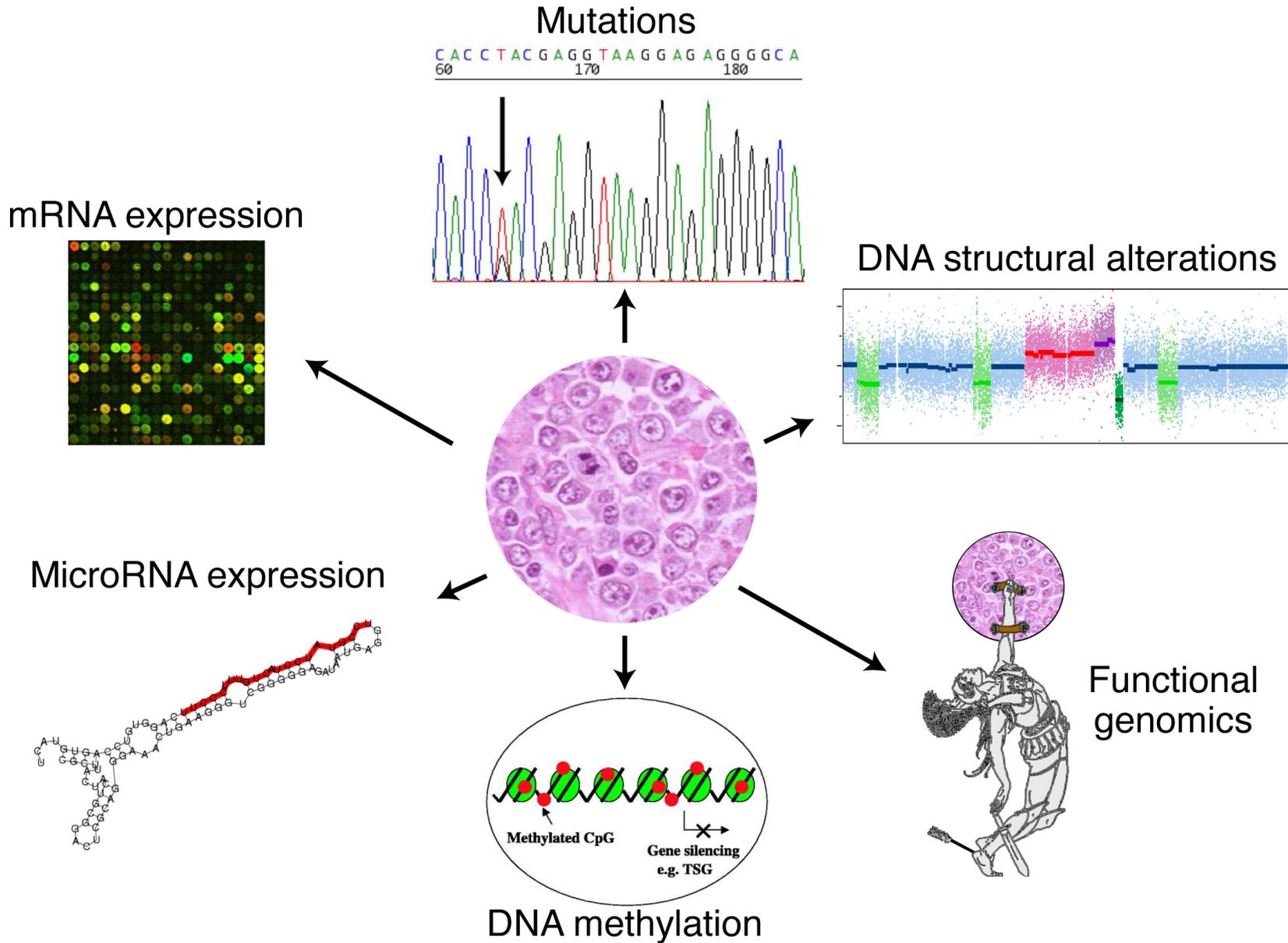




Vanquishing Cancer Through Genomics

The Genomic Assault on Cancer



High Throughput DNA sequencing Has Revolutionized Cancer Genomics



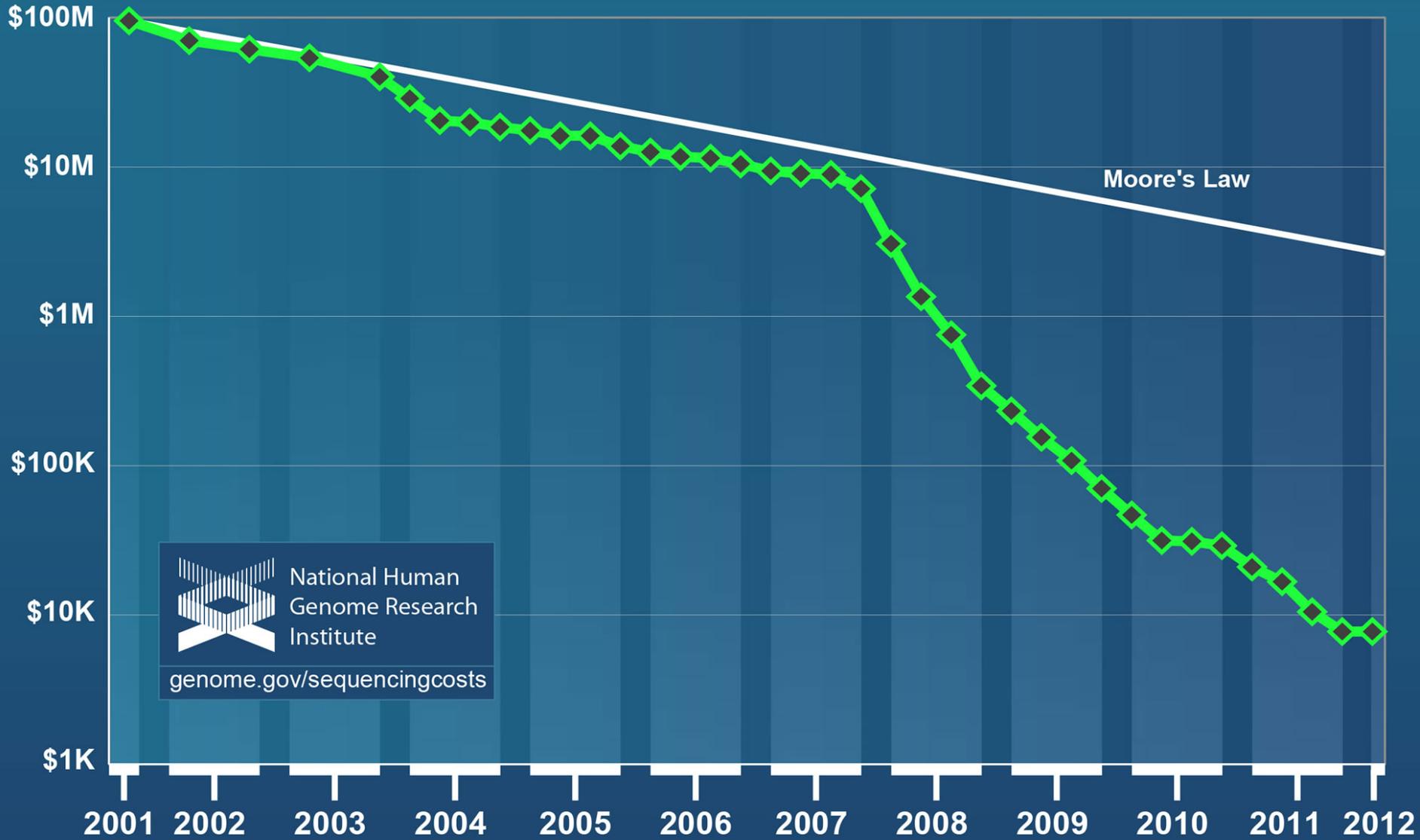
1 HiSeq2000 run / 11 days

600×10^9 bases
(2 whole genomes)

