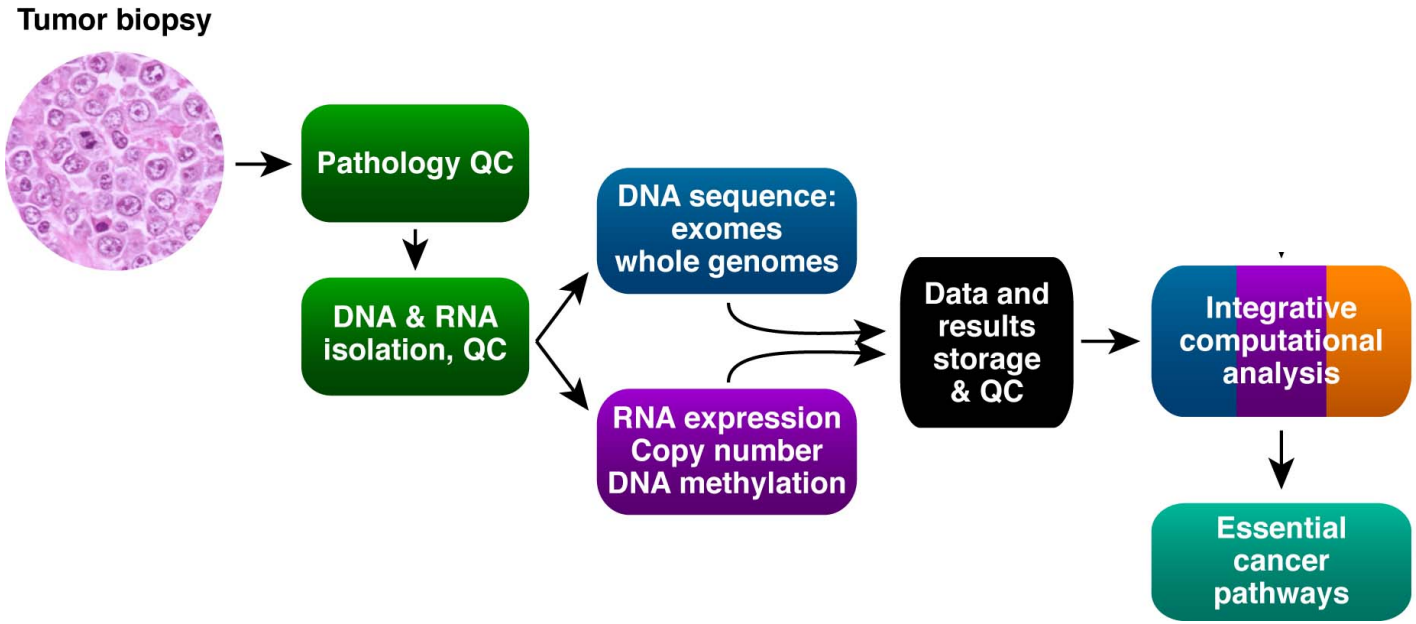
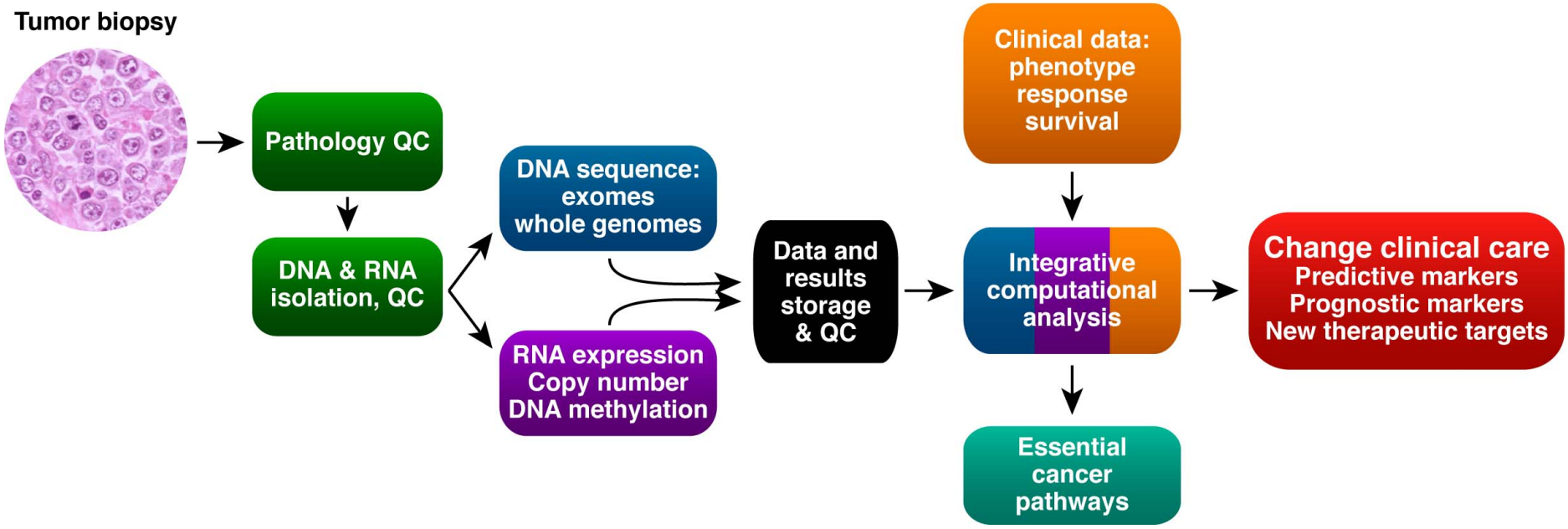
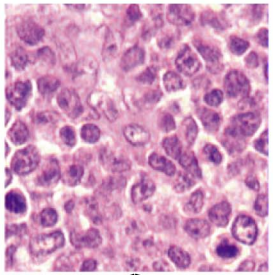
TCGA Workflow for Integrative Molecular Analysis of Cancer



Integration of a TCGA-like Pipeline Into Cancer Clinical Trials Has the Potential to Change Clinical Care



Dissecting Cancer into Molecularly and Clinically Distinct Subgroups by Gene Expression Profiling



Diffuse large B cell lymphoma

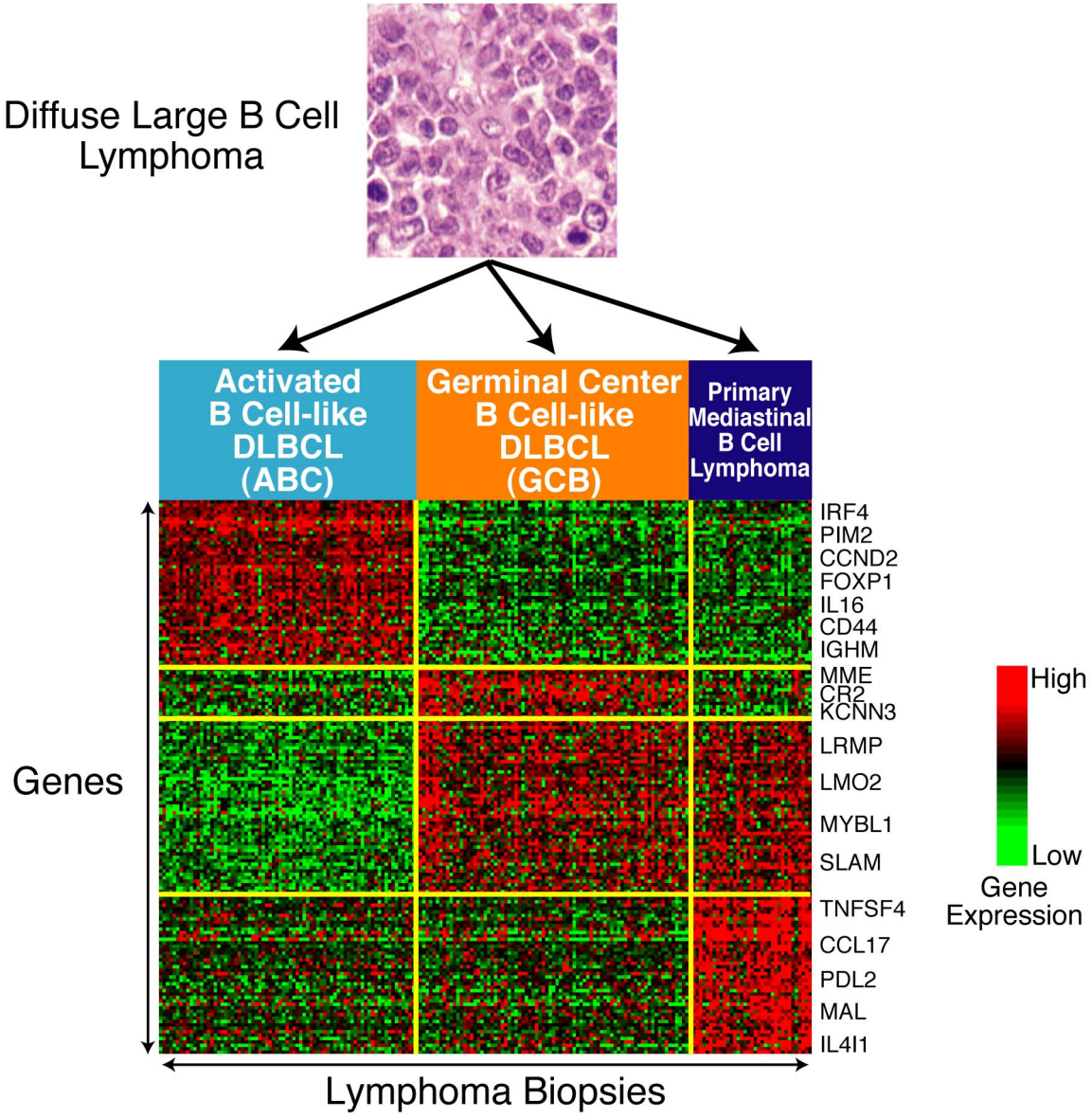
~40% of Non-Hodgkin lymphomas

~23,000 new diagnoses/yr

~50% cure rate

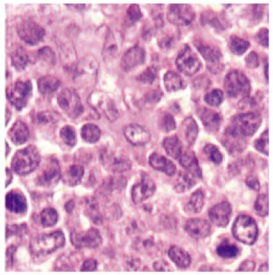
~10,000 deaths/yr

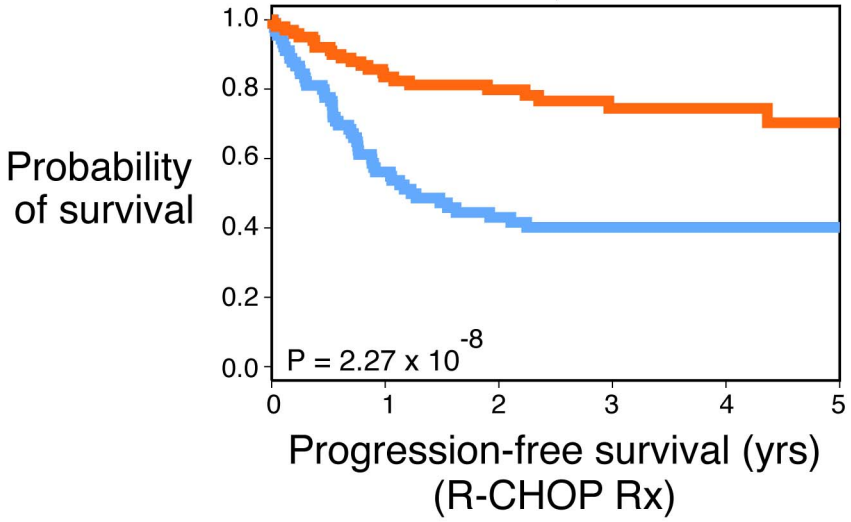
Dissecting Cancer into Molecularly and Clinically Distinct Subgroups by Gene Expression Profiling



Dissecting Cancer into Molecularly and Clinically Distinct Subgroups by Gene Expression Profiling

