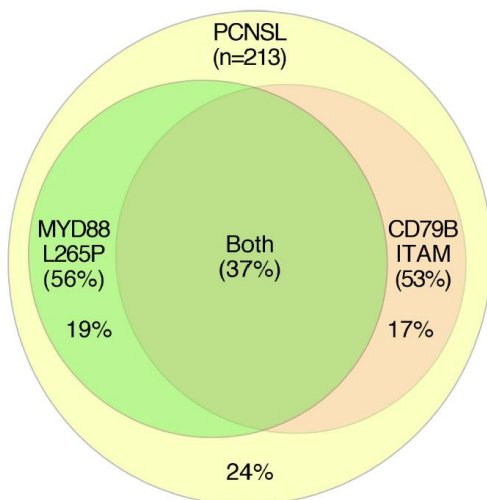
## Lenalidomide safely added to R-CHOP in DLBCL



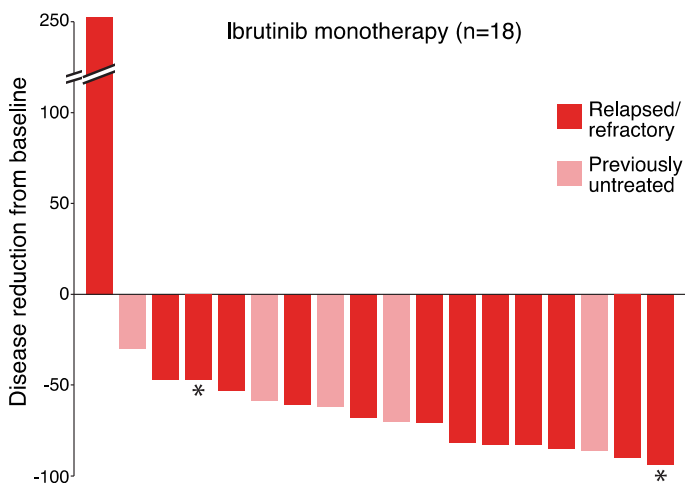
Nowakowski et al. *J Clin Oncol.* 2015 Jan 20;33(3):251-7

## Chronic active B-cell receptor signaling in rare lymphomas

VIII. Figure 2: Meta-analysis of CD79B and MYD88 sequencing data in PCNSL



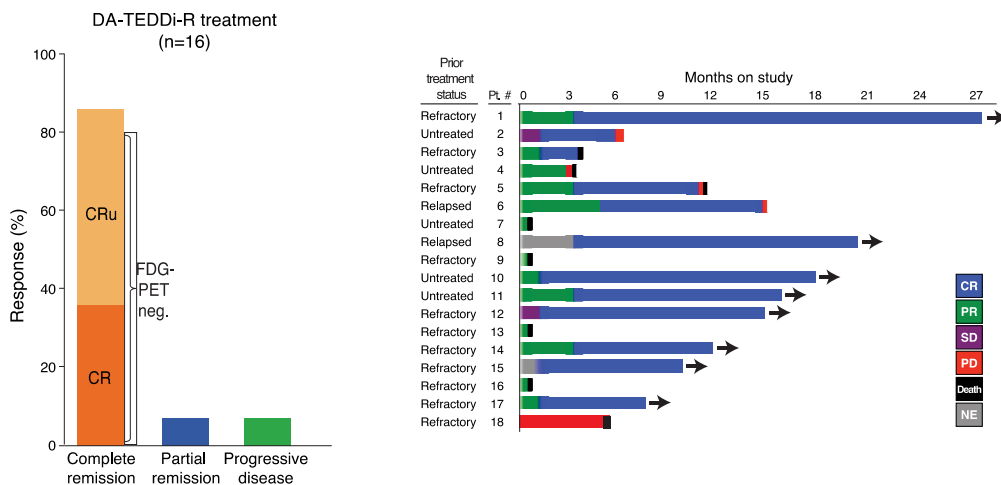
## Ibrutinib monotherapy in primary CNS lymphomas