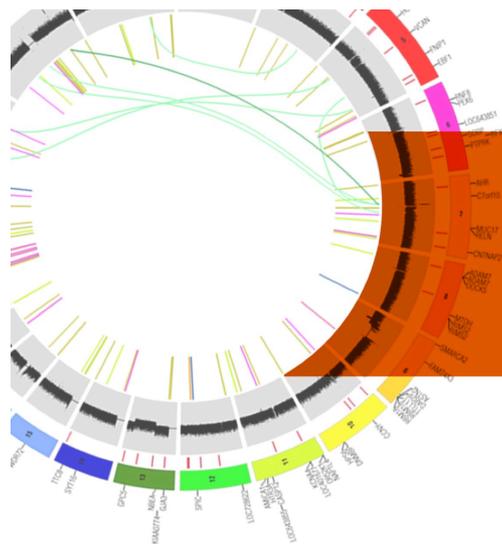
6×10^9 sequence reads

200×10^9 bytes/case

Cost per Genome



NCI Center for Cancer Genomics Programs



The Cancer Genome Atlas 

TCGA

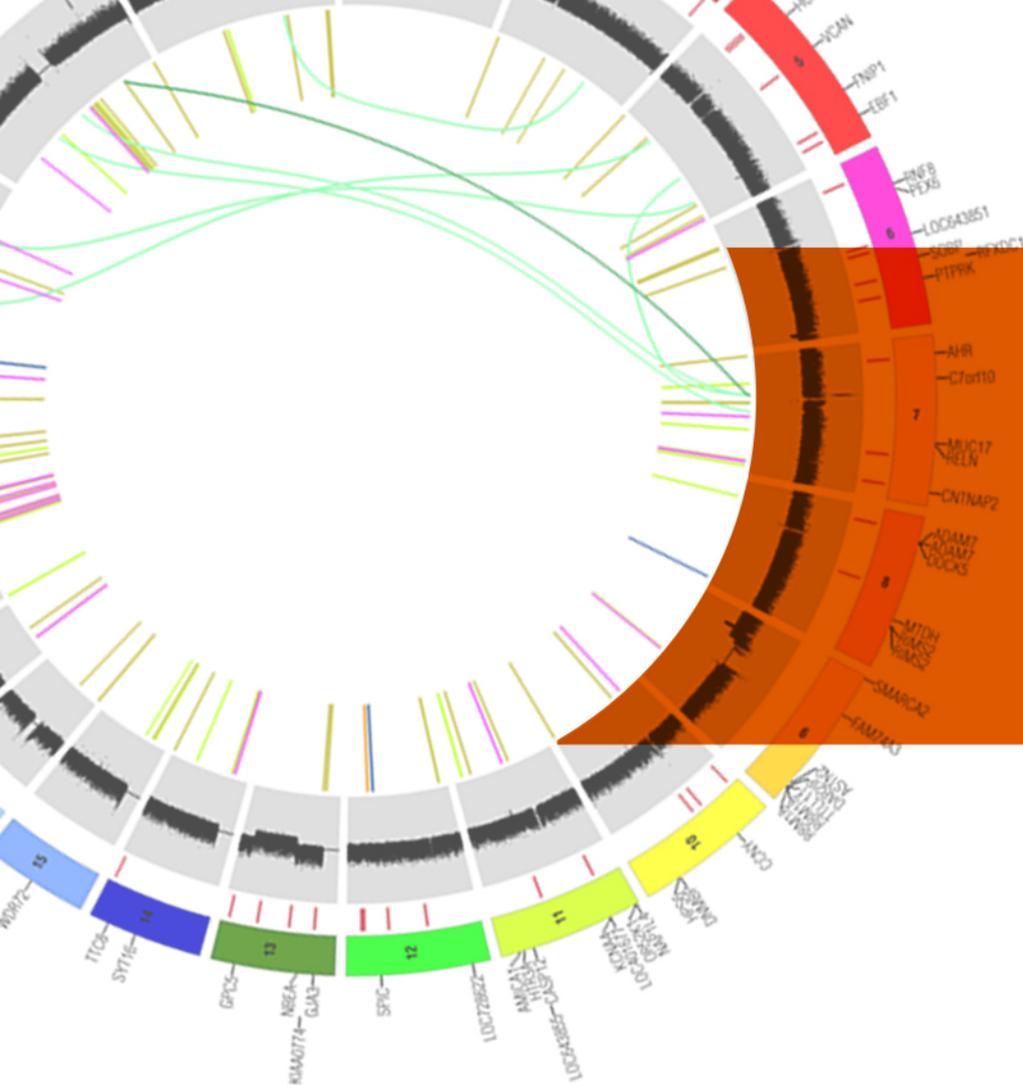
 **TARGET**
Therapeutically Applicable Research
to Generate Effective Treatments

A banner for the TARGET program featuring a young girl with blue eyes and an orange top, set against a background of chemical structures and a DNA double helix.

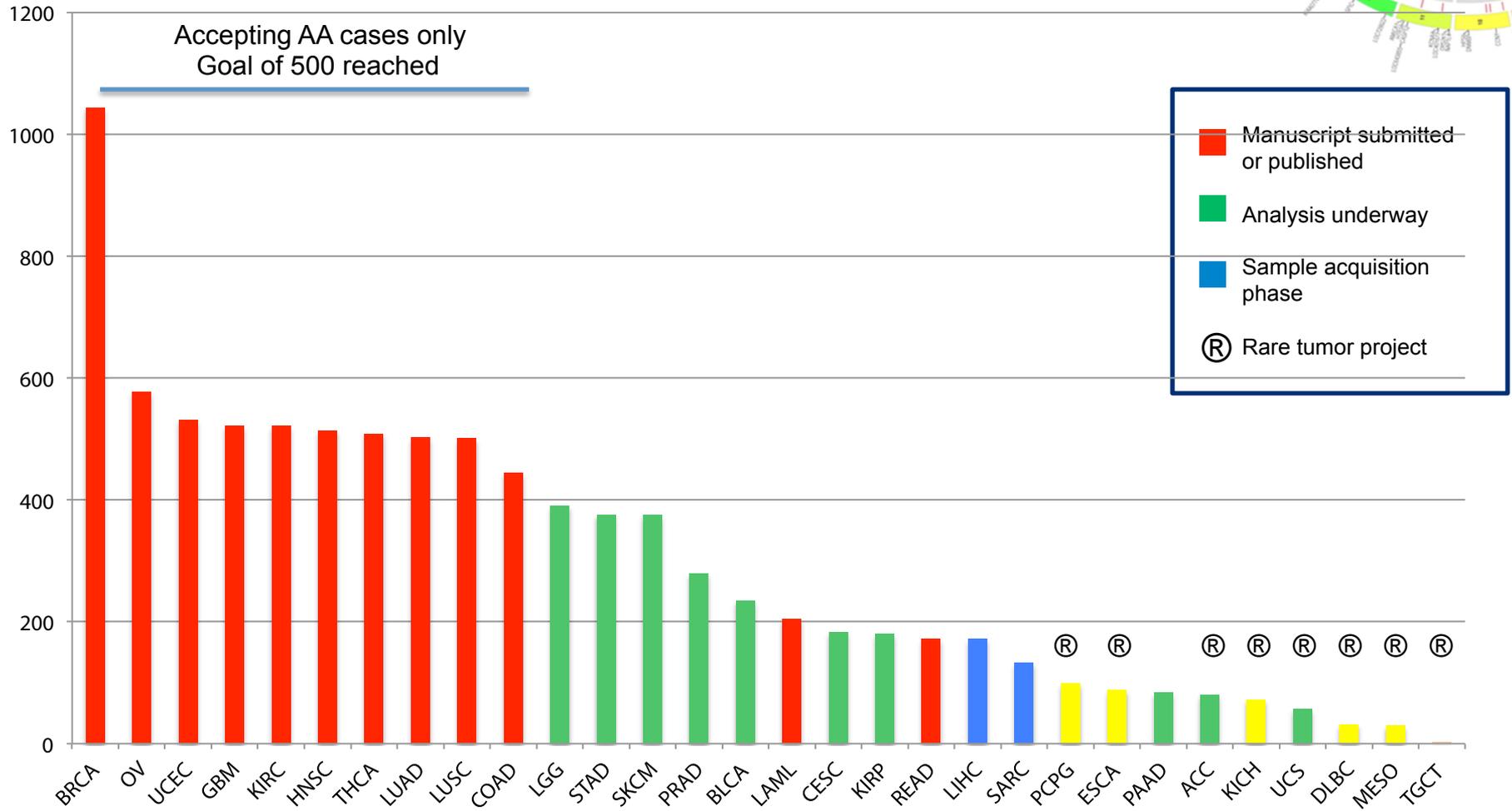
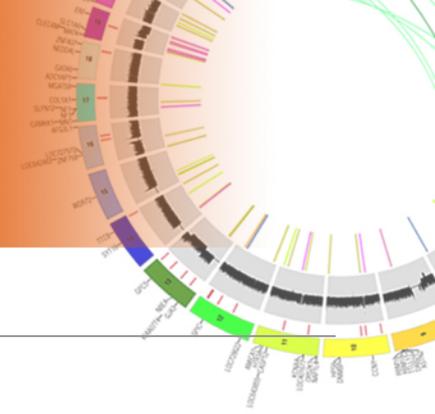
CTD²: A Bridge from Genomics to
Cancer Therapeutics