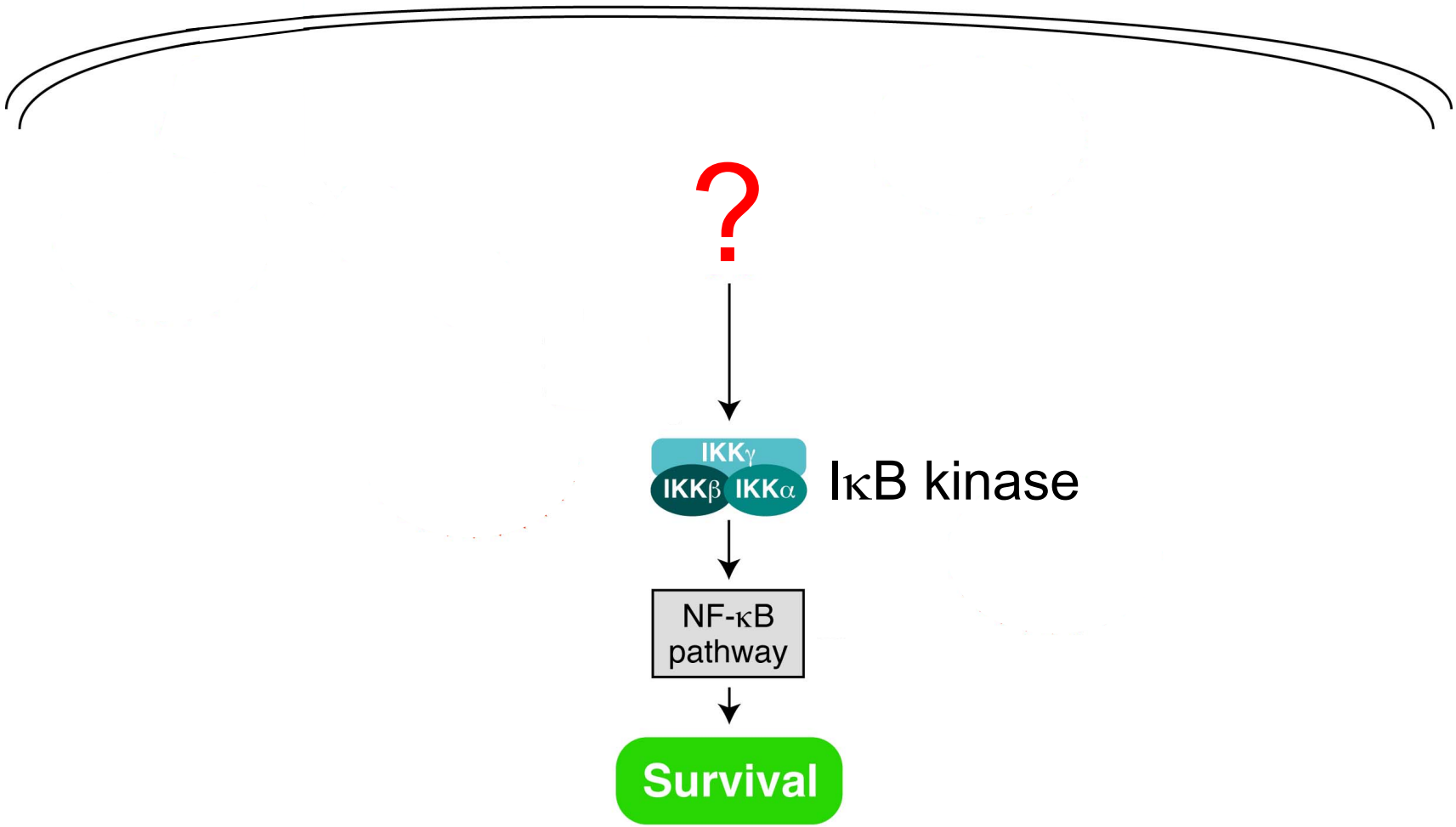
Diffuse Large B Cell Lymphoma



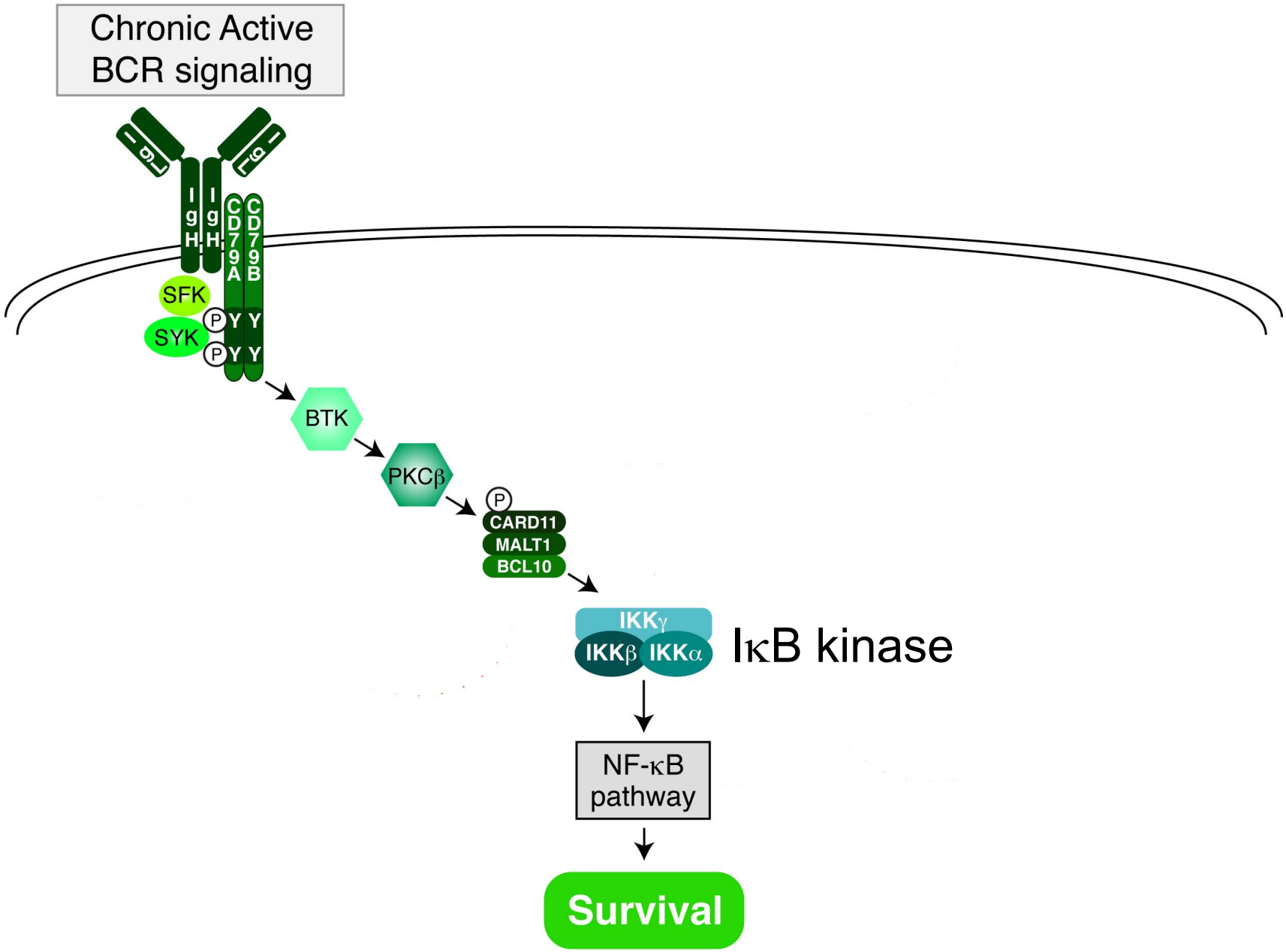


	3-year progression-free survival
GCB DLBCL	75%
ABC DLBCL	40%

Oncogenic Activation of NF-κB in ABC DLBCL



Chronic Active B Cell Receptor Signaling in ABC DLBCL



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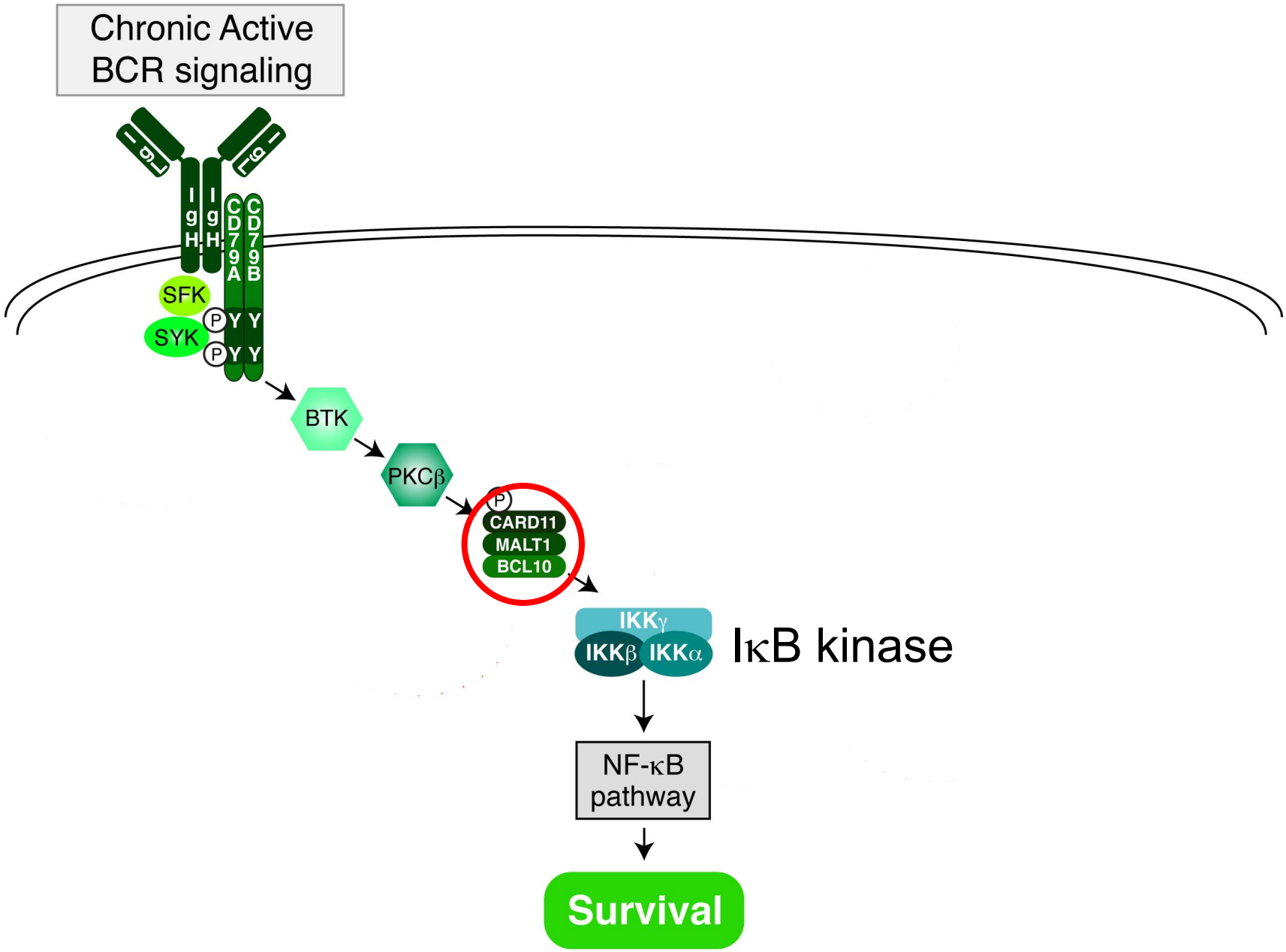

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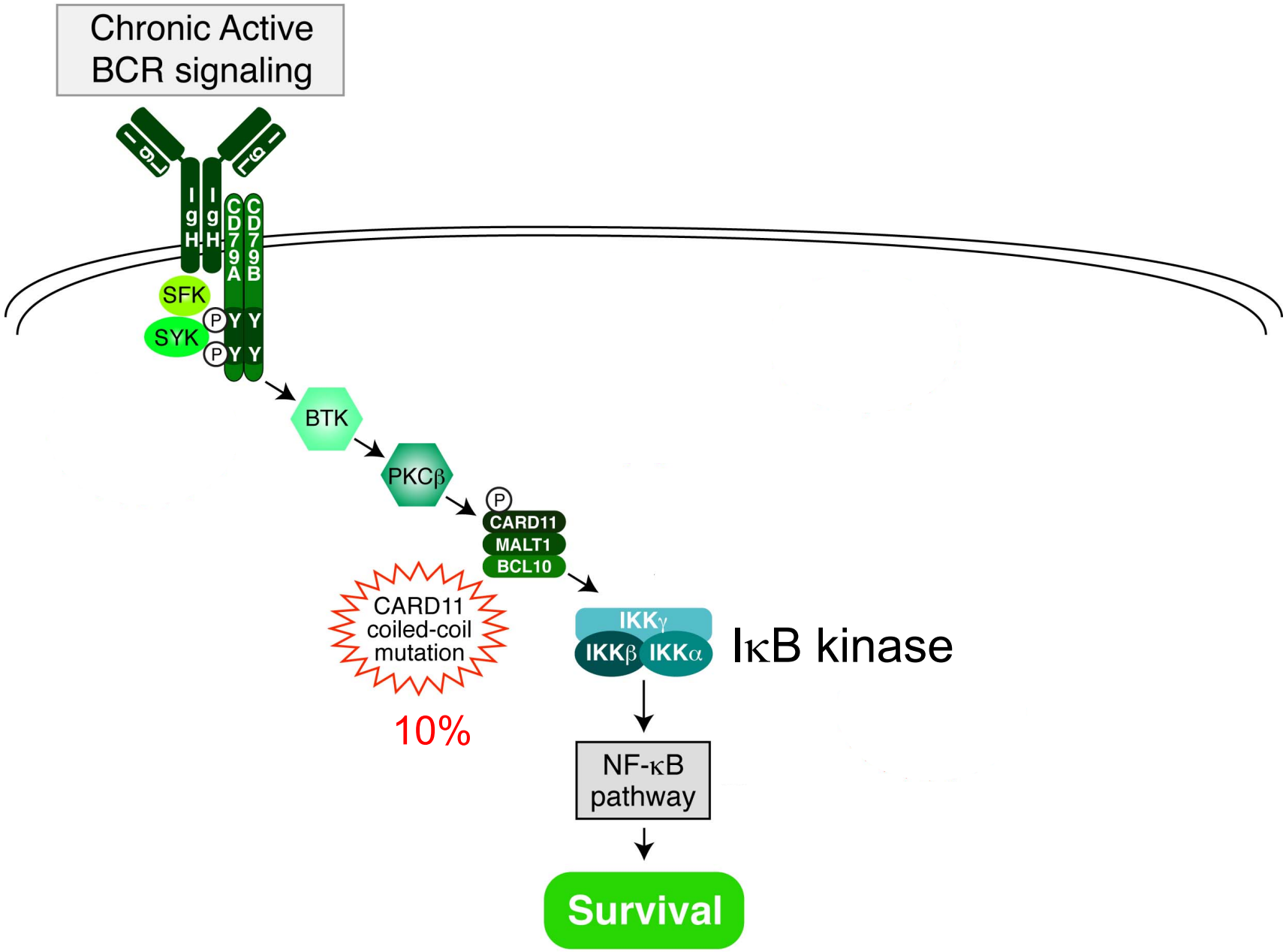

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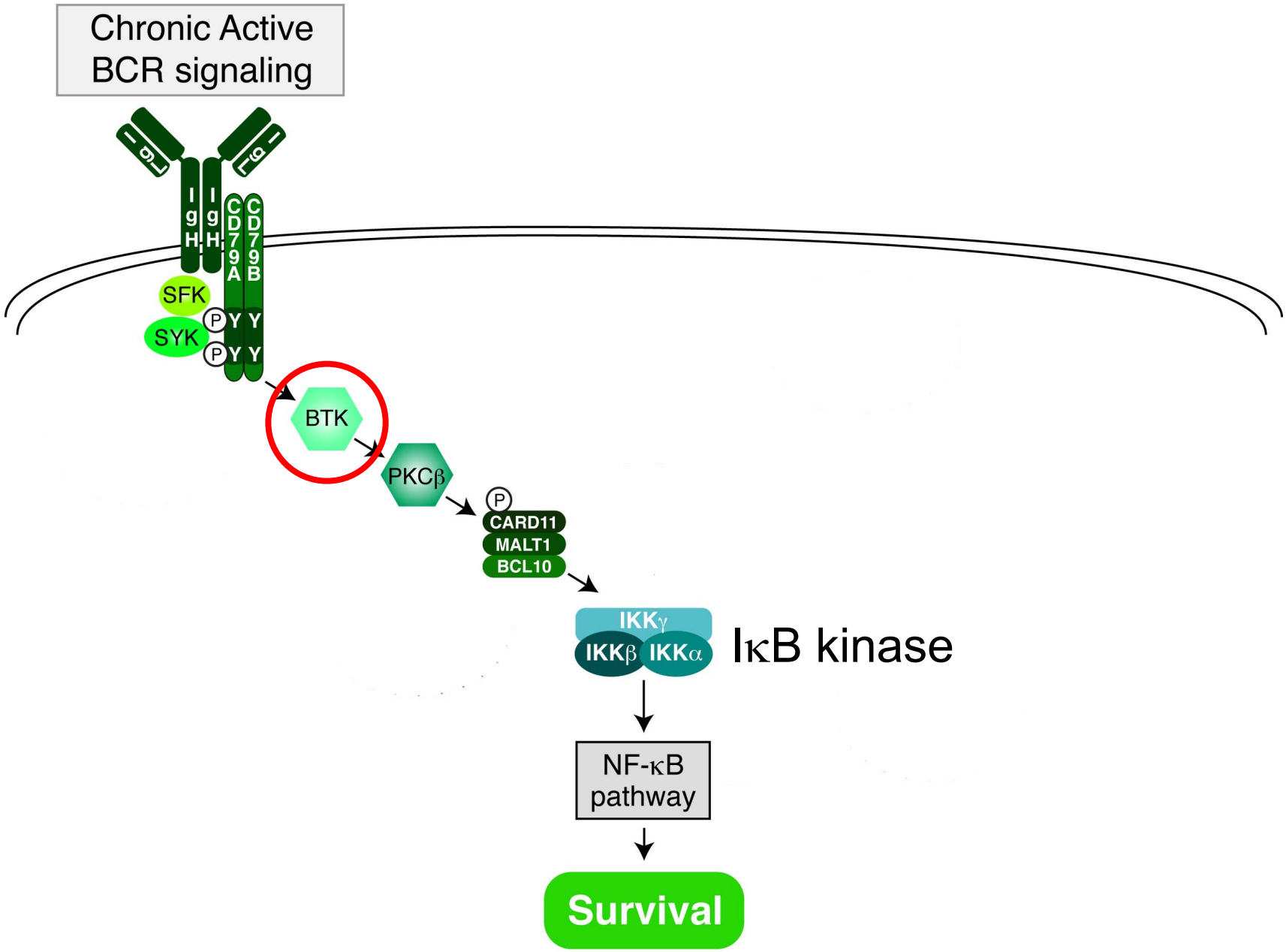