Lionakis, Dunleavy et al. *Cancer Cell*. 2017 Jun 12;31(6):833-843



## Ibrutinib + chemotherapy impressive responses in PCNSL



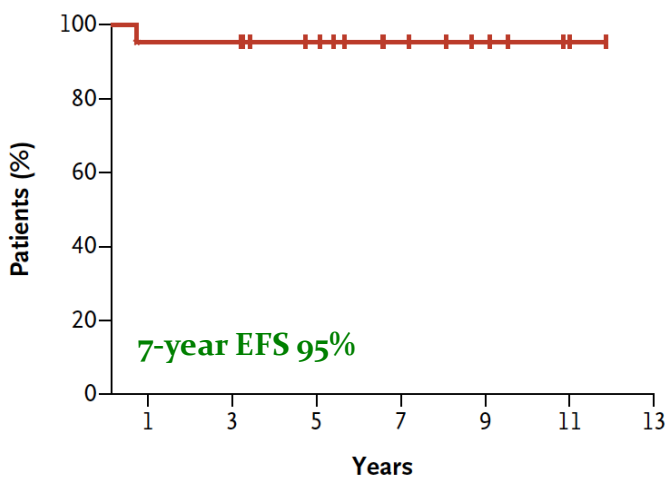
Lionakis, Dunleavy et al. *Cancer Cell*. 2017 Jun 12;31(6):833-843