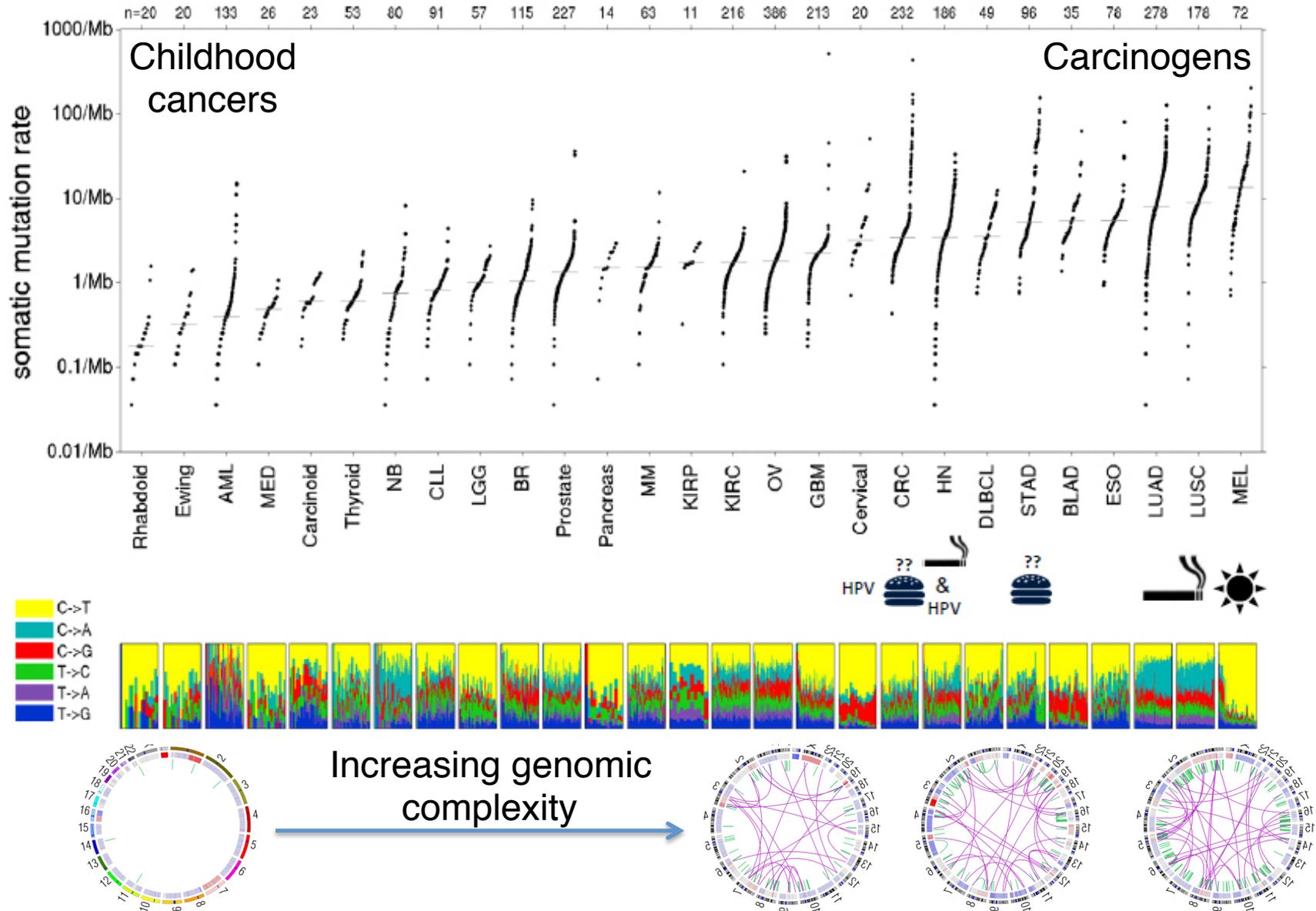
TCGA – Lessons from structural genomics



Tumor Project Progress



The Mutational Burden of Human Cancer



ARTICLE

OPEN

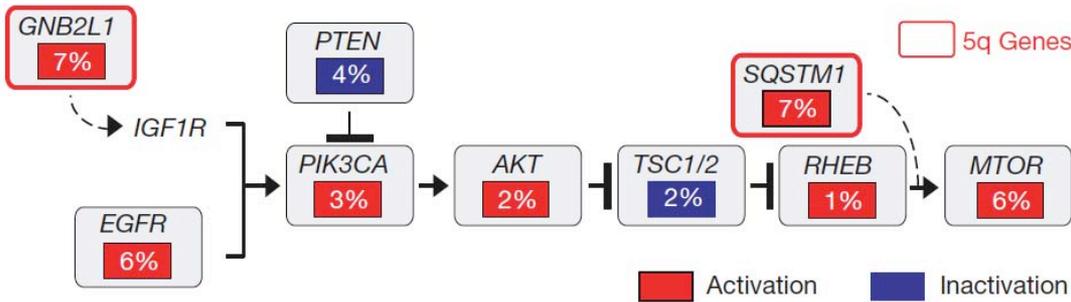
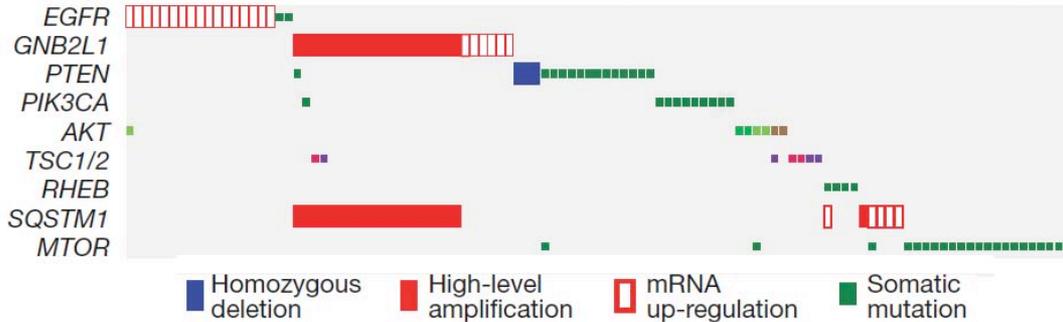
doi:10.1038/nature12222

Comprehensive molecular characterization of clear cell renal cell carcinoma

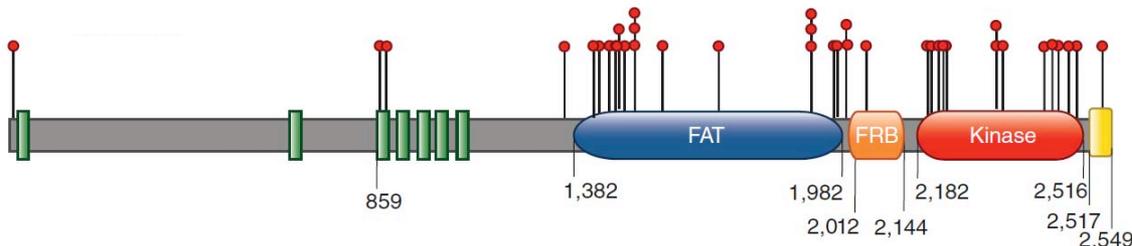
The Cancer Genome Atlas Research Network*

Frequent Activation of the PI(3)K Pathway in Clear Cell Renal Carcinoma

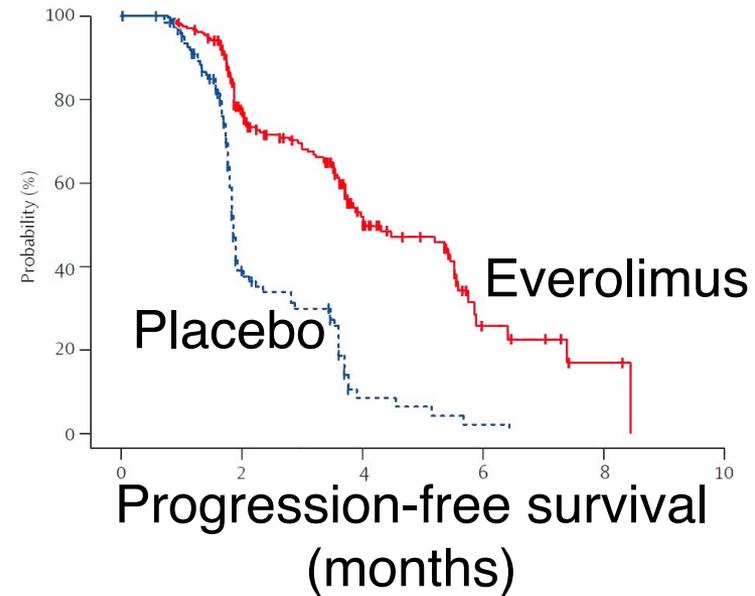
PI(3)K aberrations (28% of cases)



mTOR mutations



Response of RCC To Everolimus



TCGA Nature 499:45 (2013)
 Sato et al Nat Gen 45:860 (2013)
 Hakimi et al Nat Gen 45:849 (2013)
 Motzer et al Lancet 372:449 (2008)