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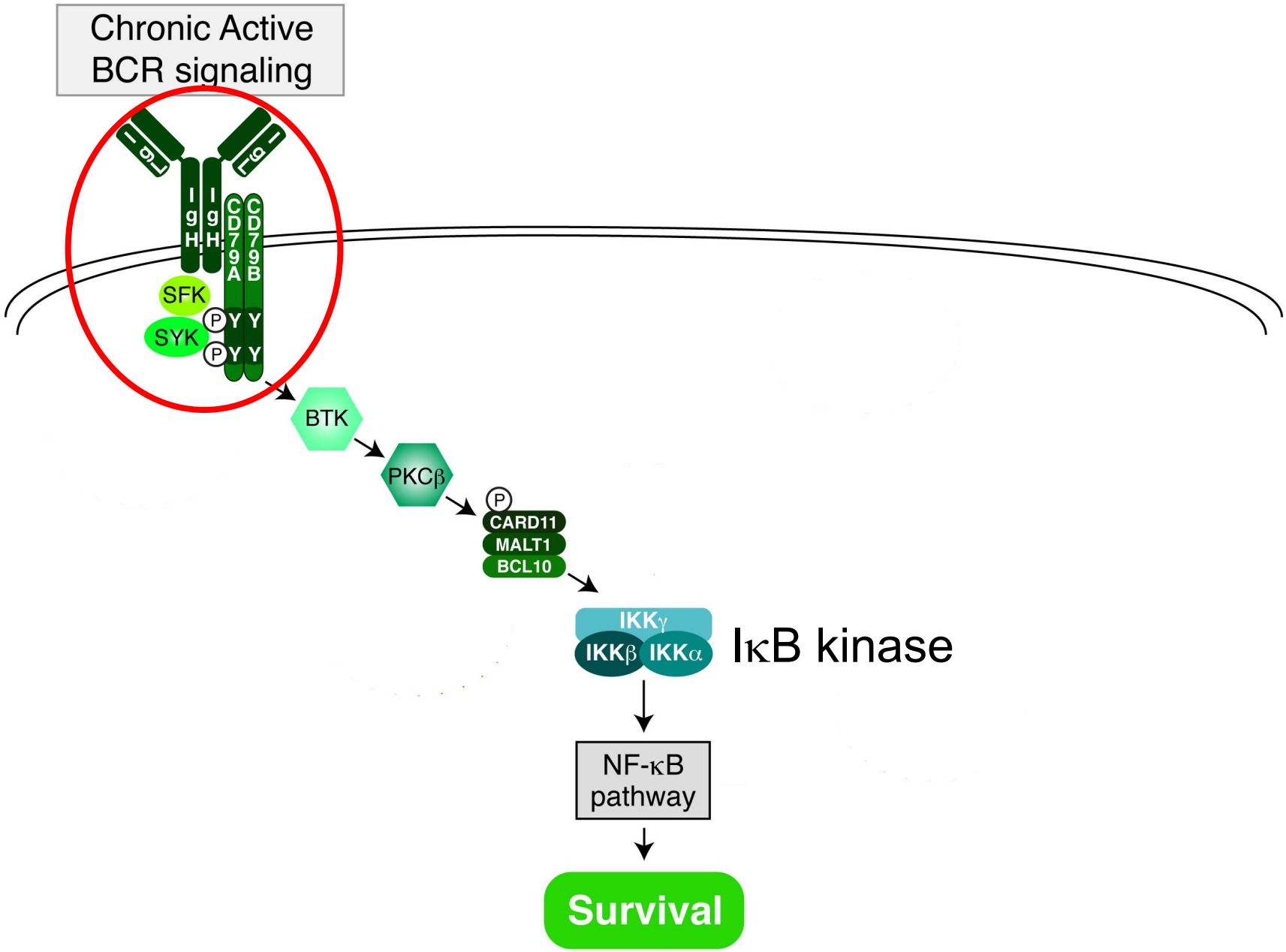
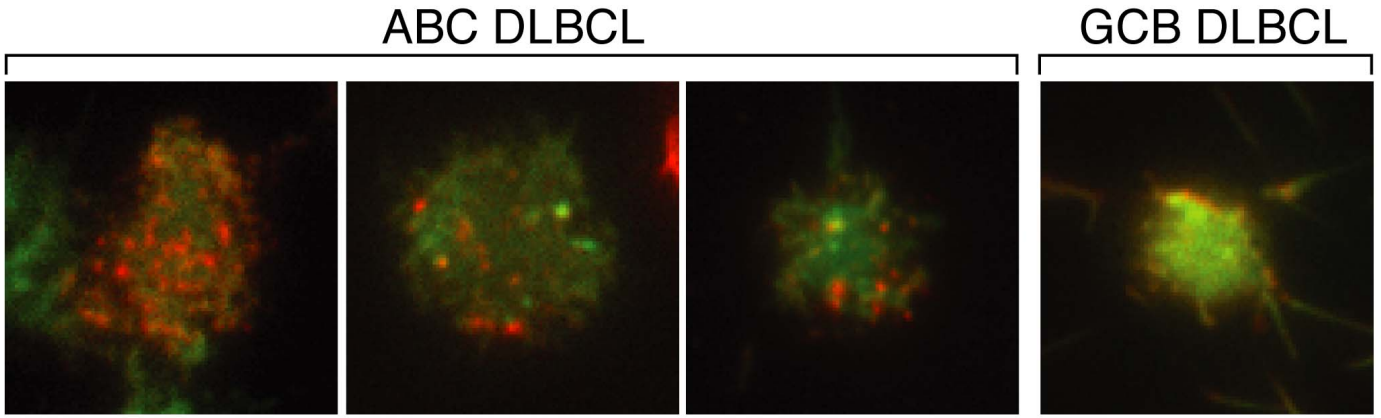
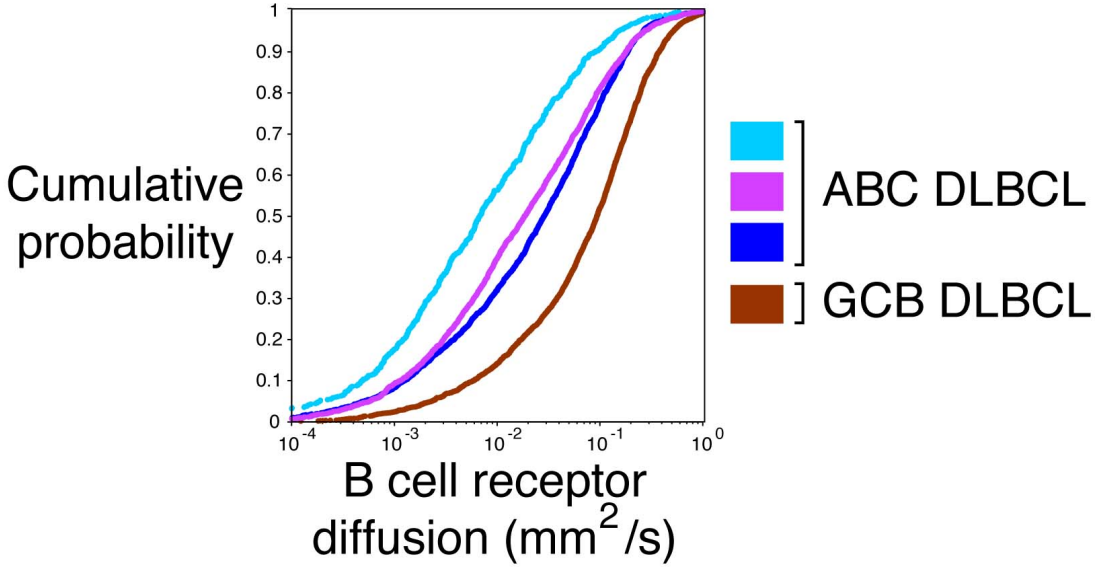
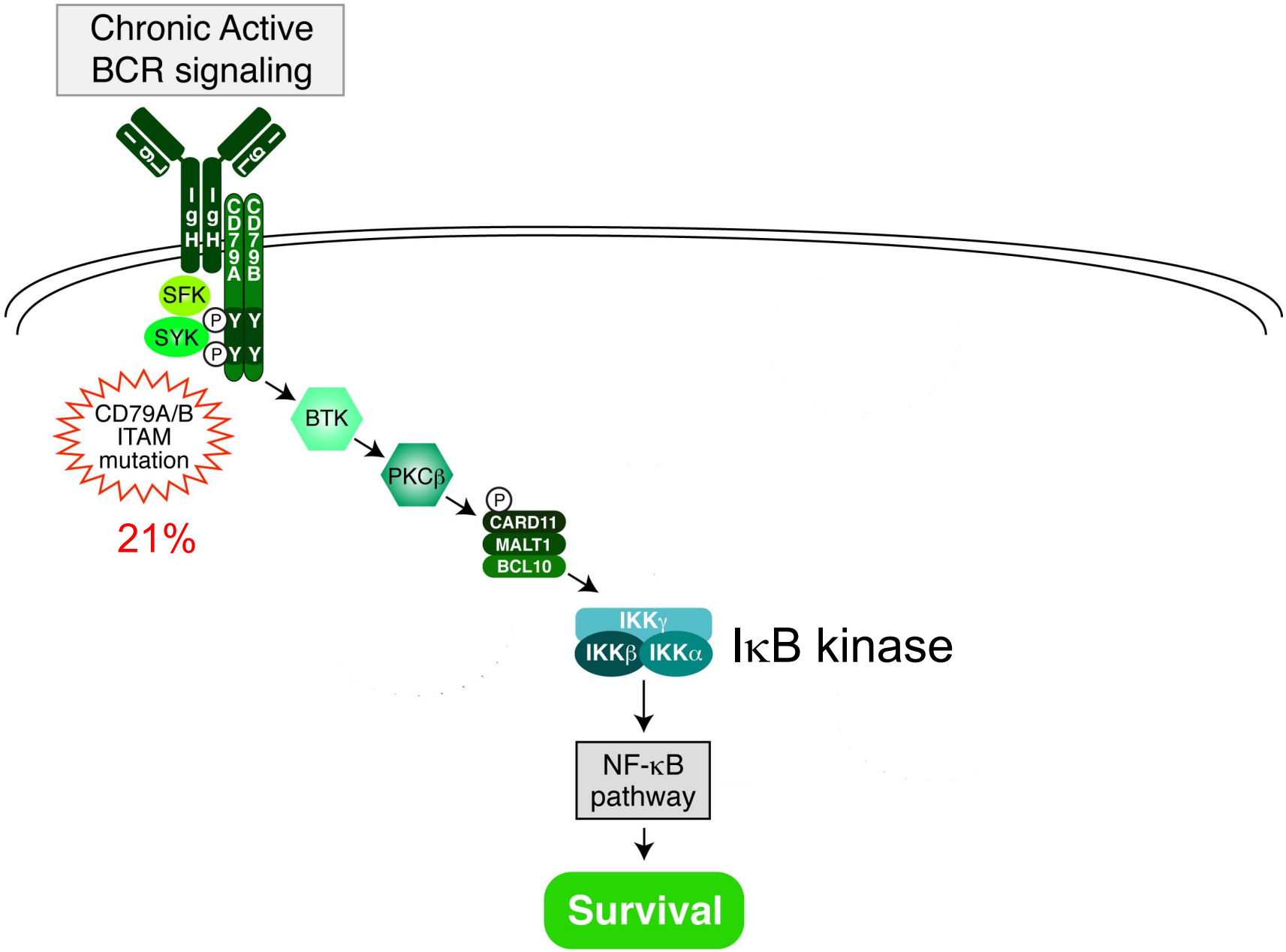


The B Cell Receptors in ABC DLBCLs Are Clustered and Immobile

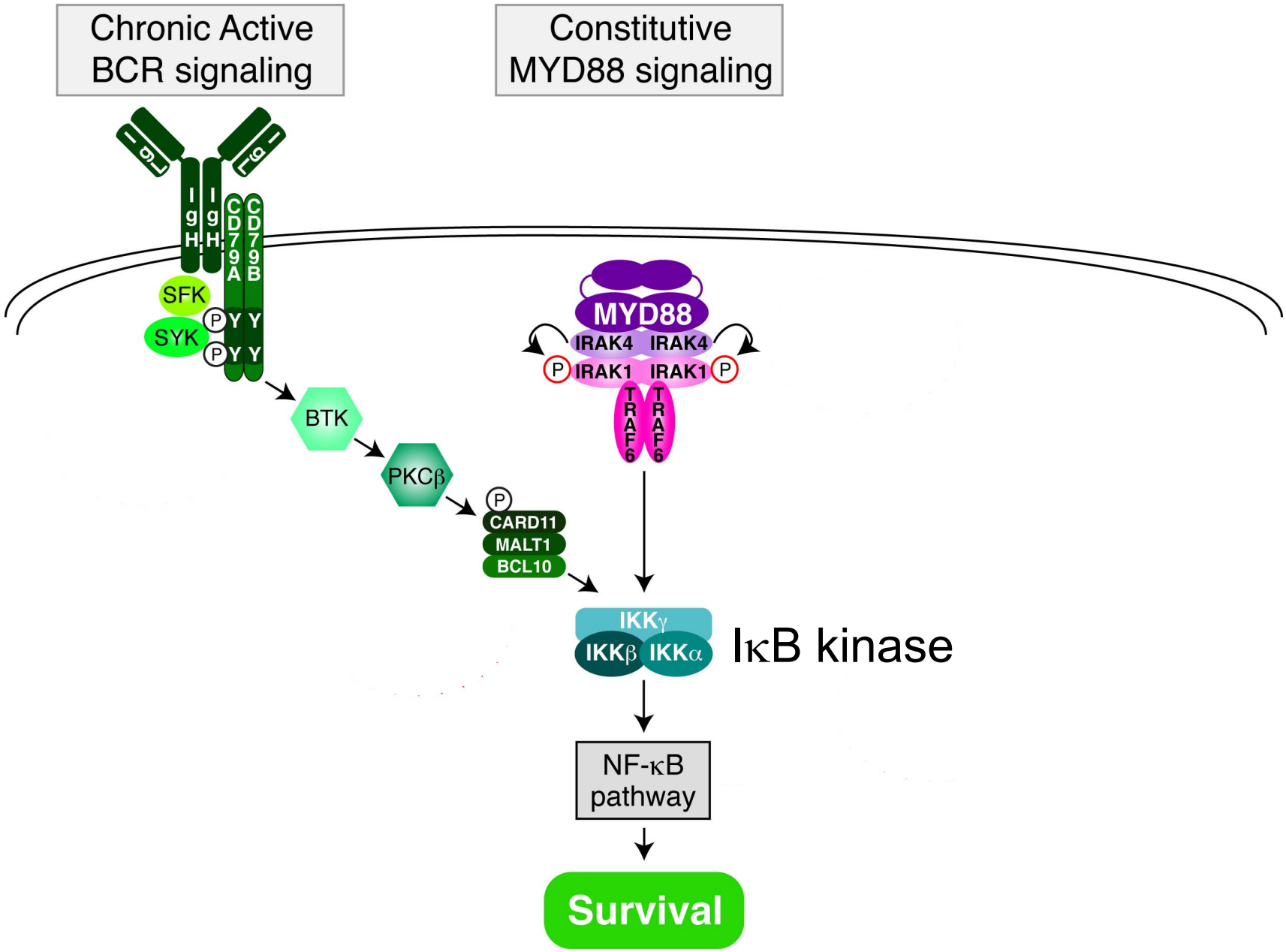




Chronic Active B Cell Receptor Signaling in ABC DLBCL



Constitutive MYD88 Signaling in ABC DLBCL



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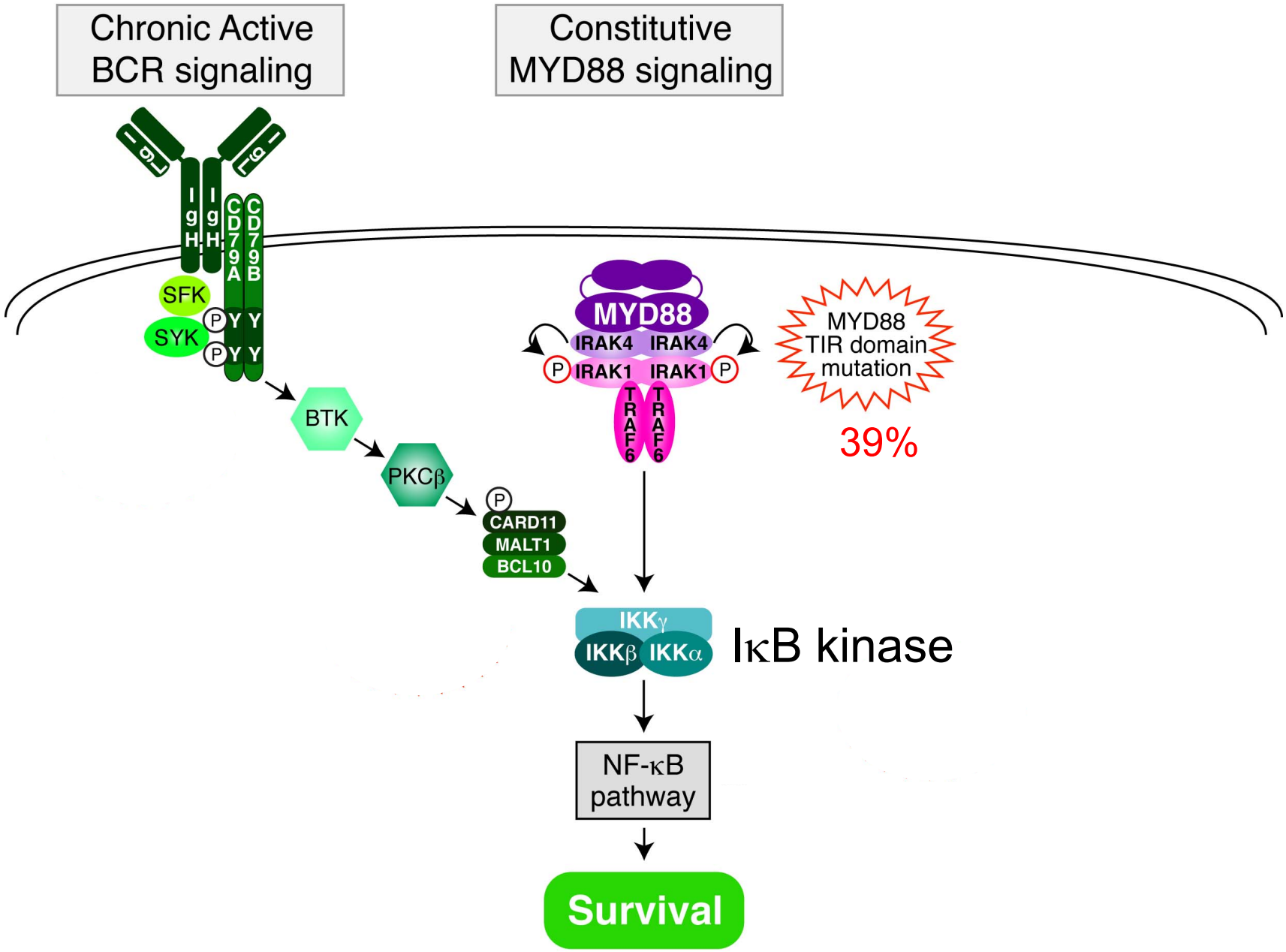
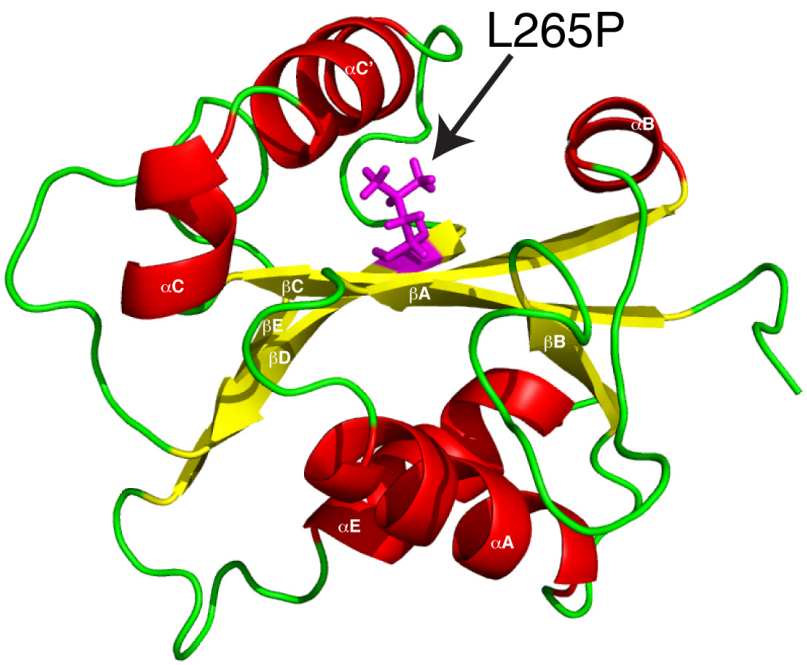
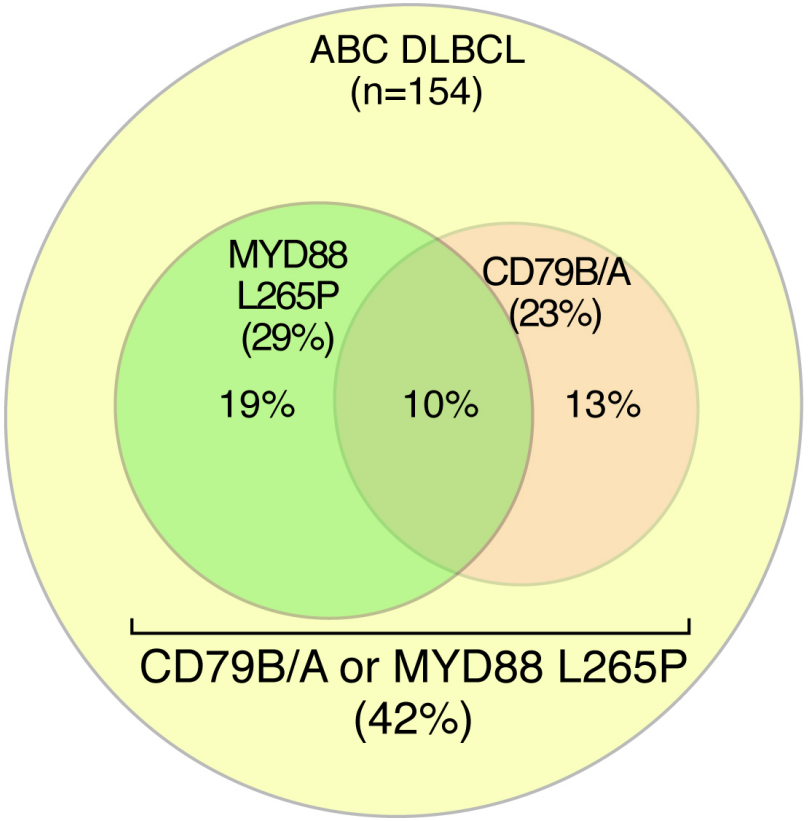