## Burkitt lymphoma

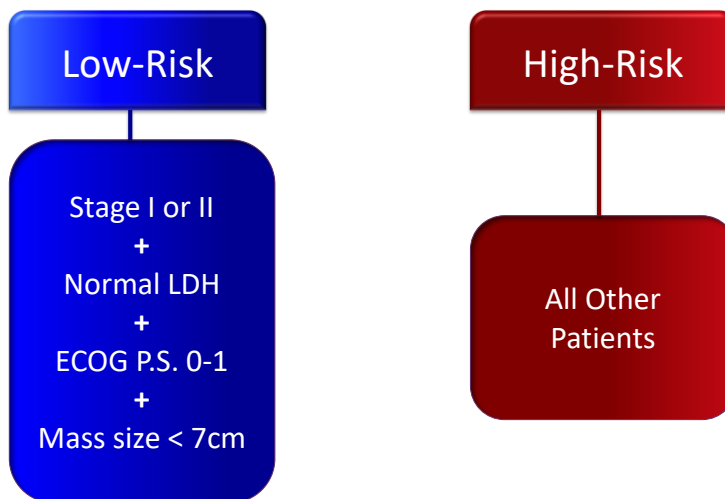


## NCI Study: DA-EPOCH-R in adults with BL

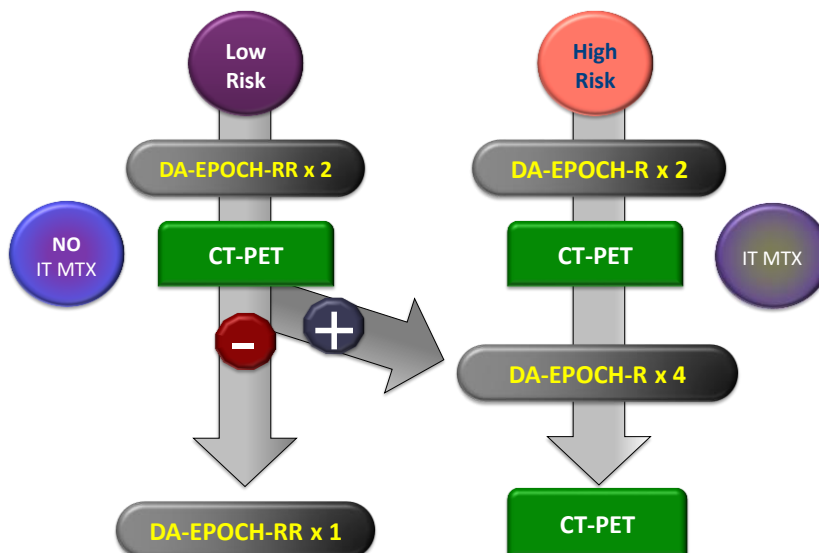


Dunleavy et al. *N Engl J Med.* 2013;369(20):1915-25

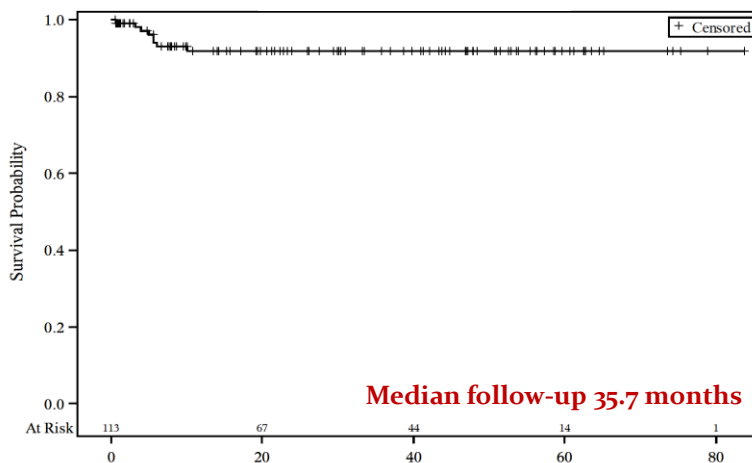
### NCI 9177: Pre-treatment categories



### NCI 9177: Treatment schema



### NCI 9177: Event-free survival

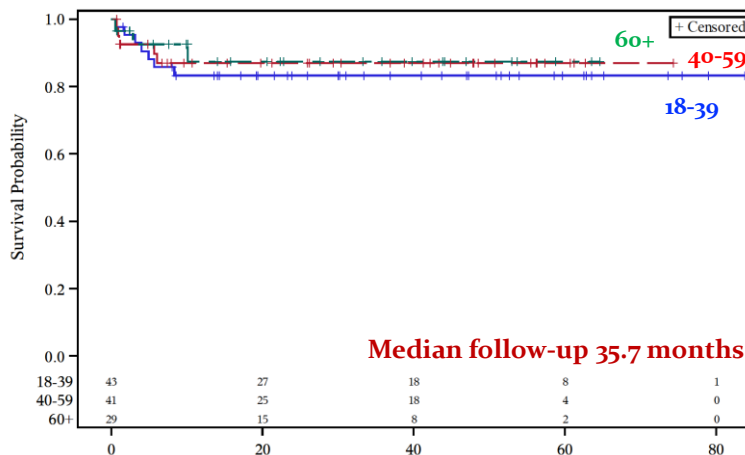


	N	EFS	95% CI
All patients	113	85.7%	(77.3-91.1)



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### NCI 9177: Event-free survival in age groups



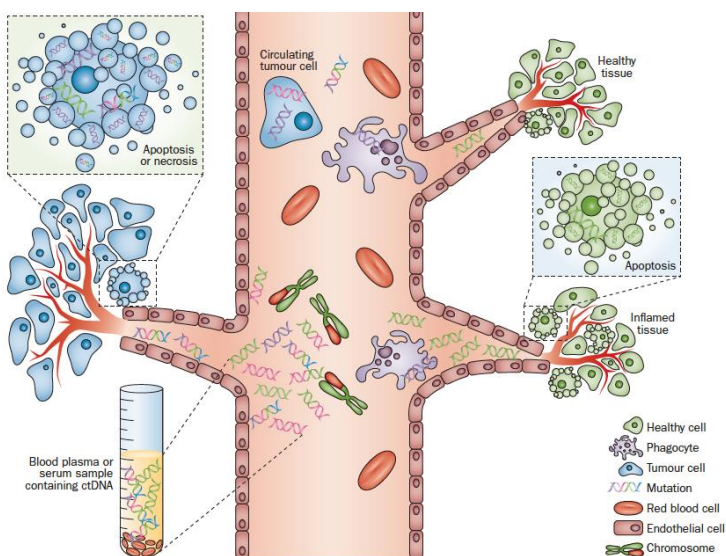
	N	EFS	95% CI
Age 18-39	43	83.3%	(68.1-91.7)
Age 40-59	41	87.1%	(71.6-94.4)
Age 60+	29	87.4%	(65.2-95.8)

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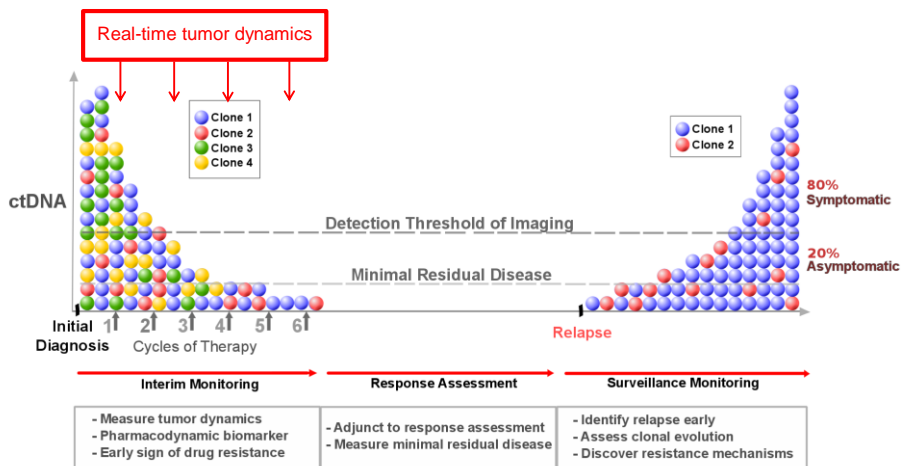