ARTICLE

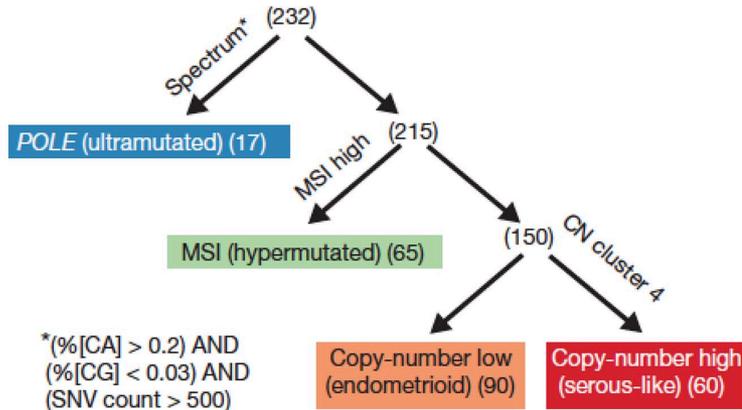
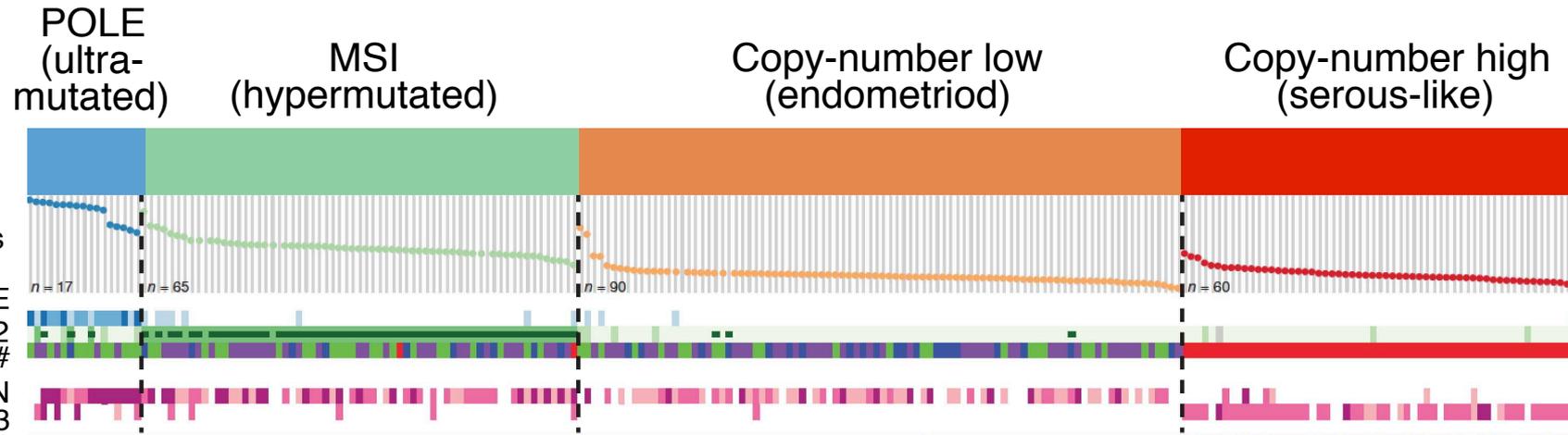
OPEN

doi:10.1038/nature12222

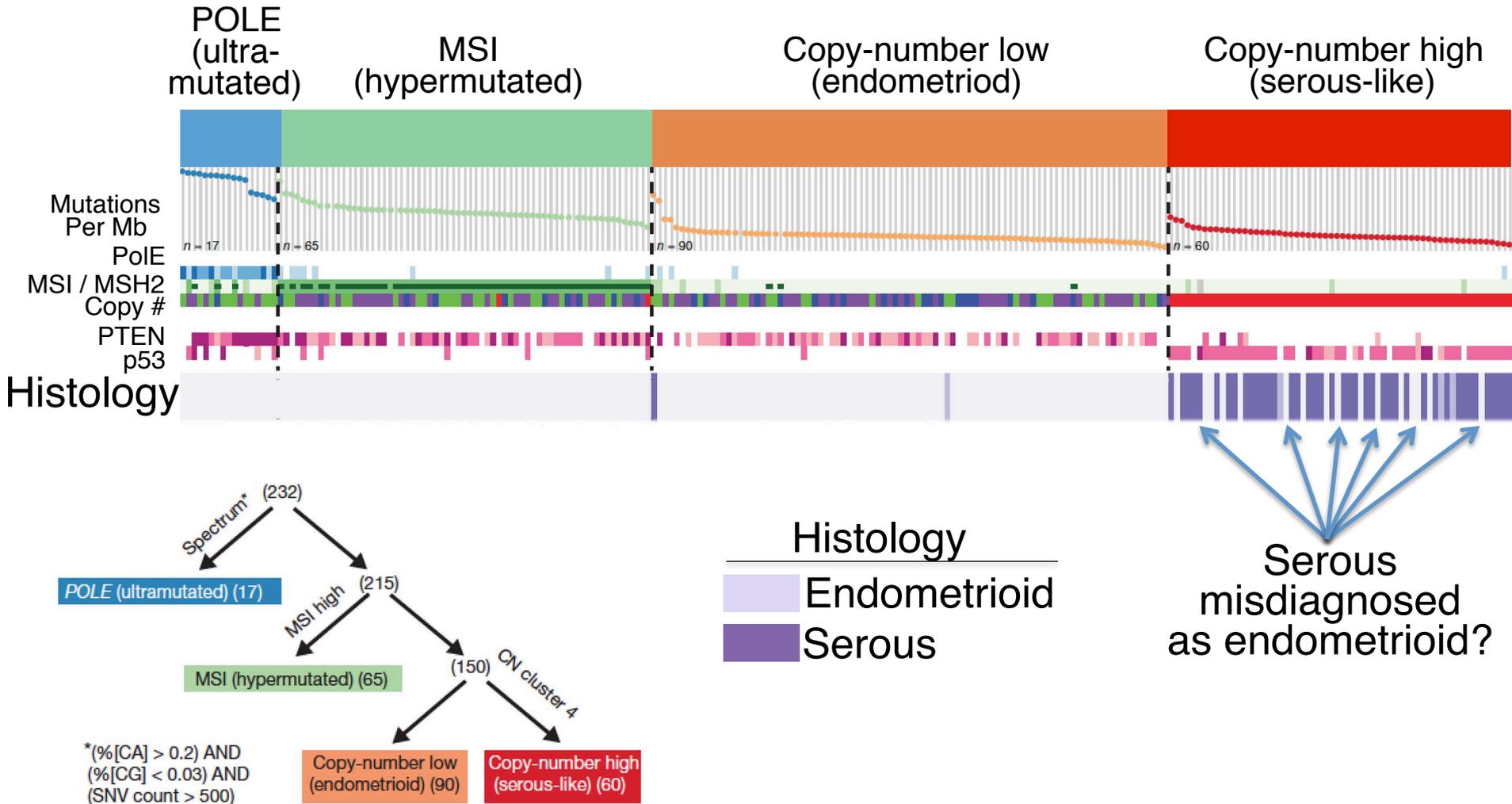
Comprehensive molecular characterization of clear cell renal cell carcinoma

The Cancer Genome Atlas Research Network*

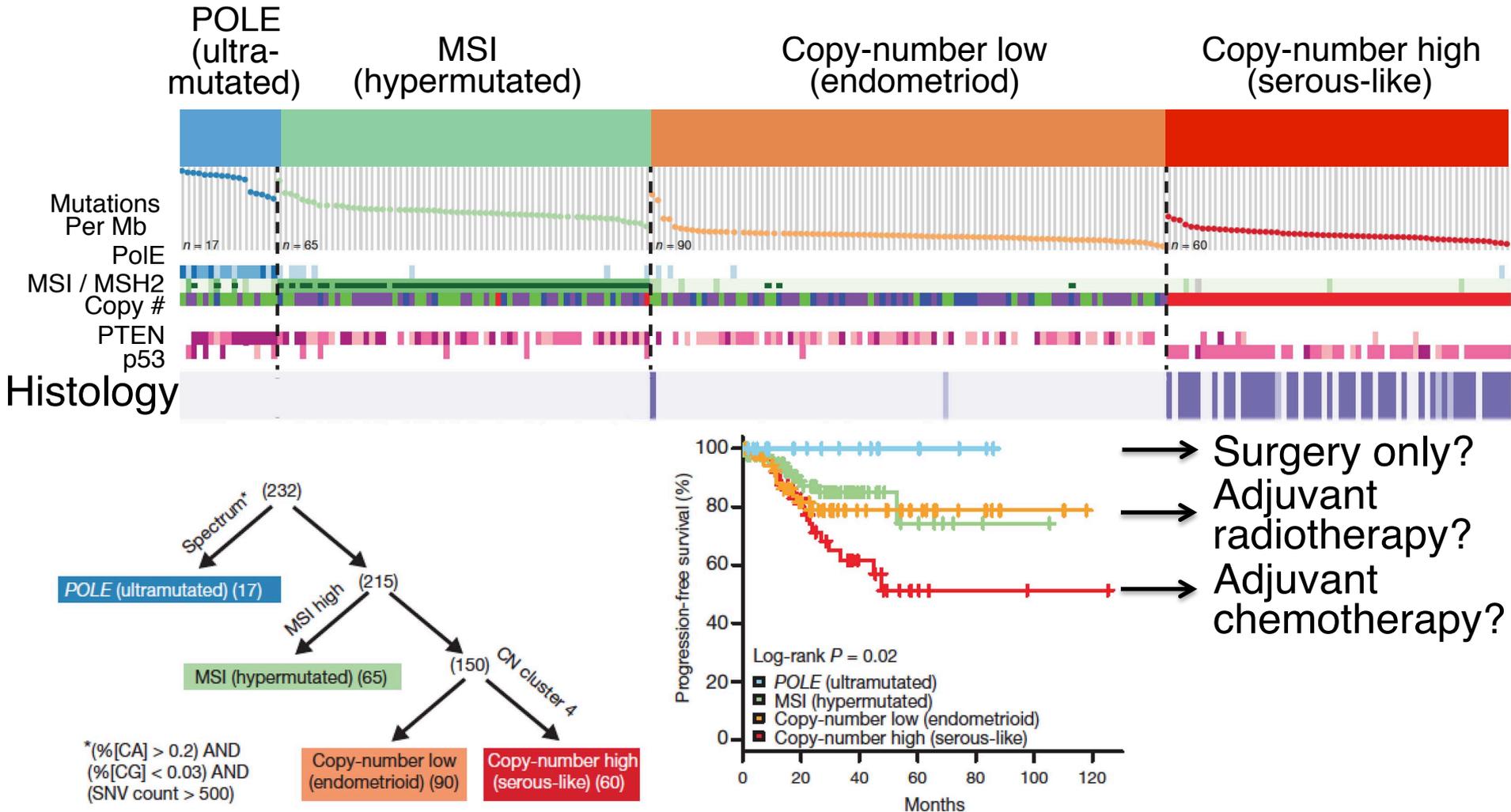
Four Molecular Subgroups of Endometrial Cancer Defined by Integrative Analysis