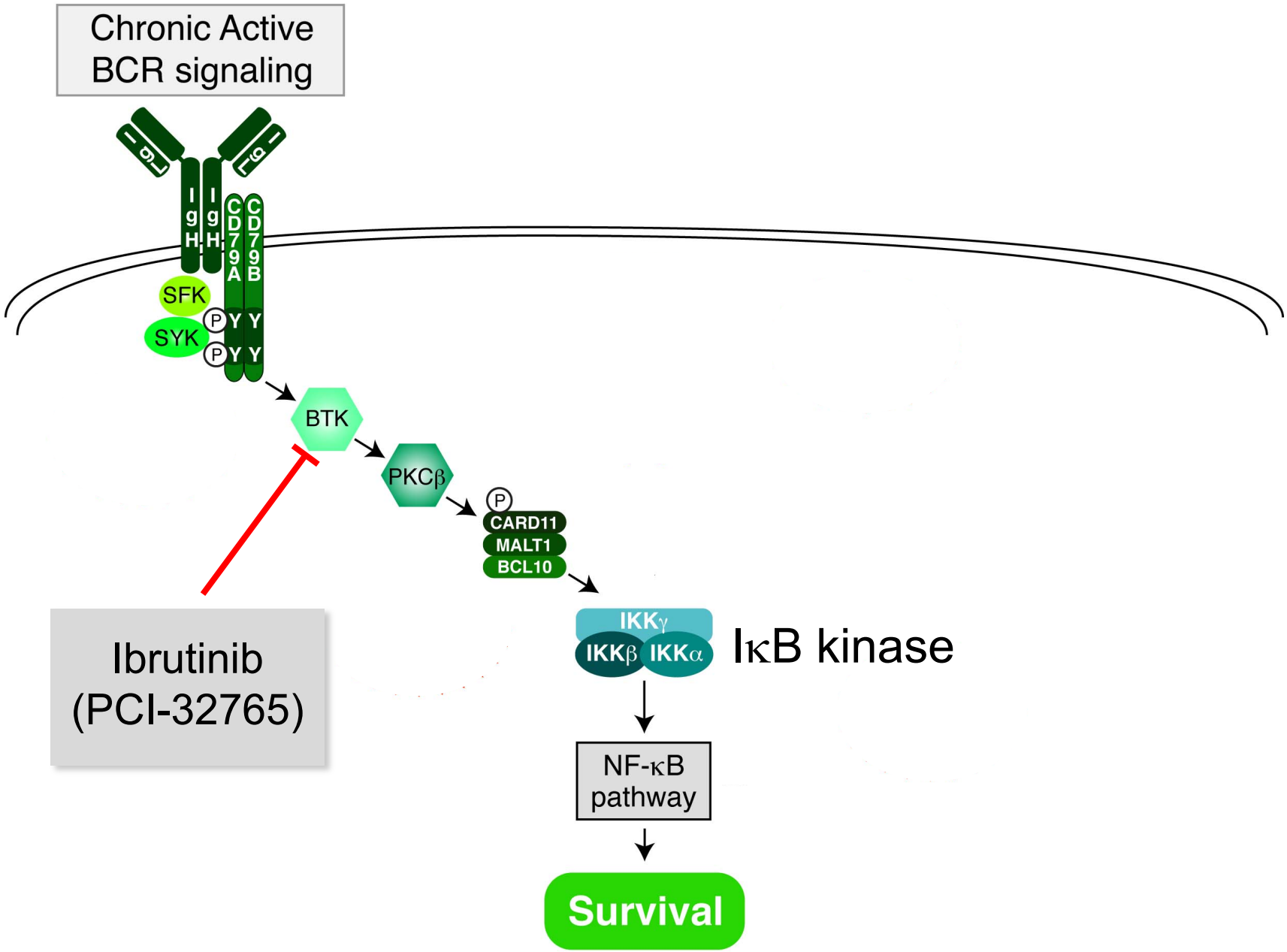
Significant Overlap of CD79B/A and MYD88 L265P Mutations in ABC DLBCL



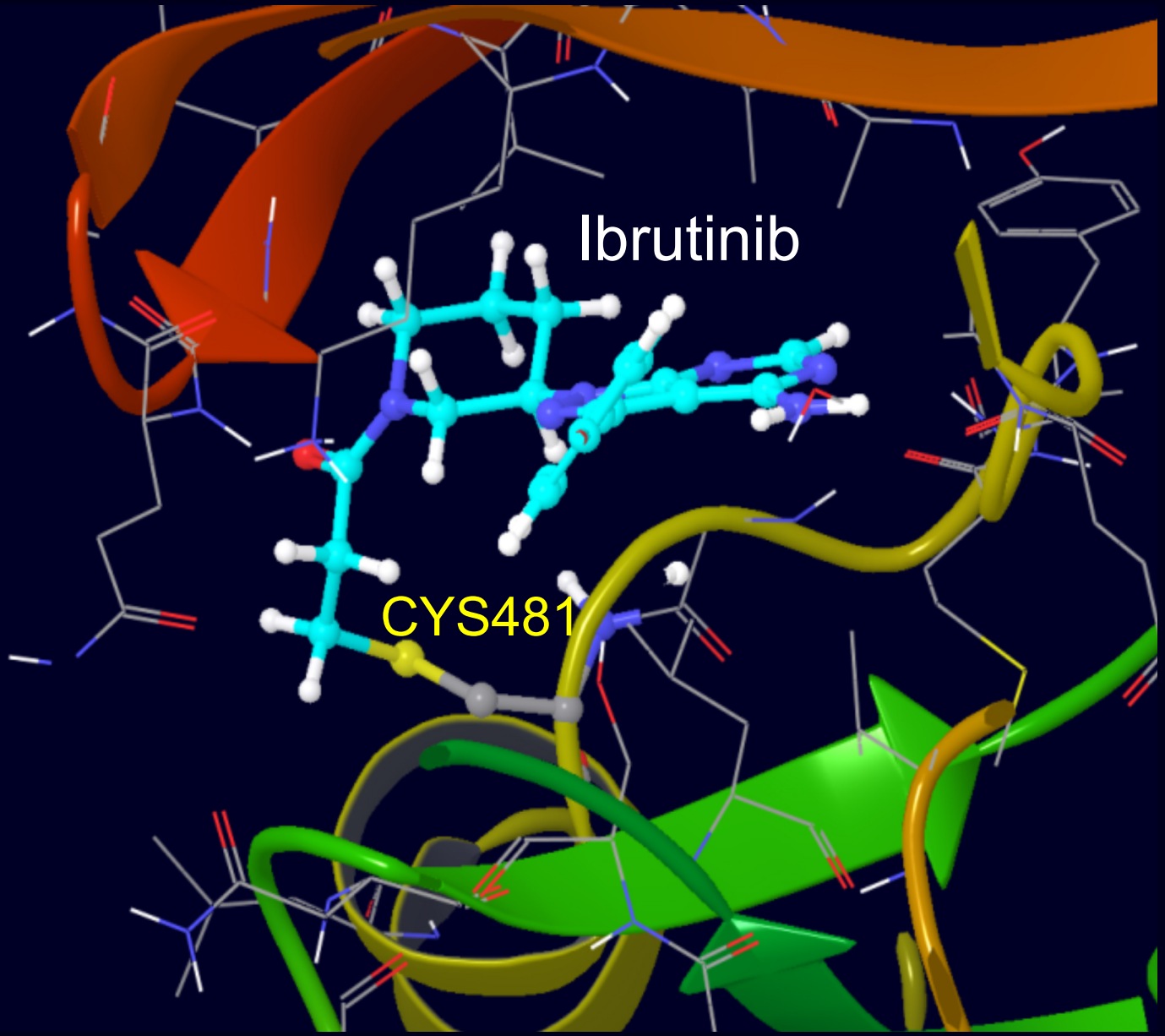
MYD88 TIR domain



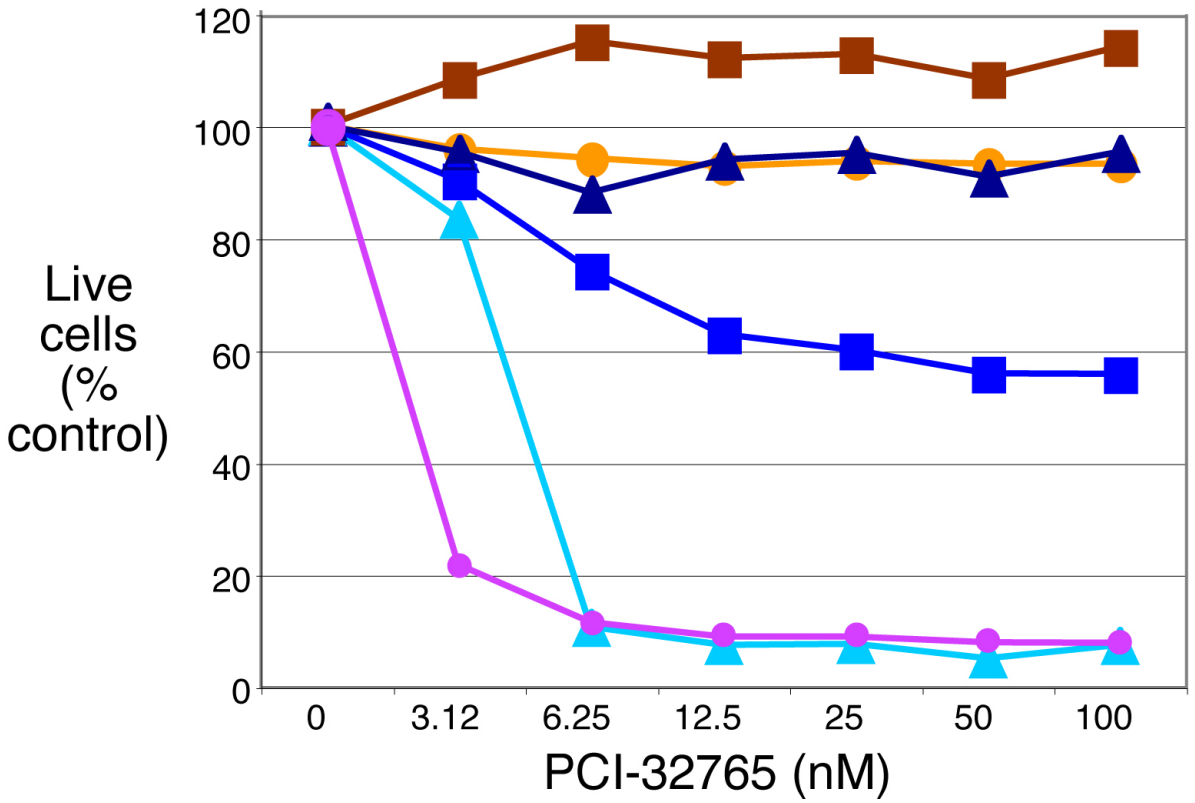
Blockade of BCR Signaling in ABC DLBCL with Ibrutinib



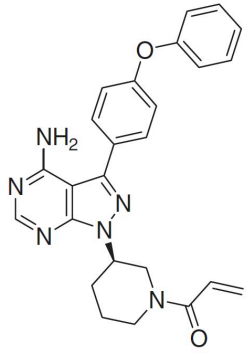
Ibrutinib Covalently Binds to the BTK Active Site



The BTK Inhibitor Ibrutinib is Toxic for ABC DLBCLs With Chronic Active B Cell Receptor Signaling



		CARD11 status
ABC DLBCL	OCI-Ly10	Mutant
	HBL1	WT
	TMD8	WT
	OCI-Ly3	WT
GCB DLBCL	BJAB	WT
	OCI-Ly19	WT



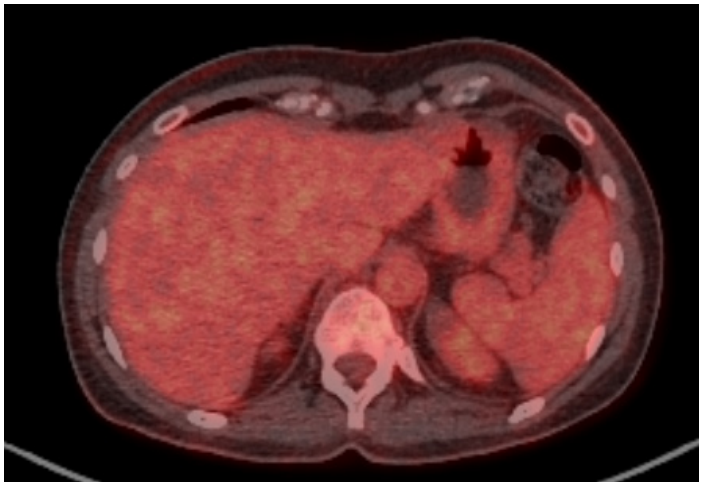
Clinical Trials of Ibrutinib in Relapsed/refractory DLBCL

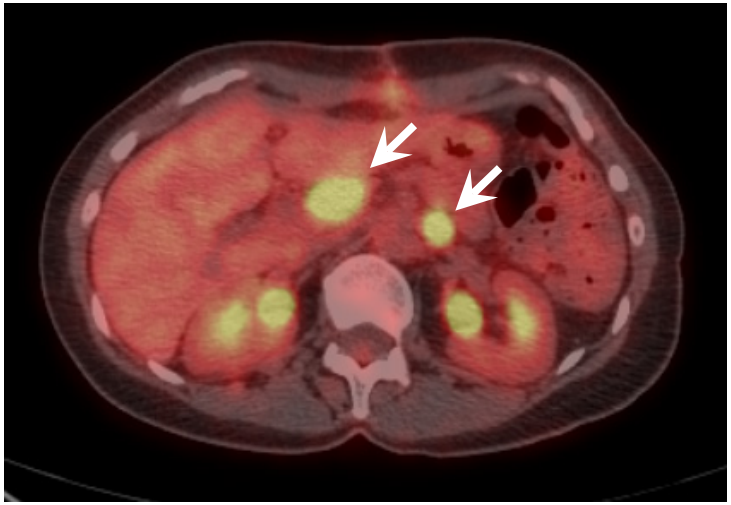
- Pilot trial (NCI)
  - Relapsed/refractory DLBCL (ABC subtype)
  - Subtype determined by immunohistochemistry and confirmed by gene expression profiling
  - Ibrutinib 560 mg p.o. daily
  - n=10 (completed)

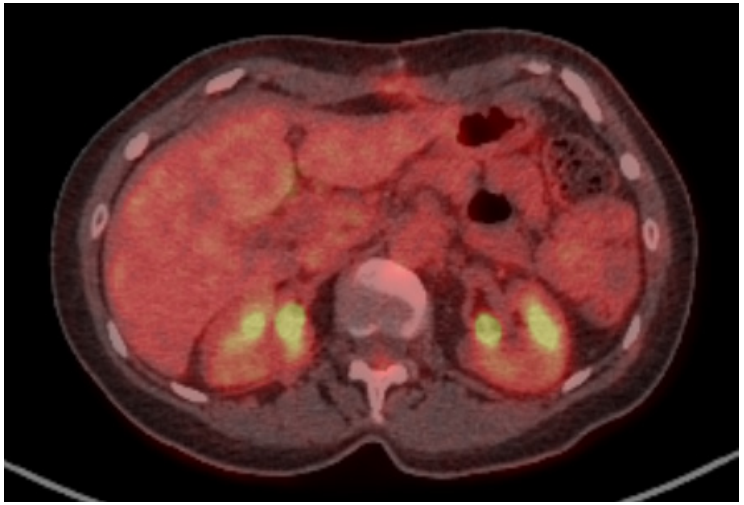
Patient #2 on Pilot Trial of Ibrutinib in Relapsed/refractory ABC DLBCL

- 52 year old female
  ABC DLBCL
- CD79B Y196C mutation
  MYD88 wild type
- Relapse following 2 prior chemotherapies
  DA-EPOCH-R: Complete response and relapse
  DA-EPOCH-R + Campath: Complete response and relapse
- Single agent treatment with ibrutinib
- Complete response at week 8 by CT and PET scan
- Sustained complete response at > 2 years on ibrutinib