## How can we monitor tumor response?

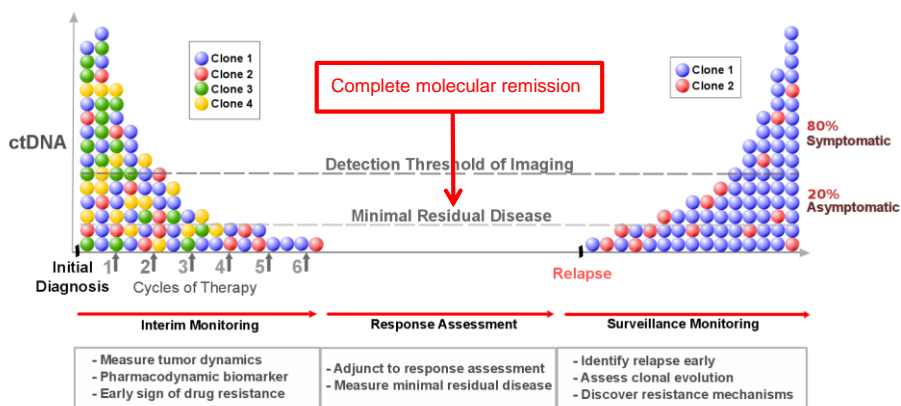
## Monitoring the blood for tumor-specific molecules



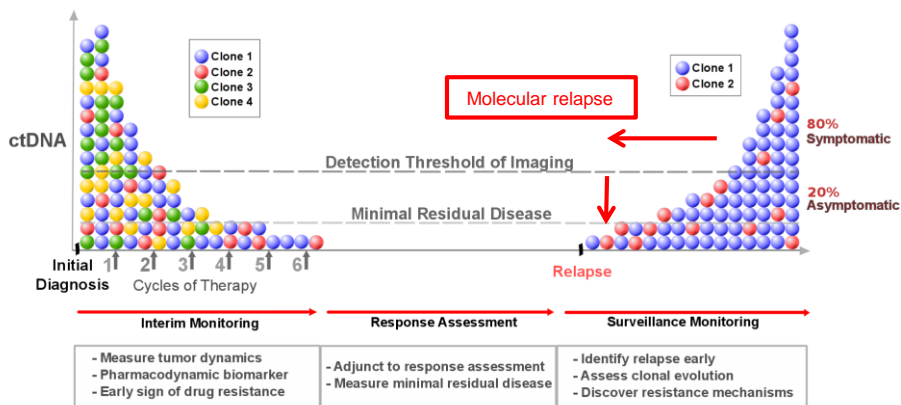
## Interim monitoring: early signs of resistance



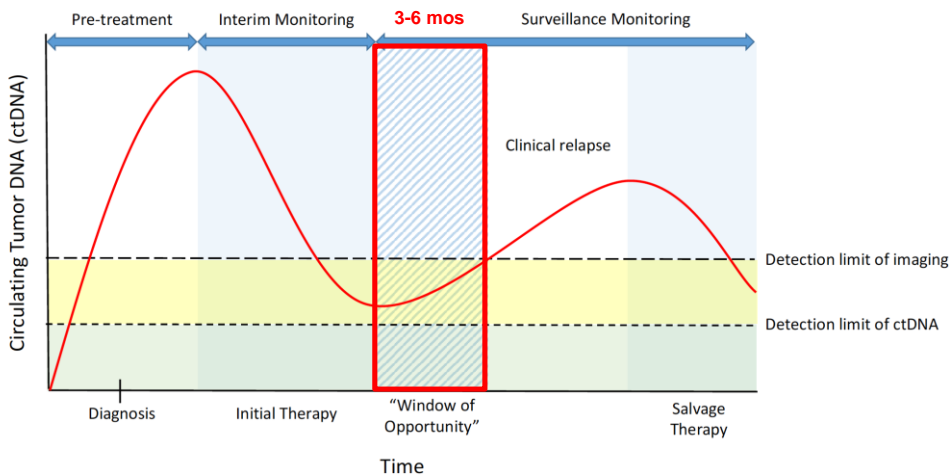
## Response: define molecular remissions