Molecular Subgroups Refine Histological Diagnosis Of Endometrial Carcinoma



Molecular Diagnosis of Endometrial Cancer May Influence Choice of Therapy



Novel Cancer Therapies
Based on
Structural Genomics



TARGET

Therapeutically Applicable Research
to Generate Effective Treatments



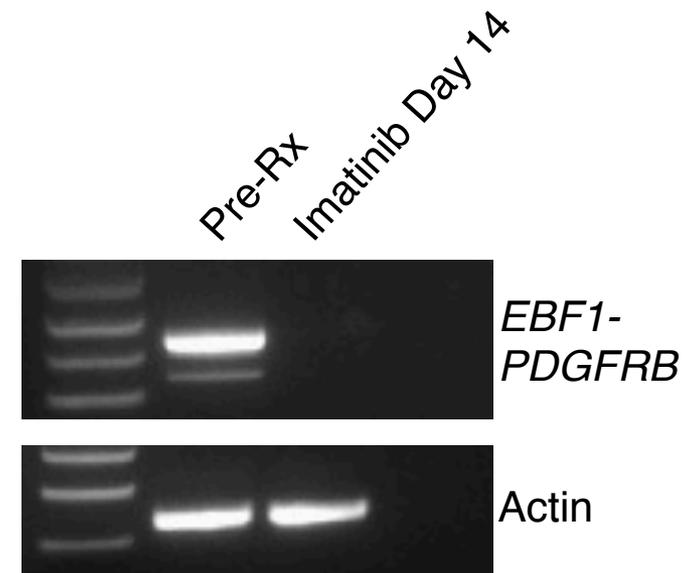
Comprehensive characterization (GEP, CNA, and WXS or WGX; epigenetics is part of most, but not all projects) of 100-200 cases of:

- Acute lymphoblastic leukemia, dx and relapse
- Acute myeloid leukemia (AML), dx and relapse
- Neuroblastoma (stage 4)
- Osteosarcoma
- Wilms tumor (relapsed patients of favorable histology and anaplasia)

Response of Pediatric B-ALL With a Novel EBF1-PDGFRB Translocation to Imatinib

- 10 year old male
- Refractory B-ALL – 70% blasts at day 29
- Sagittal vein thrombosis
- Cytogenetics: 5q alteration, otherwise normal
- RNA-seq => *EBF1-PDGFRB* translocation

- Commenced imatinib
- Immediate clinical improvement
- 1 week: morphologic remission
- 2 weeks: MRD 0.017%



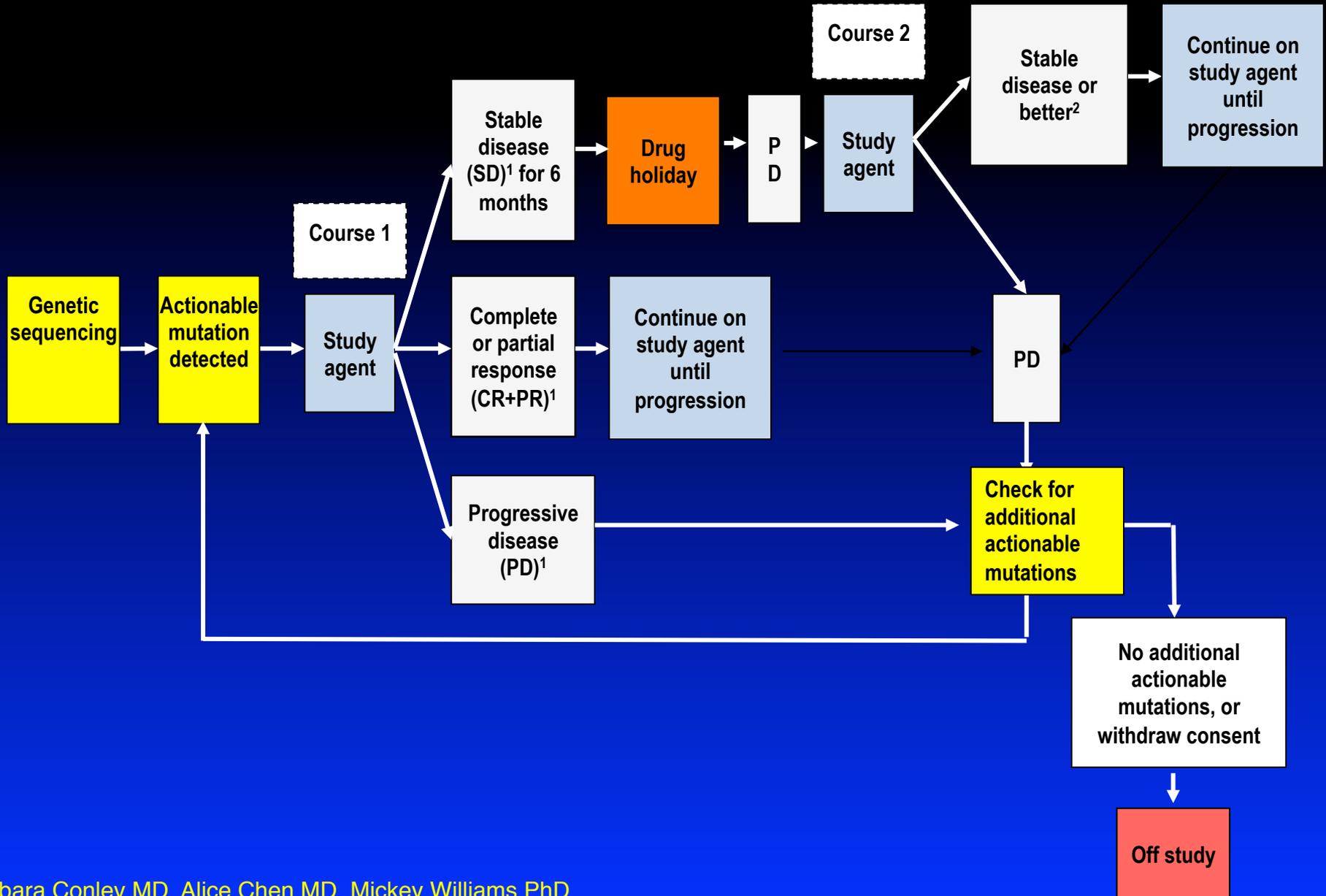
How to get the right drug to the right patient?

- Genotype to Phenotype
 - “Basket” studies
 - “N of 1”

Molecular Analysis for Therapy Choice (NCI MATCH)

- Screen 1500 to 3000 patients (Target enrollment 500 – 1000 patients)
- Selected CLIA labs running comparable screening diagnostic tests
- Targeted agents committed: >30
- Tumor genomics board to determine rules for assignment to study drug

NCI MATCH Schema



How to get the right drug to the right patient?

- Phenotype to Genotype
 - Exceptional responders

Response to Everolimus – MSKCC Protocol 08-123

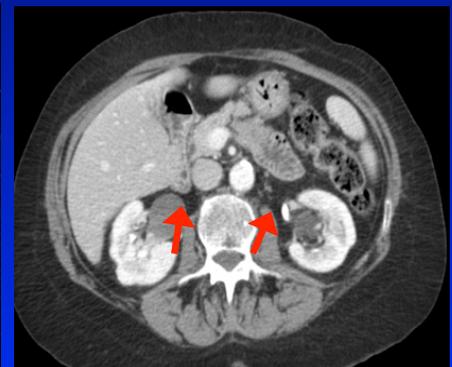
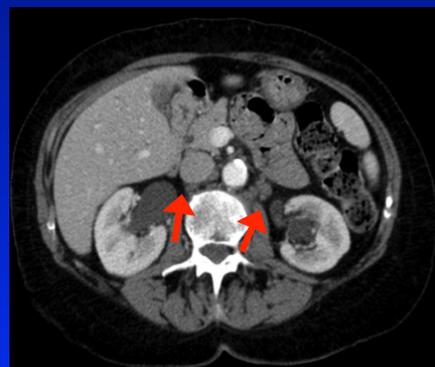
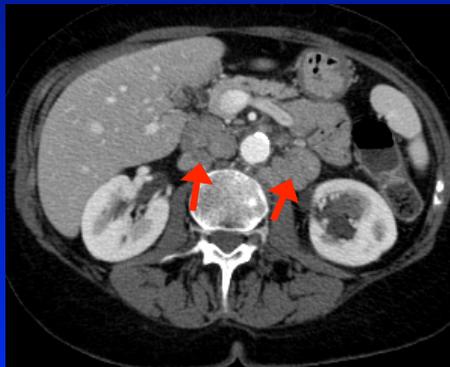
- 73 year old with metastatic bladder cancer.
- Complete response to everolimus (mTORC1 inhibitor) on MSKCC protocol 08-123.
- The patient remains on drug with no evidence of disease 24 months after starting treatment.
- This patient was one of only 2 who responded to drug (of 45 patients). The drug did not achieve it's pre-trial statistical endpoint (>70% of patients progression free at 2 months).