Complete Remission of ABC DLBCL in Patient #2 on Pilot Trial of Ibrutinib







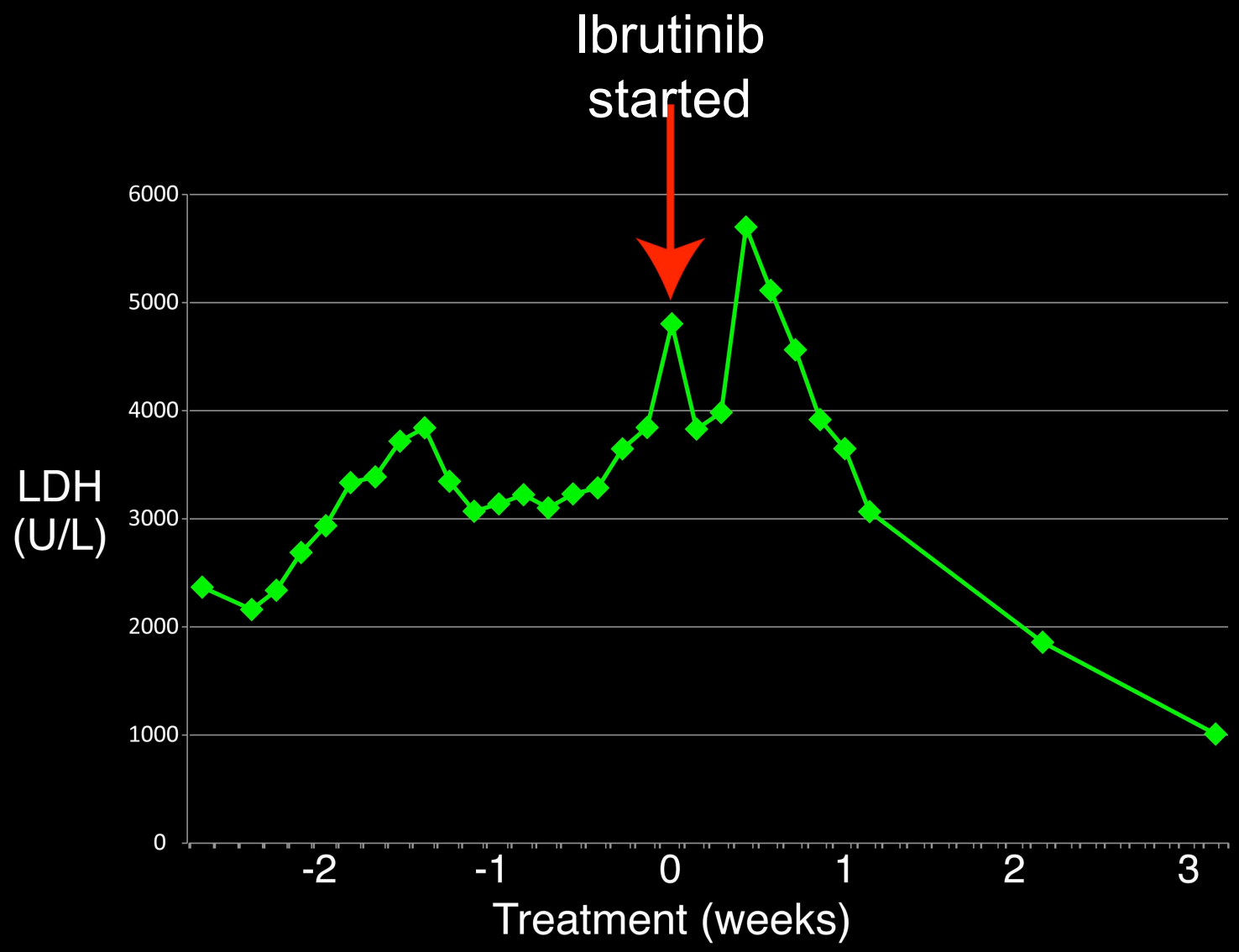
Before Rx

On Rx: week 8

Patient #9 on Pilot Trial of Ibrutinib in Relapsed/refractory ABC DLBCL

- 59 year old female
  ABC DLBCL
- CD79B wild type
  MYD88 wild type
- Primary refractory disease
  R-CHOP x 6: No response
  R-ICE x 2: No response
  Oxaliplatin + gemcitiabine x 3: No response
- Single agent treatment with ibrutinib
- Near complete response at week 3 by CT and PET scan

Rapid Normalization of LDH Following Ibrutinib Treatment



Partial Remission of ABC DLBCL in Patient #3 on Pilot Trial of Ibrutinib

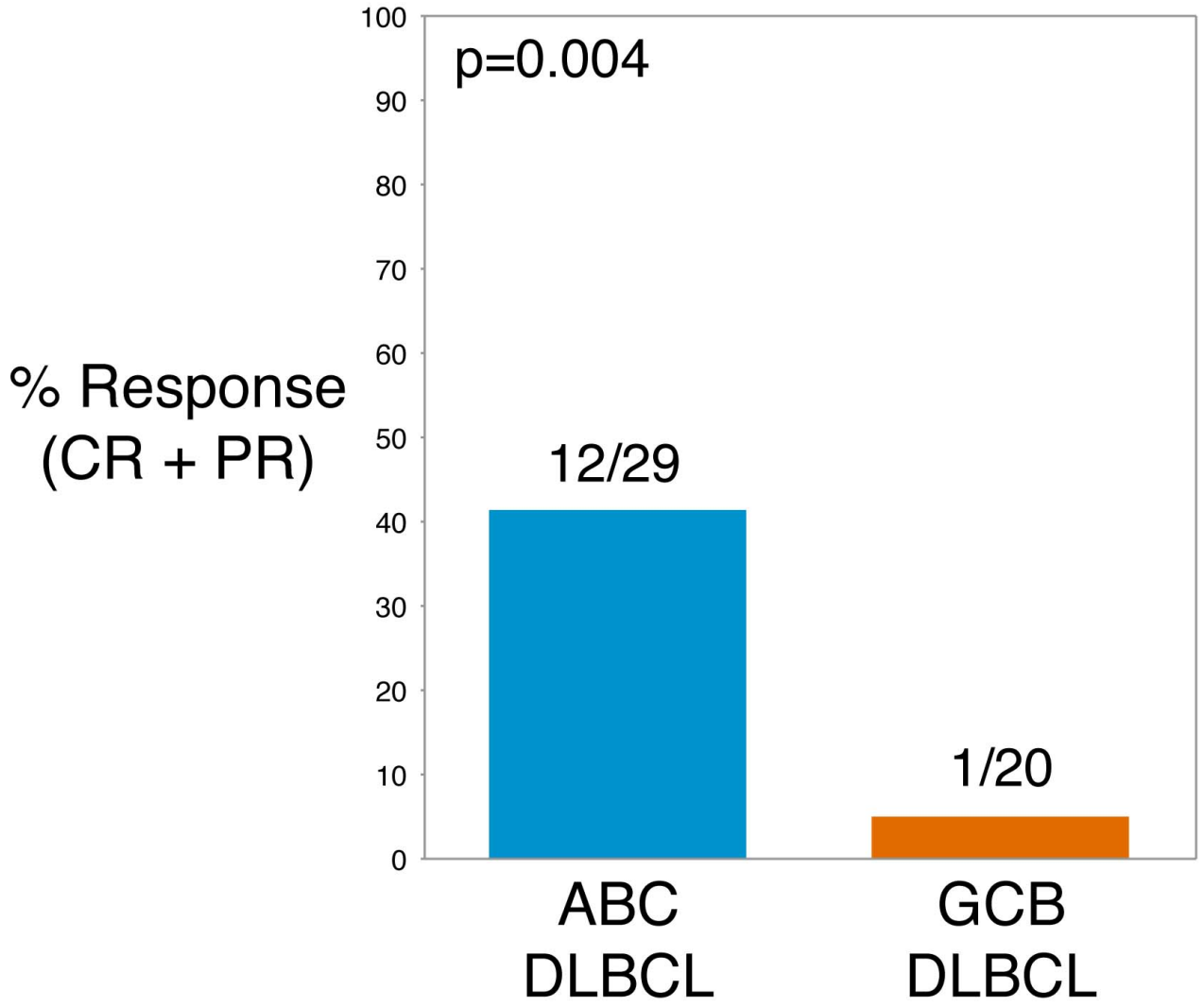
Before Rx

On Rx: week 3

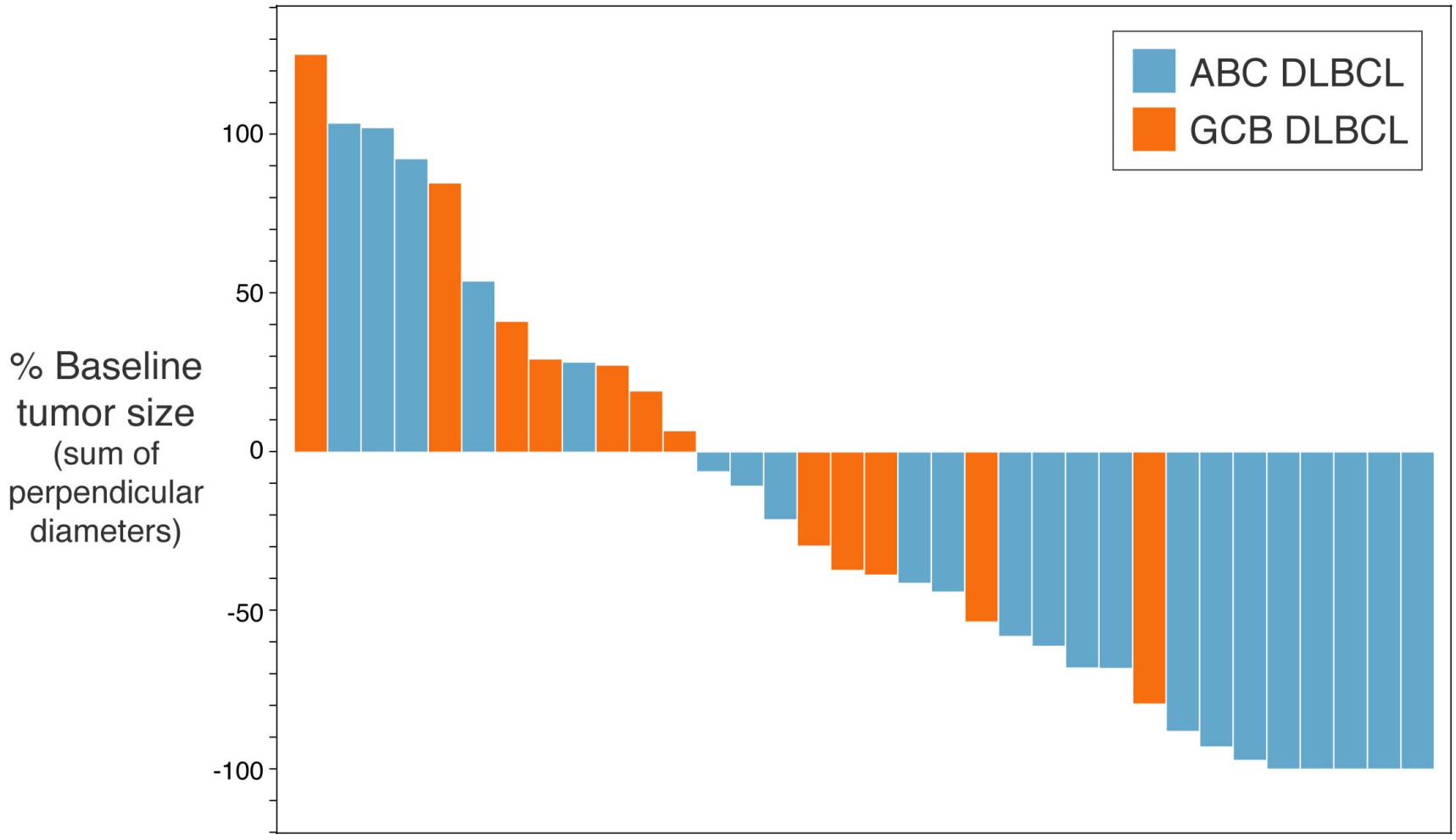
Clinical Trials of Ibrutinib in Relapsed/refractory DLBCL

- Multicenter phase 2 trial
  - Relapsed/refractory DLBCL (ABC and GCB subtypes)
  - Subtype determined by immunohistochemistry and confirmed by gene expression profiling
  - Ibrutinib 560 mg p.o. daily
  - n=70 (accrual complete)

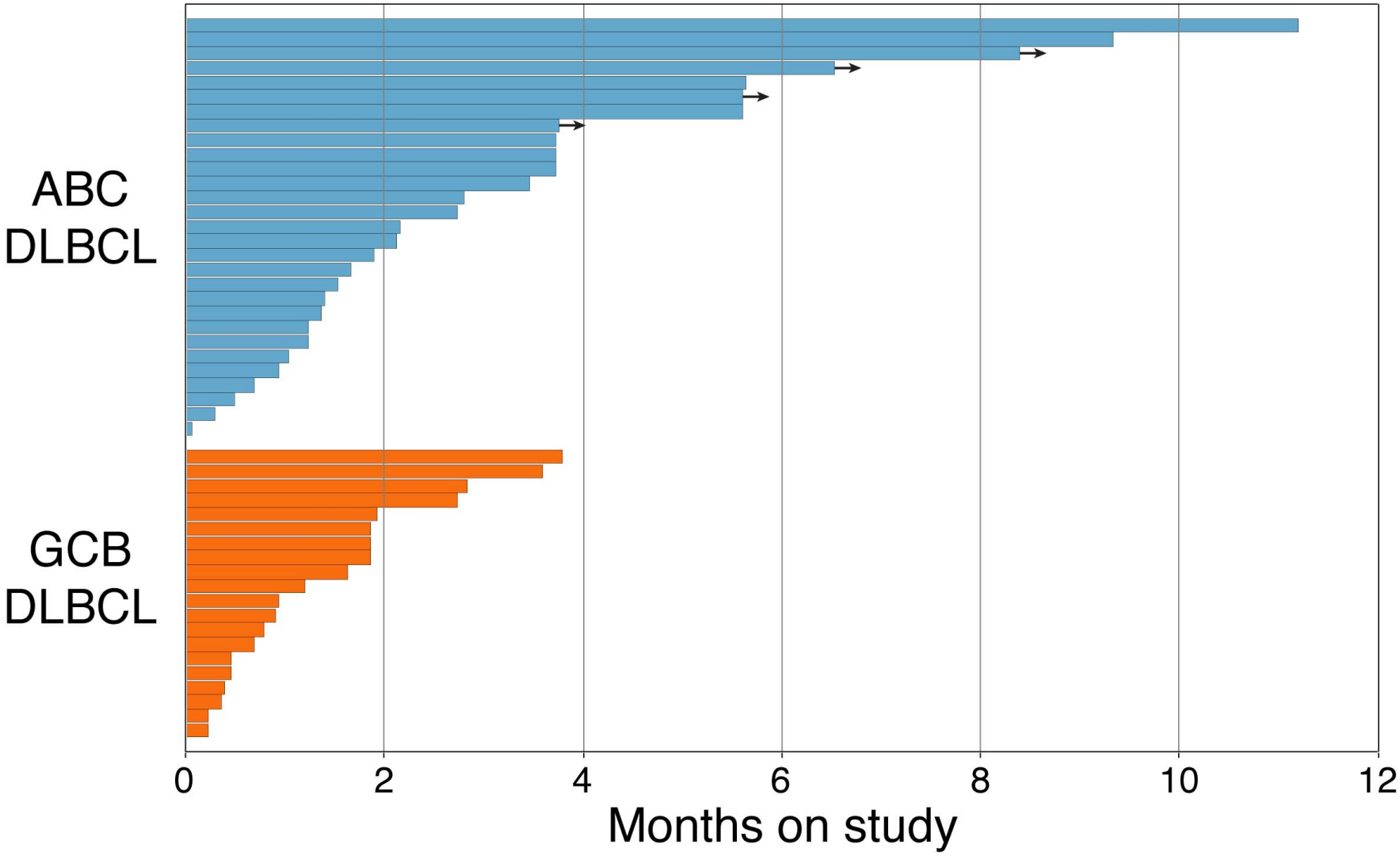
Higher Response Rate to Ibrutinib in ABC DLBCL Than GCB DLBCL



Complete and Partial Responses to Ibrutinib Are Enriched For ABC DLBCLs

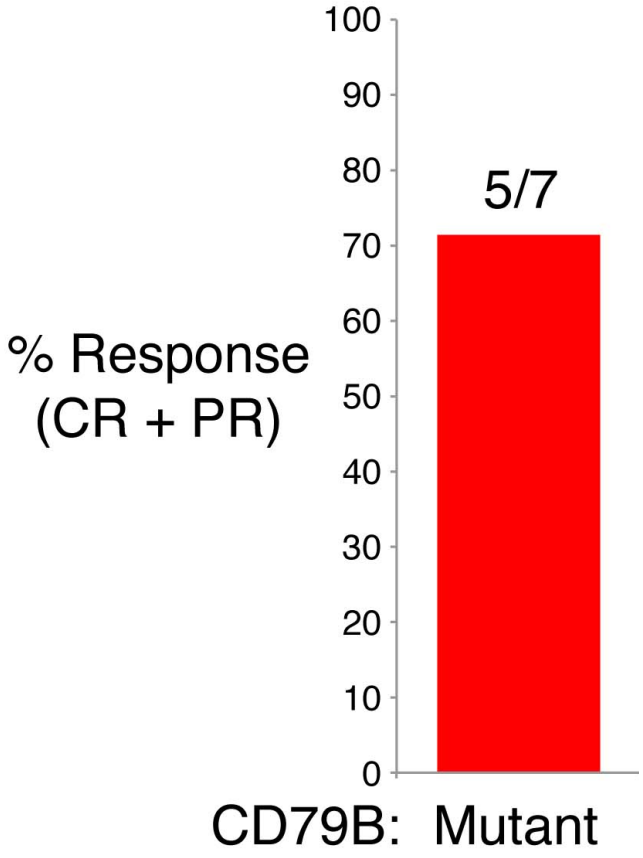


Ibrutinib Responses Can Extend Life in Patients With Relapsed/Refractory ABC DLBCL For > 6 Months

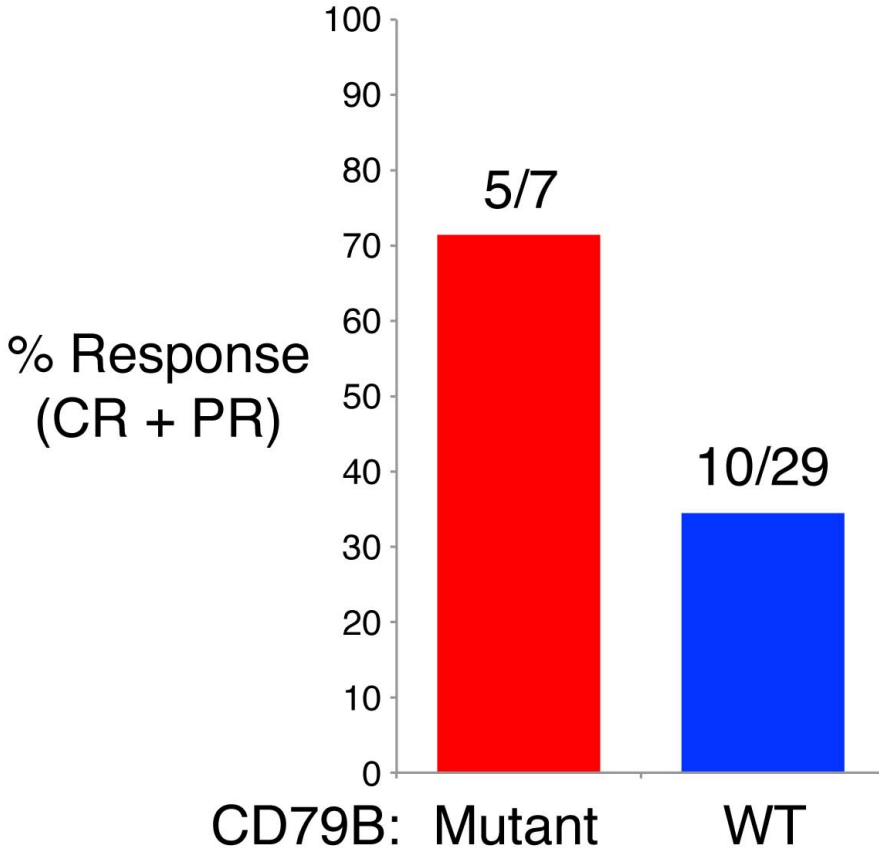


Can Analysis of Recurrent Genetic Lesions Identify Ibrutinib Responders Within ABC DLBCL?