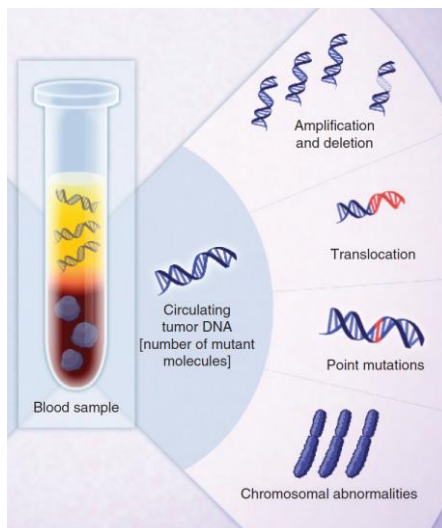
## Surveillance monitoring: detect relapse earlier



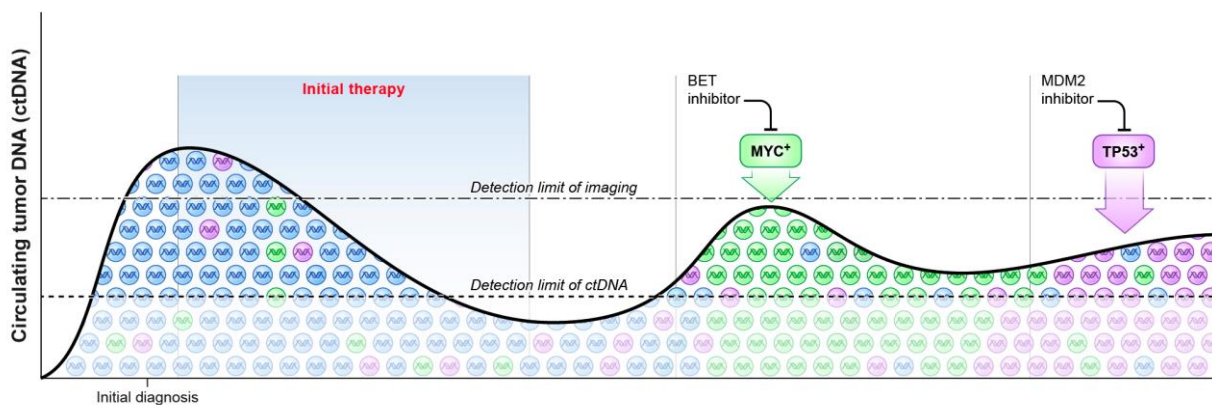
## Window of opportunity



## Cell-free DNA for as a “liquid biopsy”



## Precision monitoring of ctDNA in lymphomas



Selection pressure of therapy may shift dominant sub-clone at relapse



@RoschewskiMD



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### Q&A Session

#### Ask a question by phone:

- Press star (\*) then the number 1 on your keypad.

#### Ask a question by web:

- Click "Ask a question"
- Type your question
- Click "Submit"

Due to time constraints, we can only take one question per person. Once you have asked your question, the operator will transfer you back into the audience line.

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## The Leukemia & Lymphoma Society Offers:

- **LLS Information Specialists:** Master's level oncology professionals who can assist you through cancer treatment, financial and social challenges, and give accurate up-to-date disease, treatment, and support information.
  - **EMAIL:** [infocenter@LLS.org](mailto:infocenter@LLS.org)
  - **TOLL-FREE PHONE:** 1-800-955-4572
- **Free Education Booklets:**
  - [www.LLS.org/booklets](http://www.LLS.org/booklets)
- **Free Telephone/Web Programs:**
  - [www.LLS.org/programs](http://www.LLS.org/programs)
- **Live, Weekly Online Chats:**
  - [www.LLS.org/chat](http://www.LLS.org/chat)



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## The Leukemia & Lymphoma Society Offers:

- **Support Resources:** LLS Community, discussion boards, blogs, support groups, financial assistance, and more: [www.LLS.org/support](http://www.LLS.org/support)
- **LLS Podcast, *The Bloodline with LLS*:** Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: [www.thebloodline.org](http://www.thebloodline.org)
- **Education Video:** Free education videos about survivorship, treatment, disease updates, and other topics: [www.LLS.org/educationvideos](http://www.LLS.org/educationvideos)
- **Patti Robinson Kaufmann First Connection Program:** Peer-to-peer program that matches newly diagnosed patients and their families: [www.LLS.org/firstconnection](http://www.LLS.org/firstconnection)
- **Free Nutrition Consults:** Telephone and email consultations with a Registered Dietitian: [www.LLS.org/nutrition](http://www.LLS.org/nutrition)
- **What to ask:** Questions to ask your treatment team: [www.LLS.org/whattoask](http://www.LLS.org/whattoask)



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**THANK  
YOU FOR  
PARTICIPATING!**

**We have one goal:  
A world without  
blood cancers**