Pre-Treatment

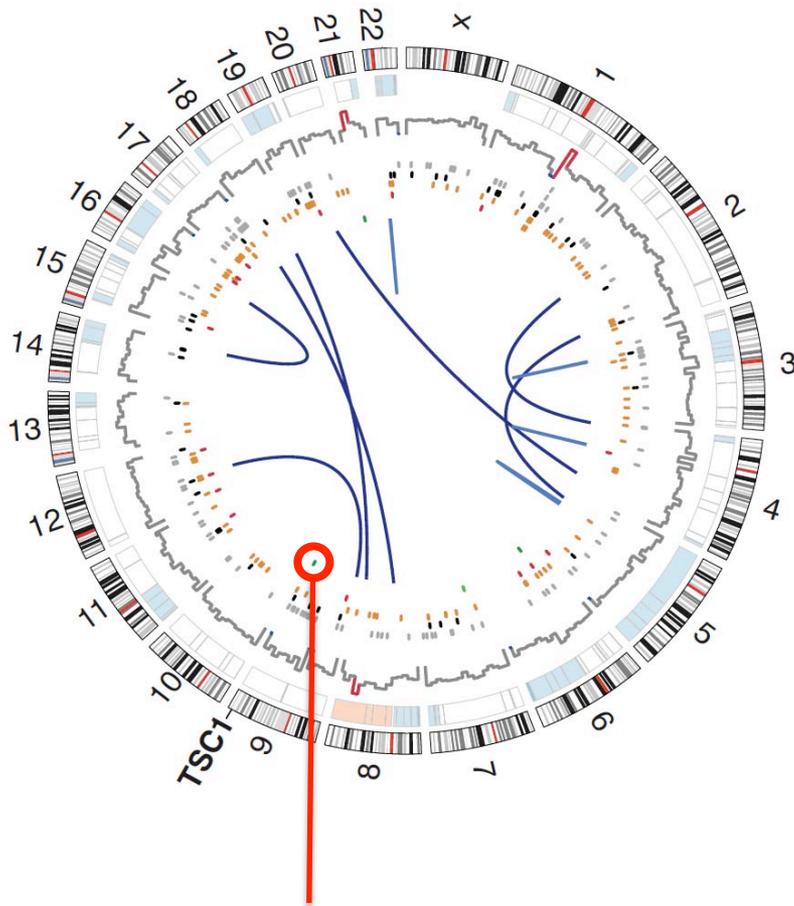
3 month

6 month

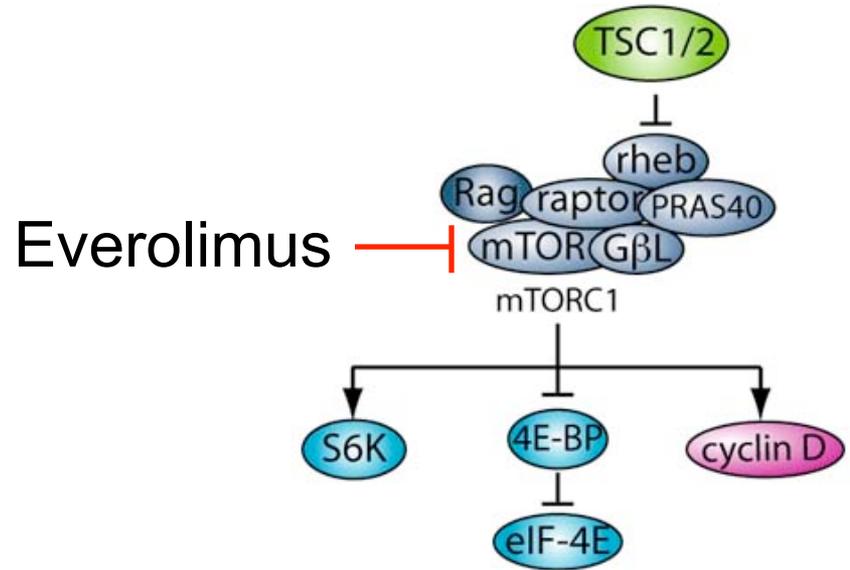
18 month



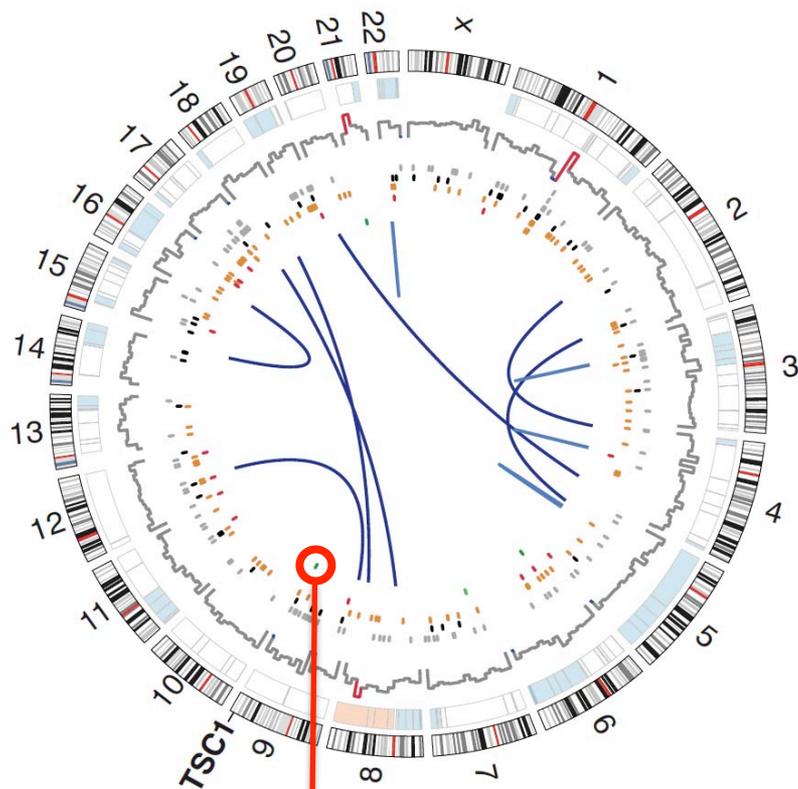
Whole Genome Sequencing Reveals Molecular Basis for Exceptional Response to Everolimus in Bladder Cancer



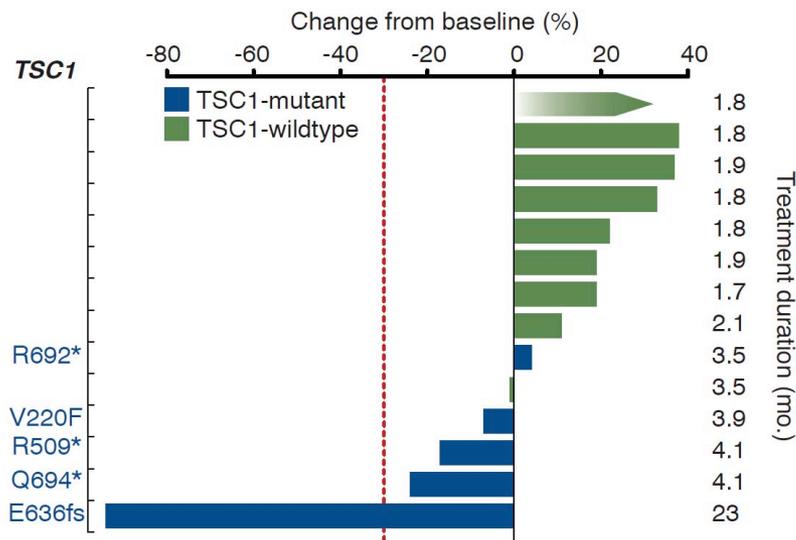
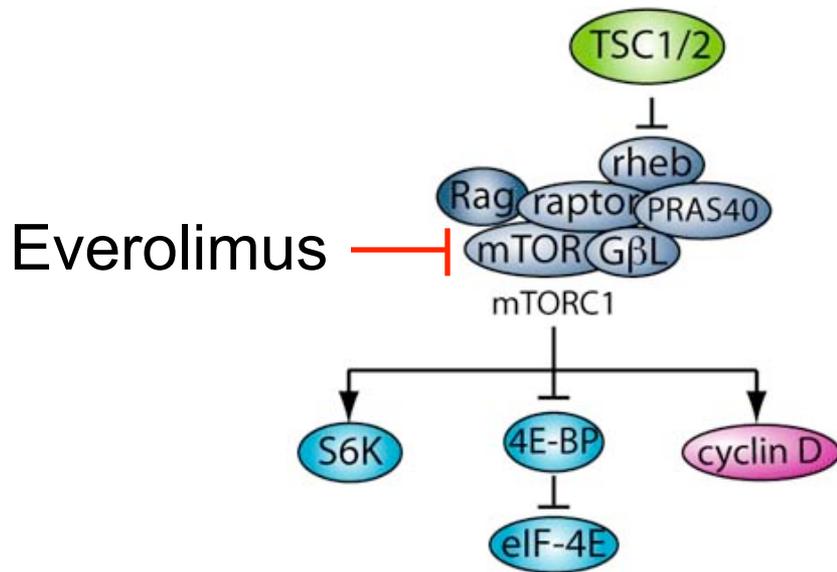
Frameshift mutation in TSC1