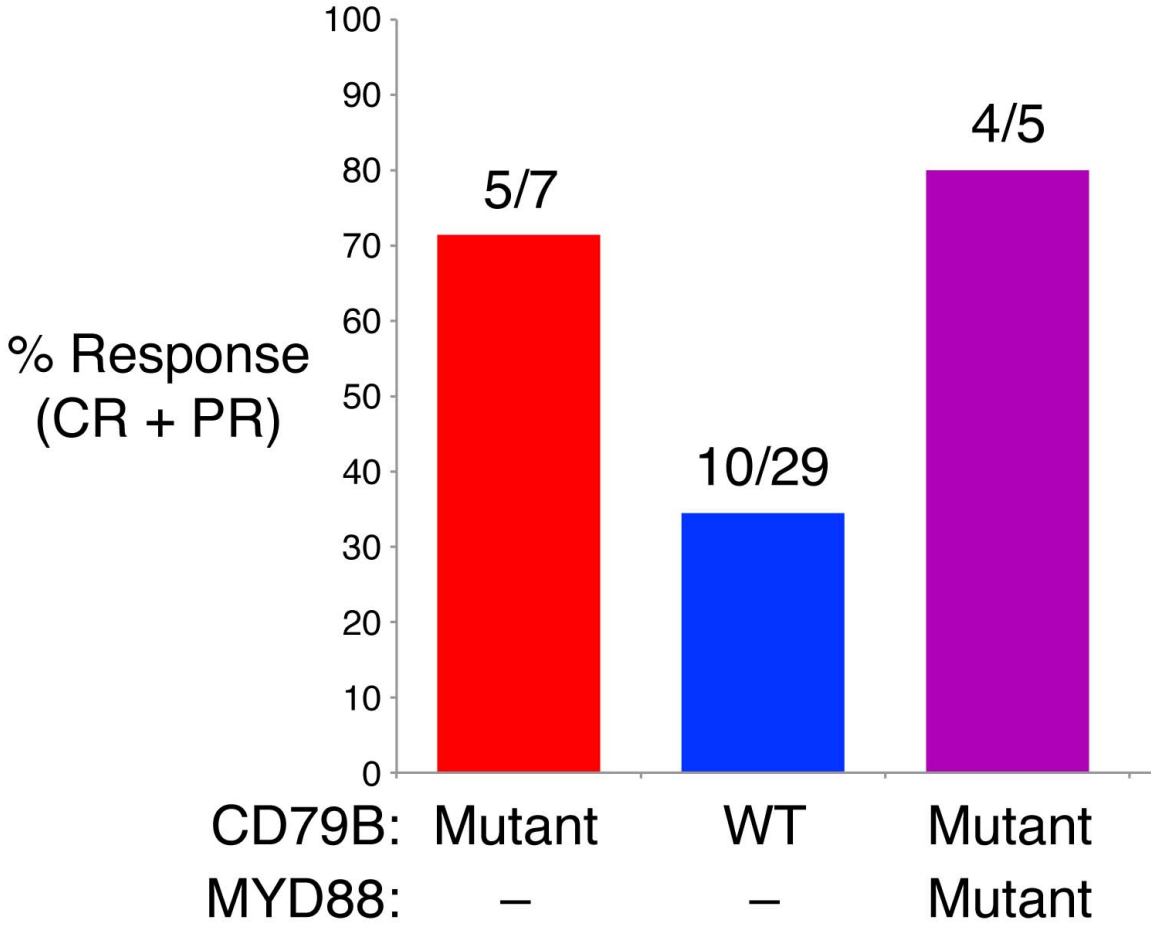
CD79B Mutant ABC DLBCL Predicts a High Rate of Response to Ibrutinib



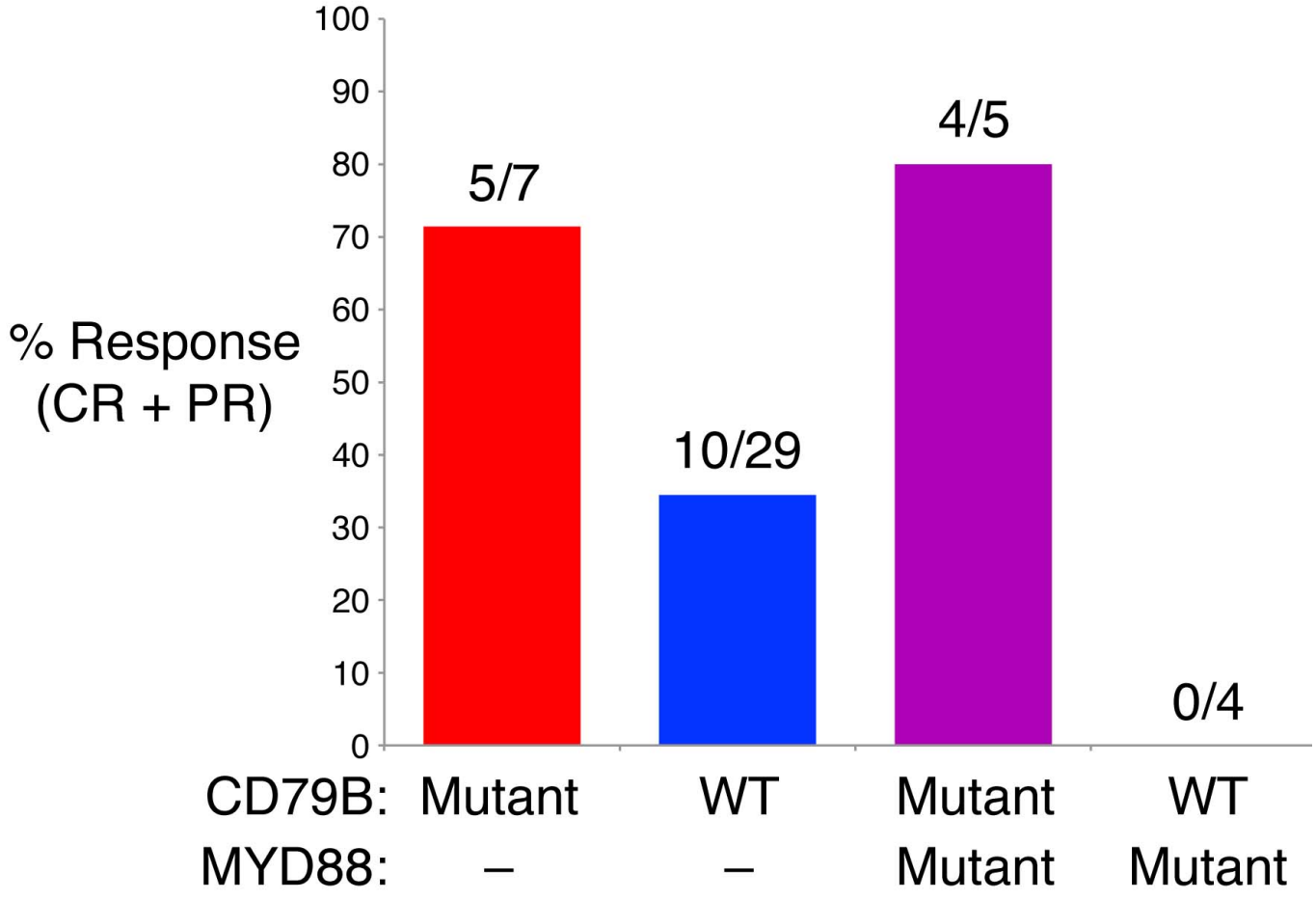
Ibrutinib Response in ABC DLBCL Does Not Require B Cell Receptor Mutation



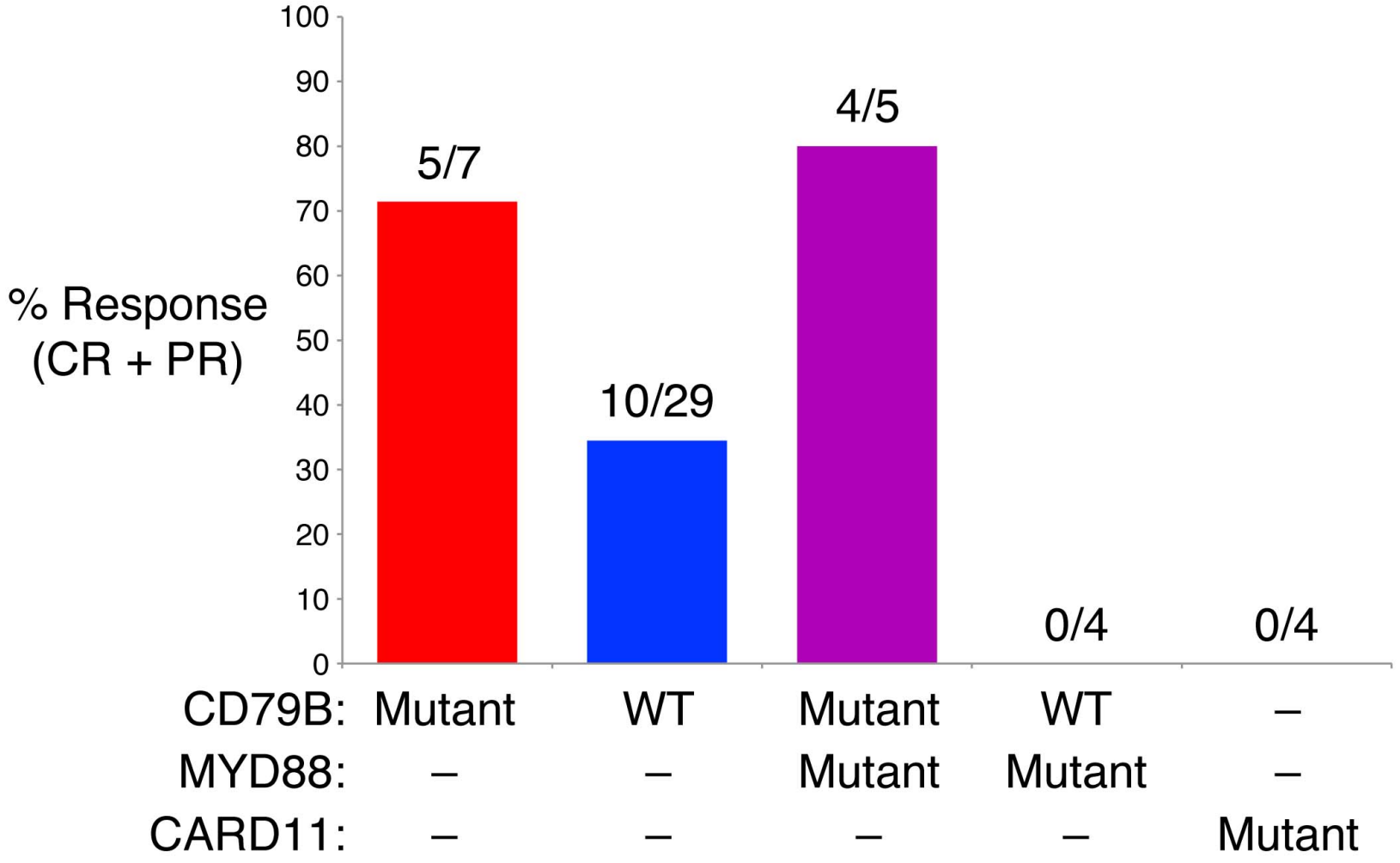
MYD88 L265P Plus CD79B Mutations Identify Ibrutinib-responsive ABC DLBCL



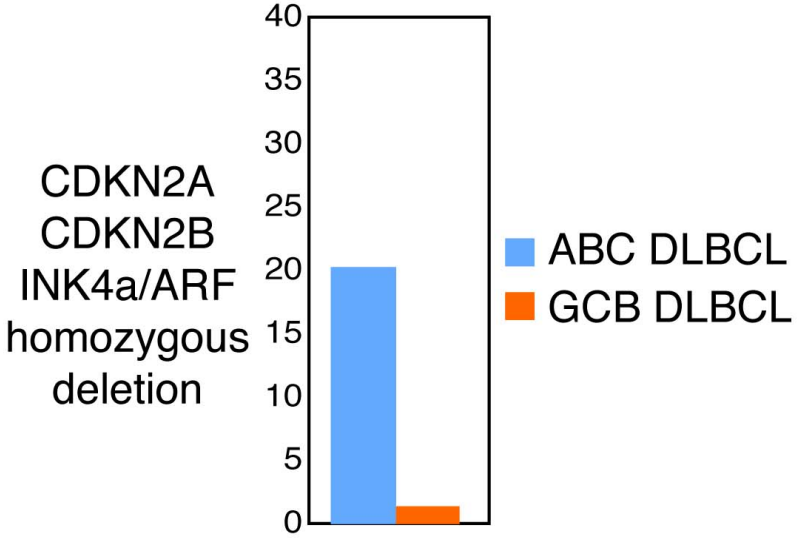
MYD88 L265P Without CD79B Mutation Predicts Ibrutinib Resistance in ABC DLBCL