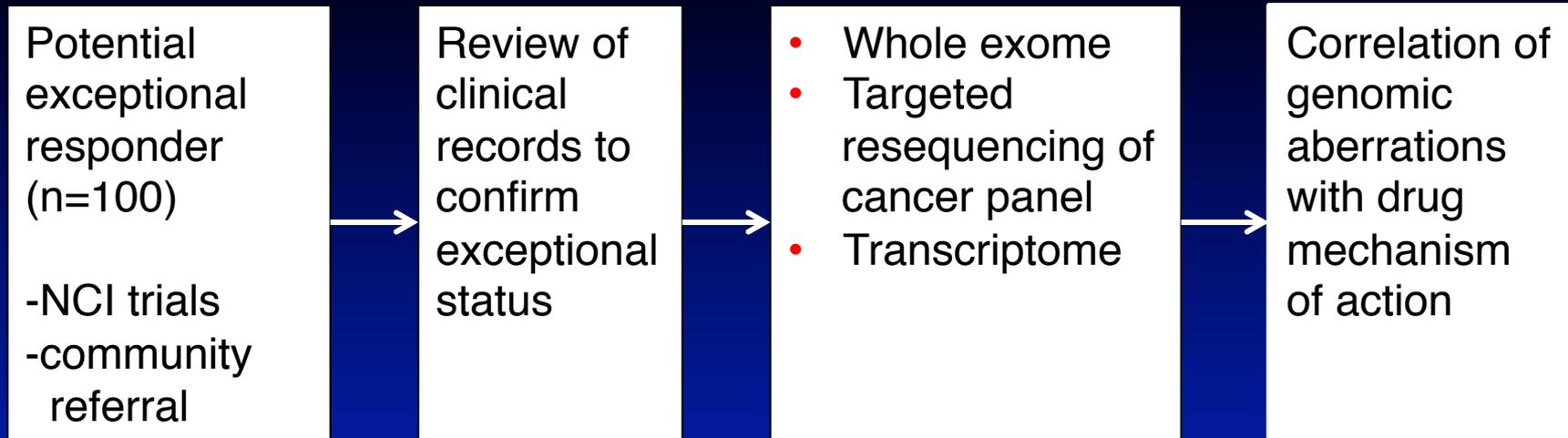
Whole Genome Sequencing Reveals Molecular Basis for Exceptional Response to Everolimus in Bladder Cancer



Frameshift mutation
in TSC1



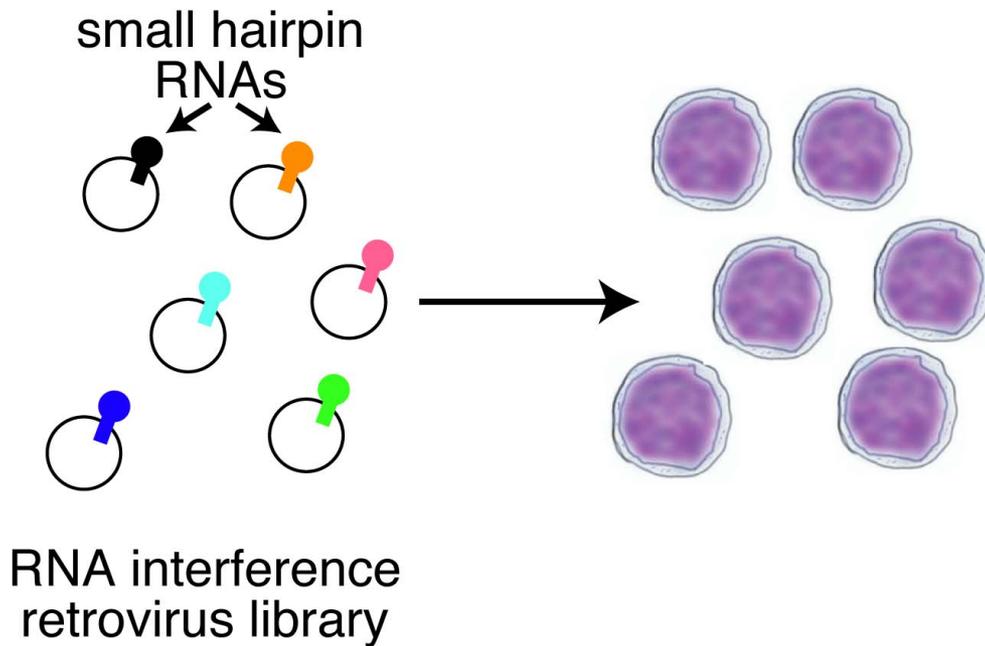
NCI Exceptional Responders Initiative



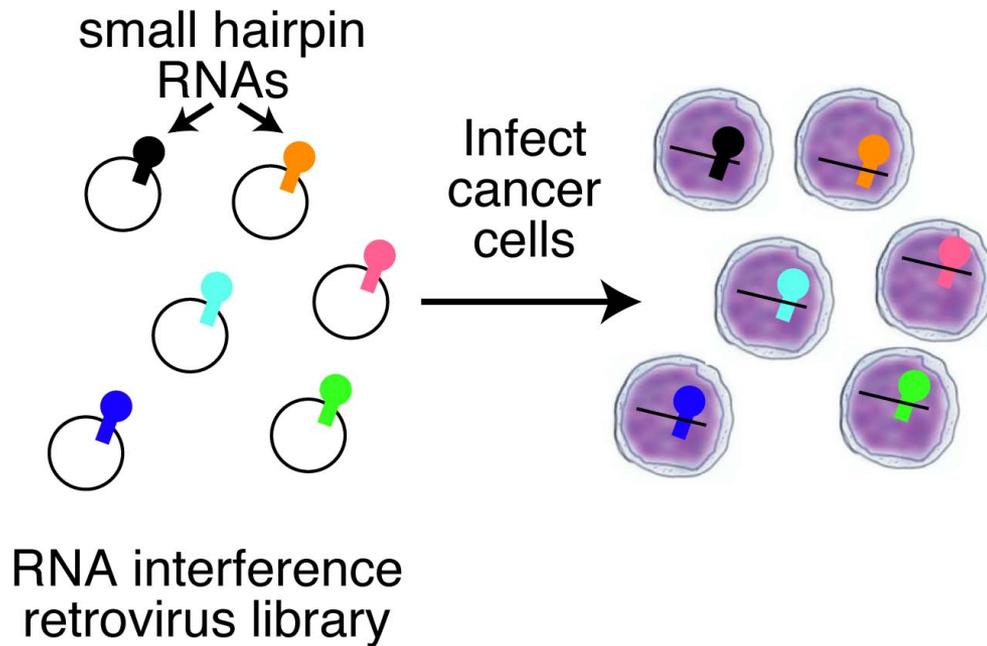


“Achilles Heel”
RNA Interference Screens
to Identify
New Molecular Targets
in Cancer