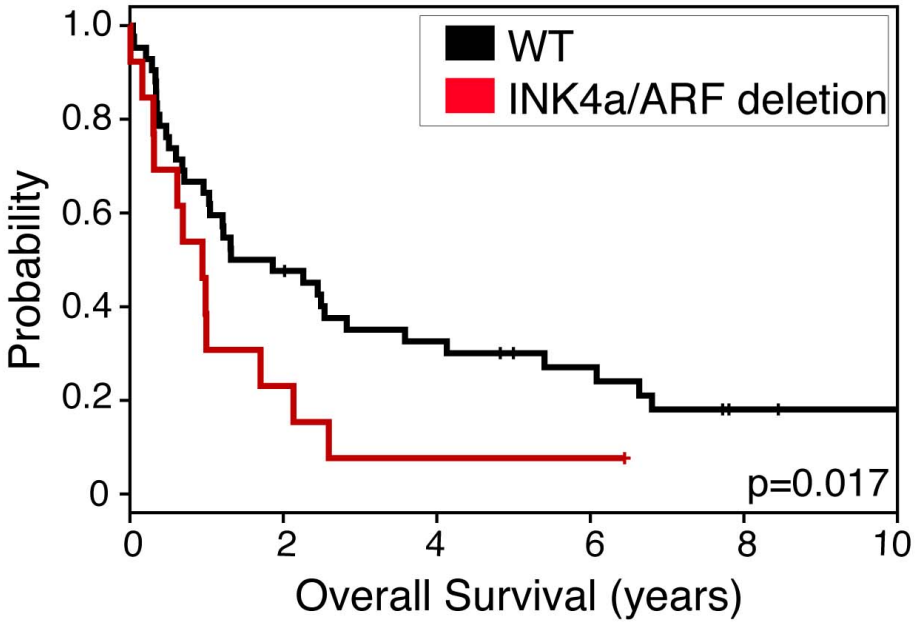


CARD11 Mutant ABC DLBCL Does Not Respond To Ibrutinib

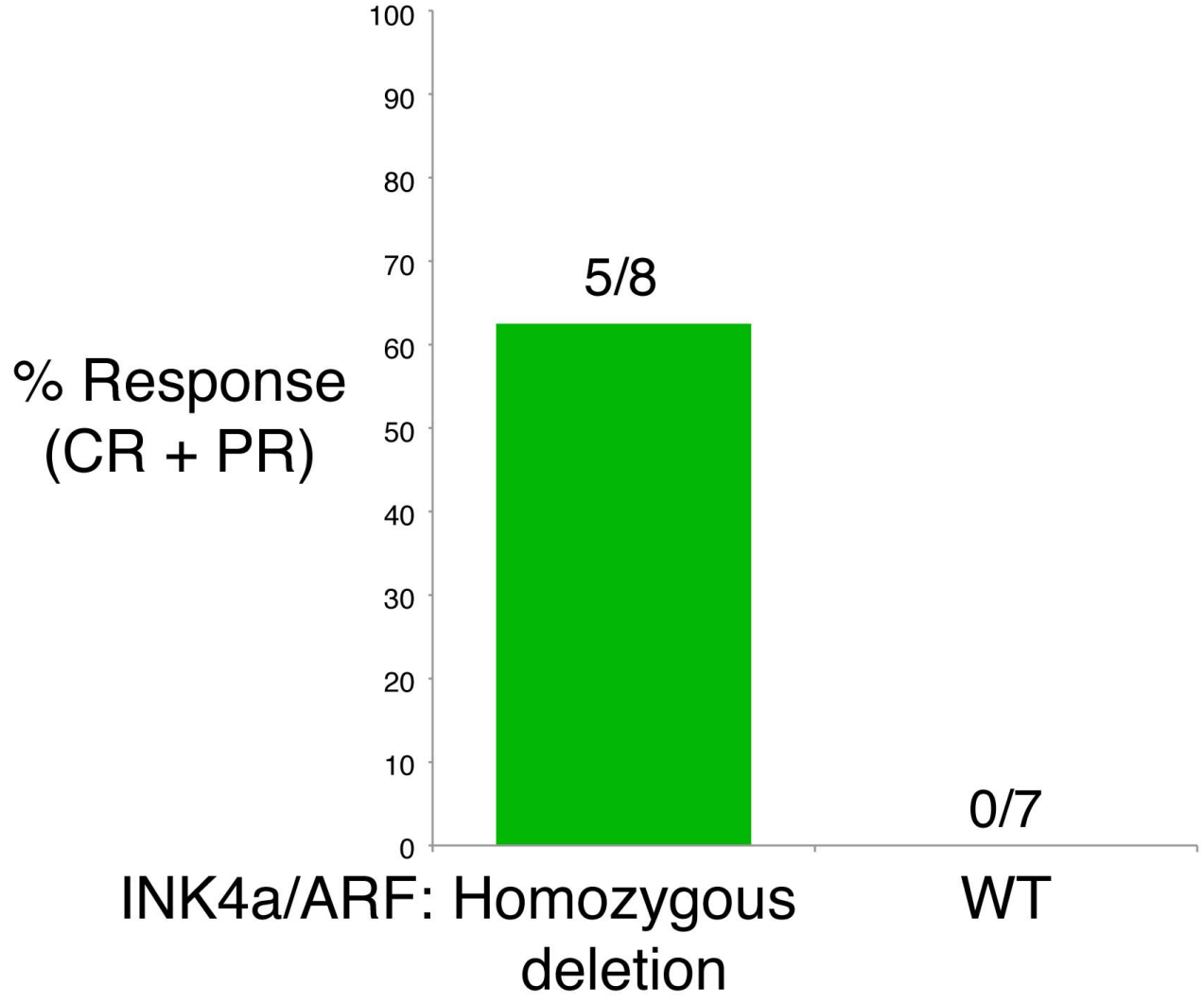


Homozygous Deletion of INK4a/ARF is Recurrent in ABC DLBCL and is Associated With Unfavorable Outcome

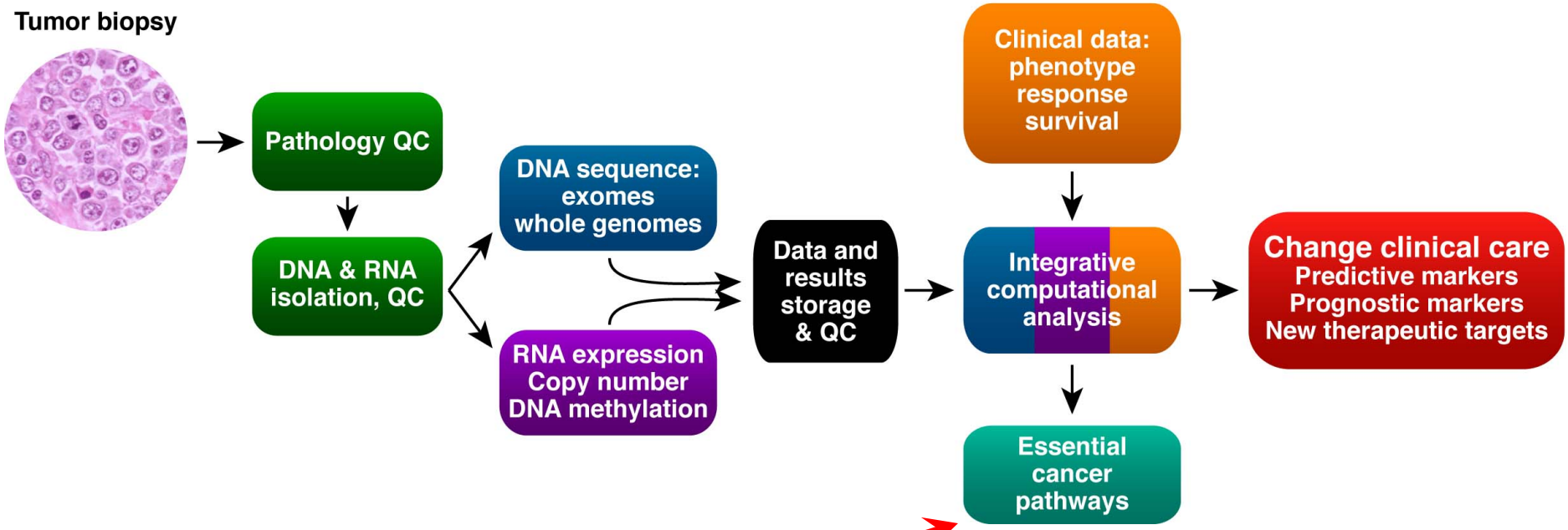




Homozygous Deletion of the INK4a/ARF Locus Predicts Ibrutinib Response

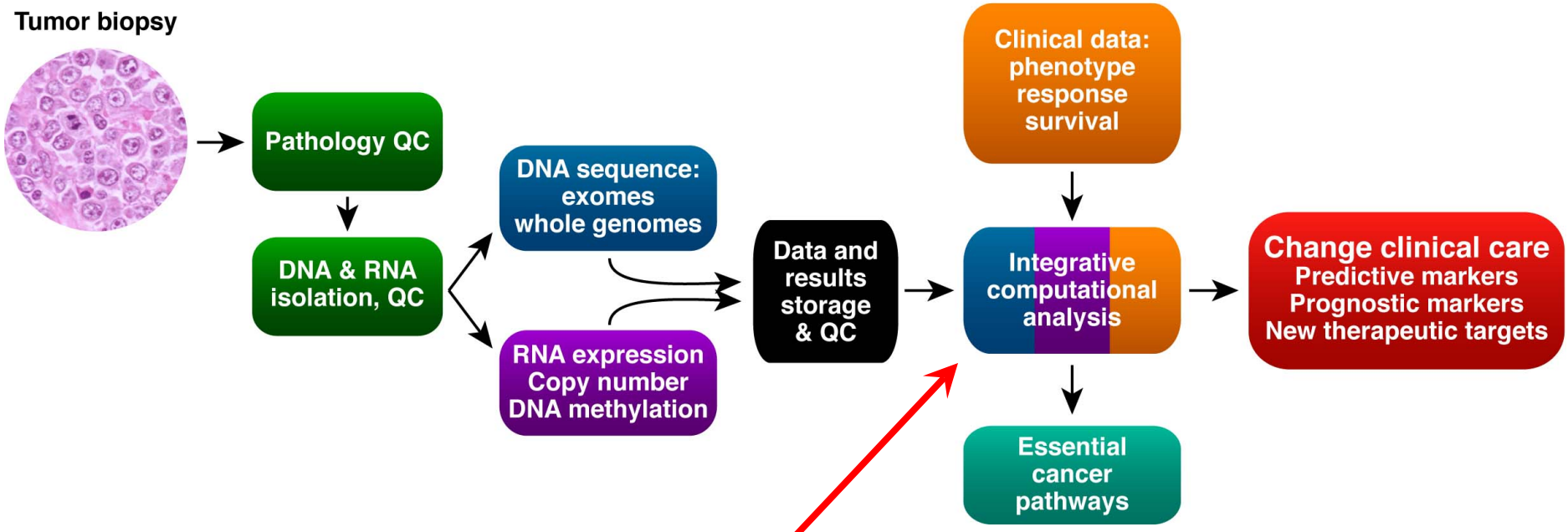


The Heterogeneity of Human Cancer Necessitates Analysis of Large Numbers of Biopsies



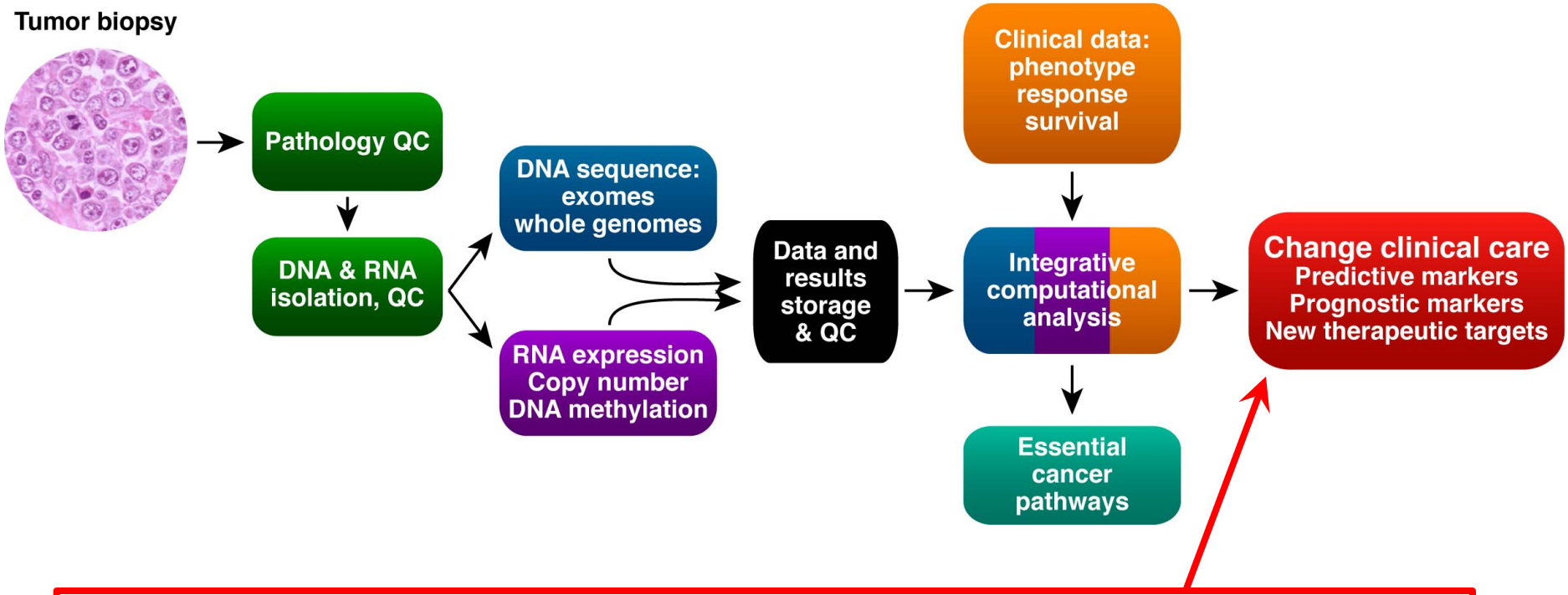
- May need to extend genetic analysis to n > 10,000 to see patterns of co-occurrence and exclusion among genetic lesions.

Integrative Analysis Will Be Key to Deciphering Response / Resistance to Therapy in Cancer



- Pathway-centric view of genetic lesions
- Gene expression signatures of response / resistance
- Pathway activity assessment by protein modifications

Towards Precision Medicine in Routine Cancer Care



- Need to make molecular diagnostic tests widely available
- Develop of a Cancer Genome Commons database to accelerate precision medicine

Acknowledgements

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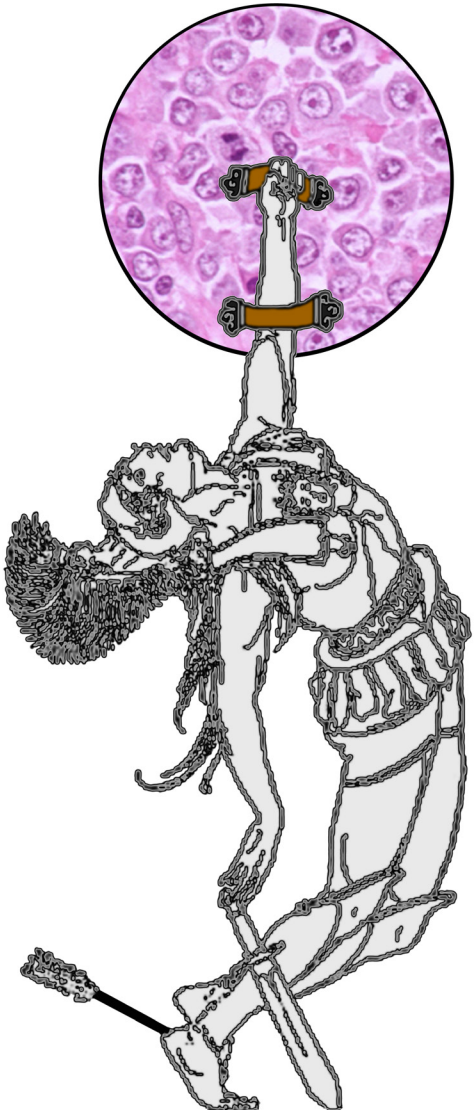
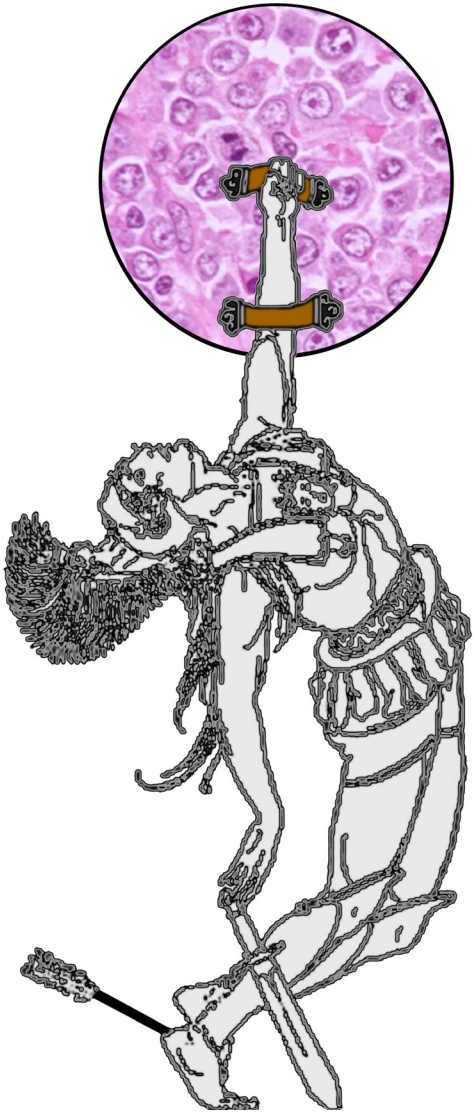
Paul Barr
Kristie A. Blum
Andrei Shustov
Ranjana Advani

Targeted Therapy of ABC DLBCL



- Ibrutinib induces complete and partial responses in relapsed/refractory ABC DLBCL but the response rate is low in GCB DLBCL

Targeted Therapy of ABC DLBCL



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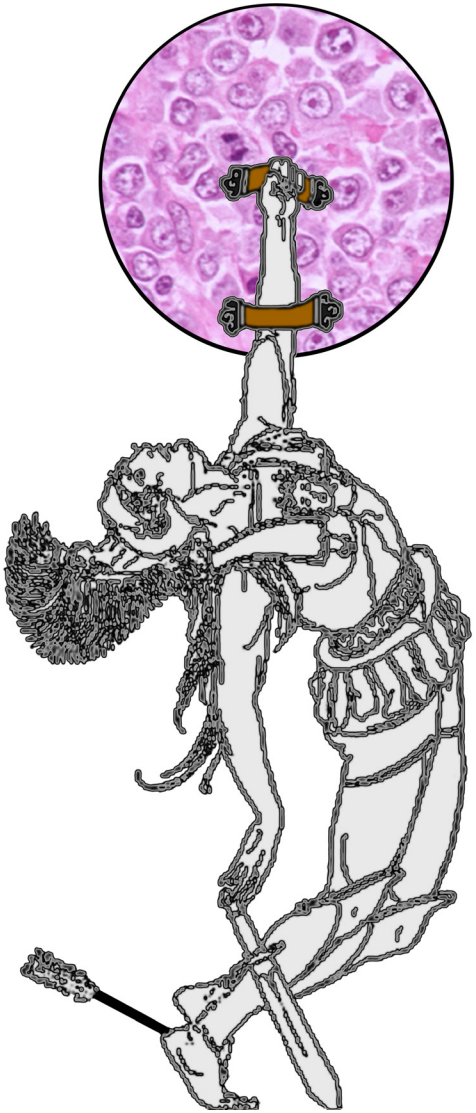
Targeted Therapy of ABC DLBCL



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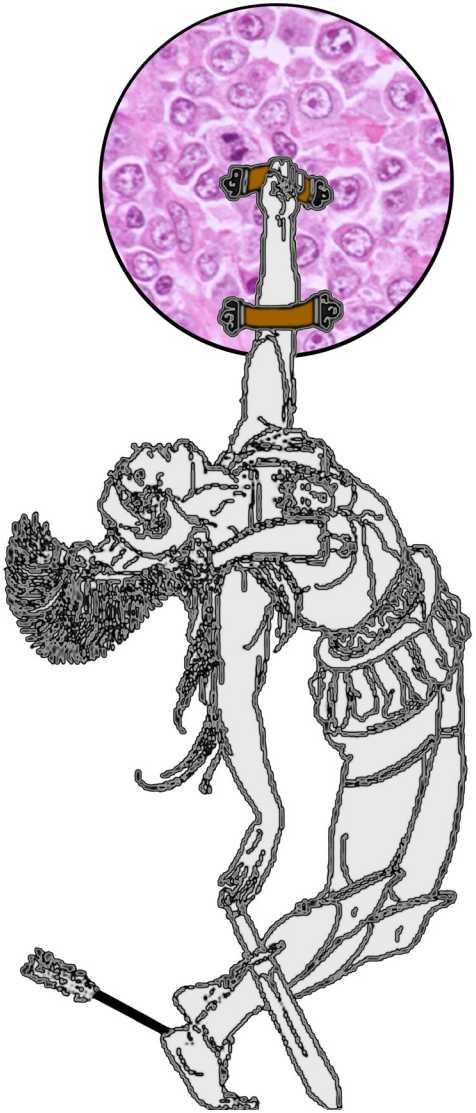

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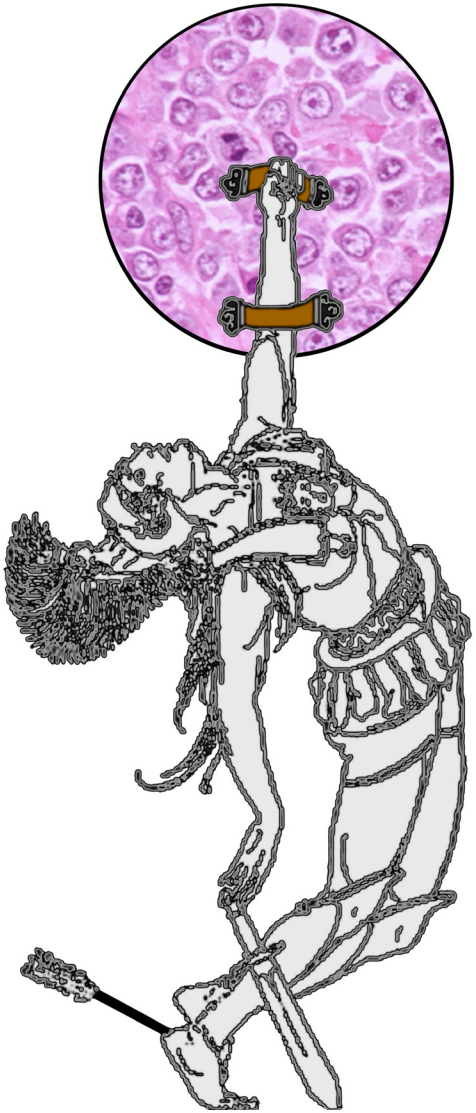
- MYD88 L265P mutations cooperate with CD79B mutations to enhance BCR signaling addiction
- ABC DLBCLs with CARD11 mutations or MYD88 L265P without CD79B mutation resist ibrutinib

Targeted Therapy of ABC DLBCL



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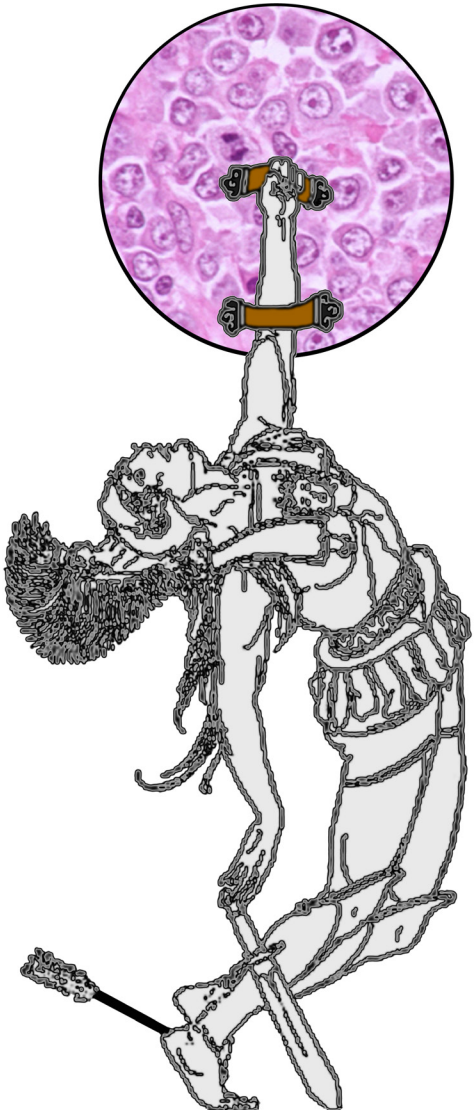
- ABC DLBCLs with CARD11 mutations or MYD88 L265P without CD79B mutation resist ibrutinib
- INK4a/ARF homozygous deletion is common in R/R ABC DLBCL and associated with ibrutinib response

Targeted Therapy of ABC DLBCL



- Ibrutinib induces complete and partial responses in relapsed/refractory ABC DLBCL but the response rate is low in GCB DLBCL
- CD79B mutations enrich for ibrutinib activity in ABC DLBCL but are not required
- MYD88 L265P mutations cooperate with CD79B mutations to enhance BCR signaling addiction
- ABC DLBCLs with CARD11 mutations or MYD88 L265P without CD79B mutation resist ibrutinib
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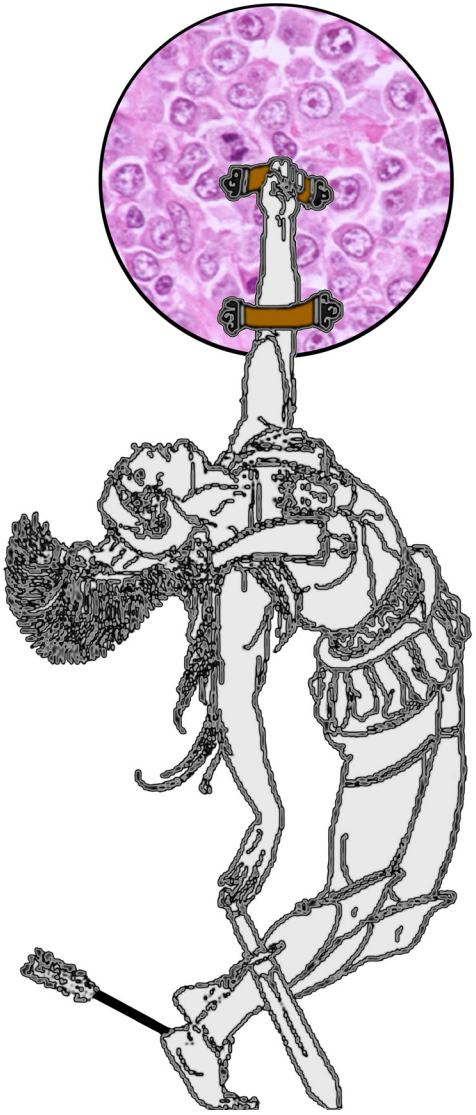

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- Larger ABC DLBCL cohorts are needed to understand the relationship of genetic events to ibrutinib response
- ABC DLBCL is a good biomarker of ibrutinib response

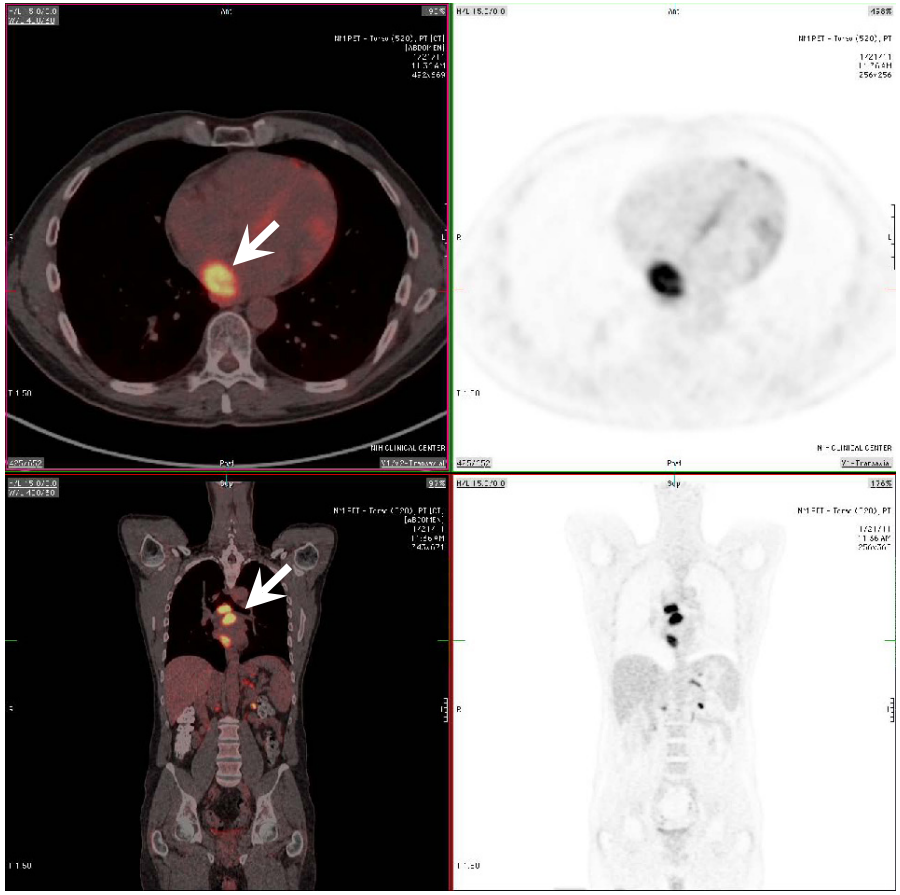
Ibrutinib Treatment Related Toxicities

- Diarrhea (grade 1)
- Nausea (grade 1)
- Fatigue (grades 1 and 2)
- Time-dependent decrease in B cell numbers
  Maintenance of serum immunoglobulin levels

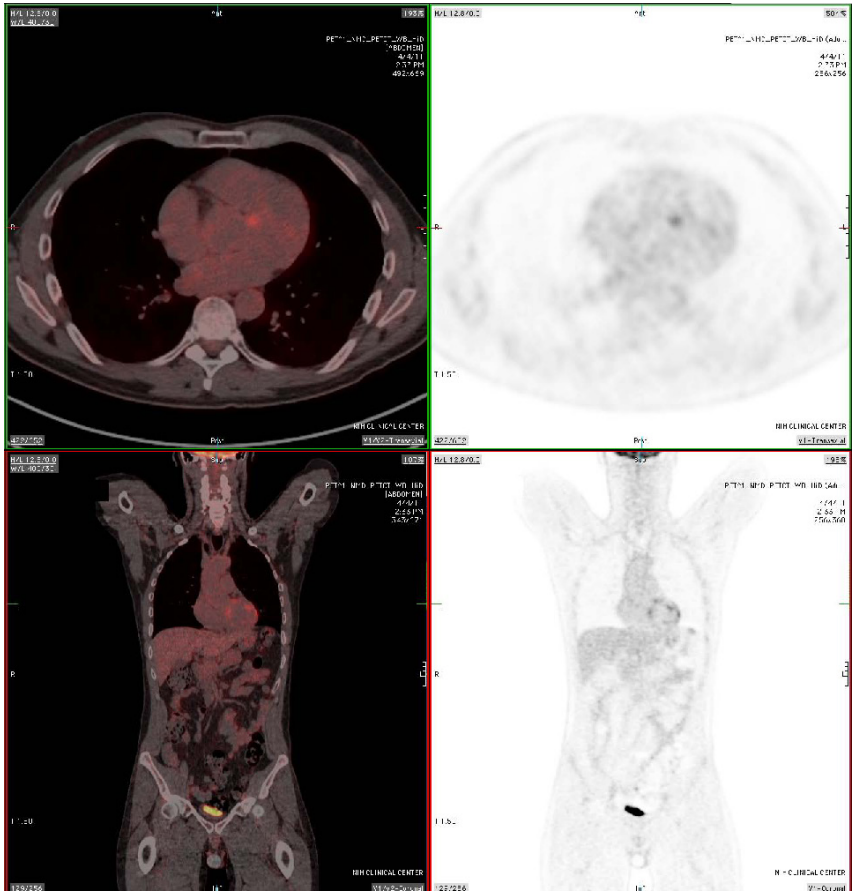
Patient #3 on Pilot Trial of Ibrutinib in Relapsed/refractory ABC DLBCL

- 48 year old male
  ABC DLBCL
- CD79B wild type
  MYD88 wild type
- Multiple prior relapses following chemotherapy and radiation
  R-CHOP x 6
  R-ESHAP
  Autologous bone marrow transplant
- Single agent treatment with ibrutinib
- Complete response at week 10 by CT and PET scan

Complete Remission of ABC DLBCL in Patient #3 on Pilot Trial of Ibrutinib



Before Rx



On Rx: week 10

Patient on Phase 2 Trial of Ibrutinib in Relapsed/refractory DLBCL

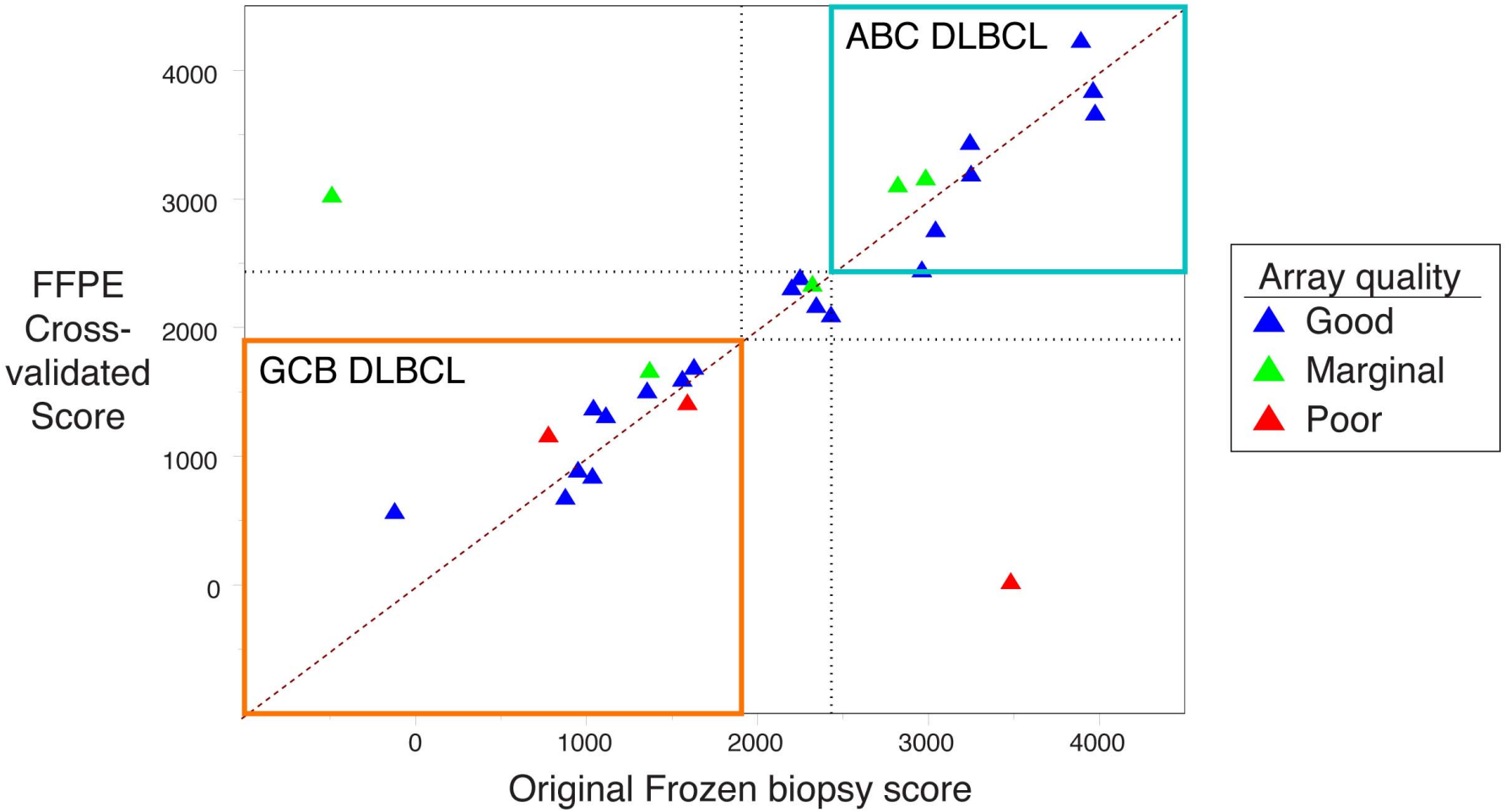
- 71 year old male
  ABC DLBCL
- CD79B Y196H mutation
  MYD88 L265P mutation
- R-CHOP + genasense + radiation: Partial response
  Ofatumamab + lenalidomide: No response
  ICE => No response
  R-DHAP => No response
- Single agent treatment with BTK inhibitor (PCI-32765)
- Complete response at week 12 by CT and PET scan

Complete Remission of ABC DLBCL in Phase 2 Trial of Ibrutinib

Before Rx

On Rx: week 12

A Gene Expression-based Classifier of ABC vs. GCB DLBCL Using FFPE Biopsies



Molecular Pathogenesis of Diffuse Large B Cell Lymphoma