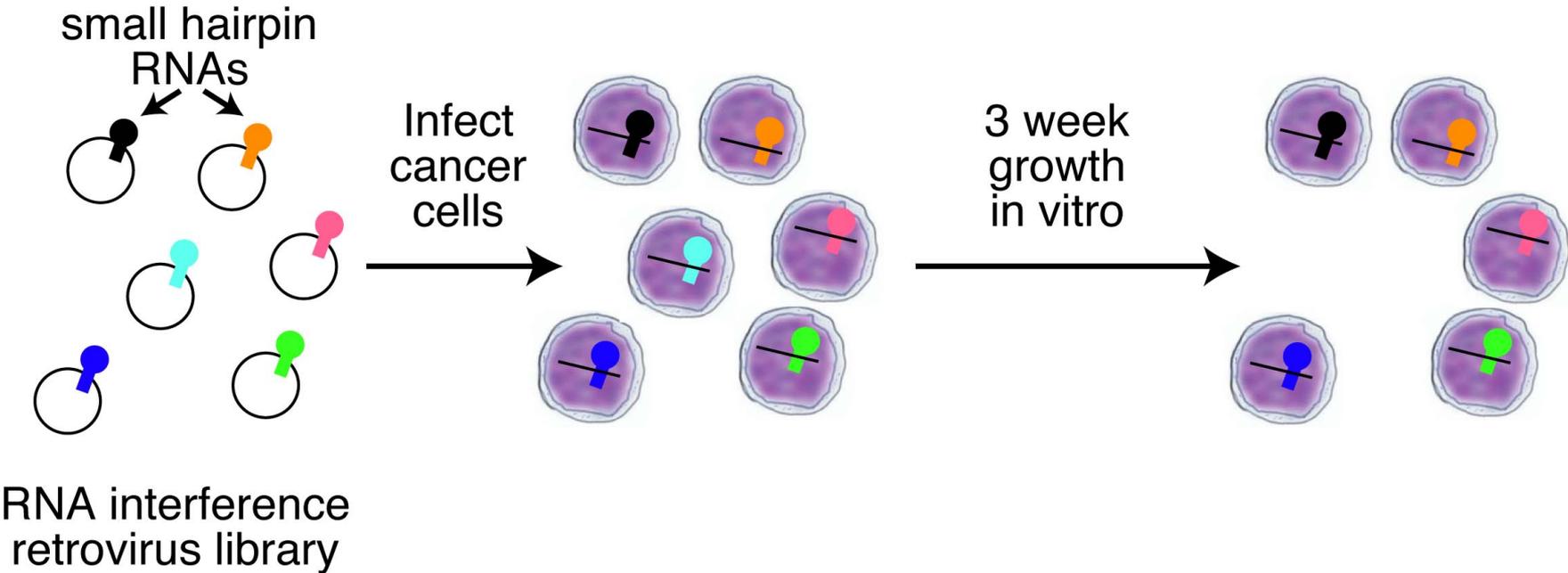
Achilles Heel Screen for Genes Essential for Cancer Cell Proliferation and Survival



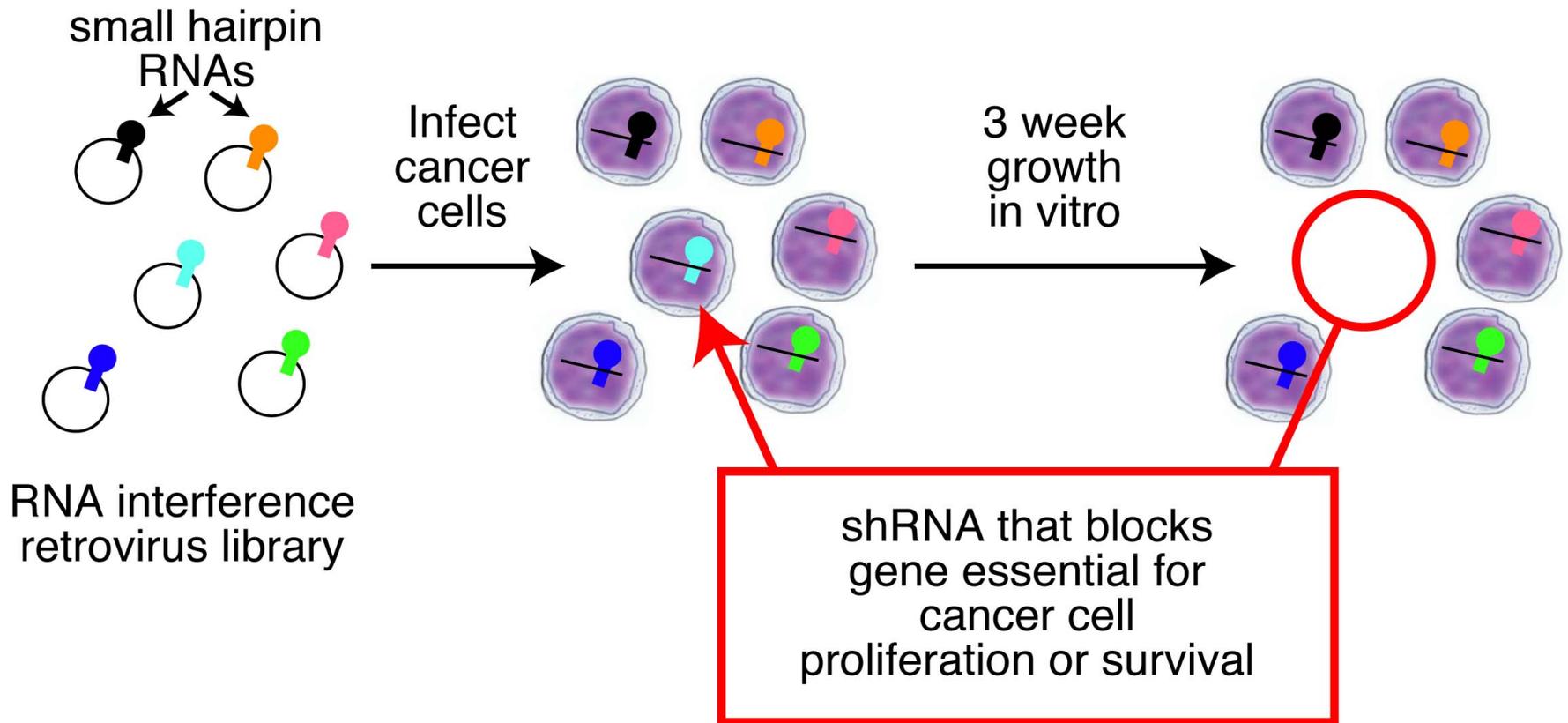
Achilles Heel Screen for Genes Essential for Cancer Cell Proliferation and Survival



Achilles Heel Screen for Genes Essential for Cancer Cell Proliferation and Survival



Achilles Heel Screen for Genes Essential for Cancer Cell Proliferation and Survival

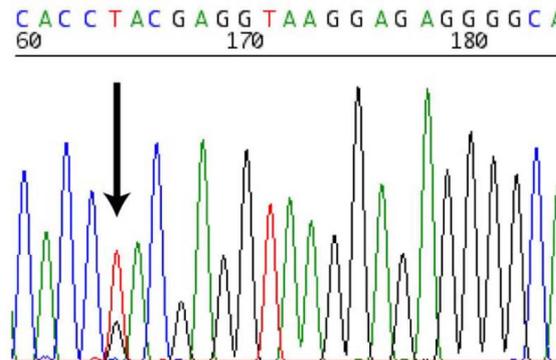


Interplay of Functional and Structural Genomics

Genome-wide
RNA interference screen



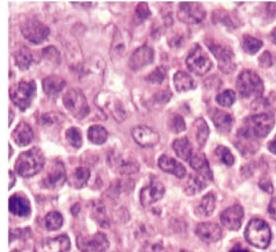
Oncogenic somatic mutation



Essential
cancer
pathways

Dissecting Cancer Into Molecularly and Clinically Distinct Subtypes by Gene Expression Profiling

Diffuse Large B Cell
Lymphoma
(DLBCL)



Diffuse large B cell lymphoma

~40% of Non-Hodgkin lymphomas

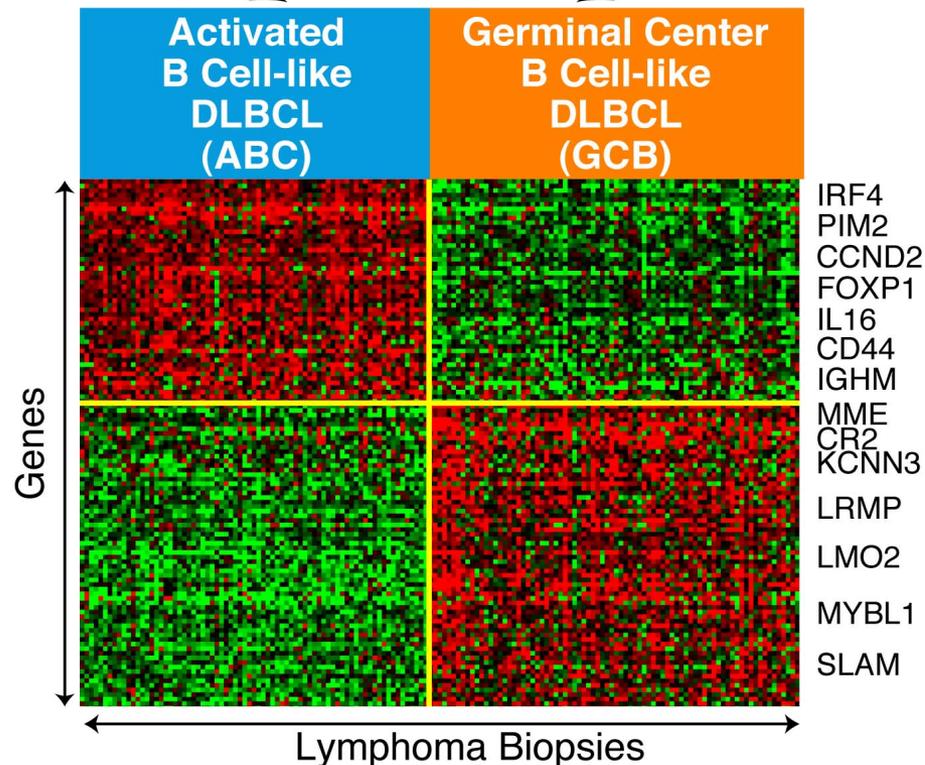
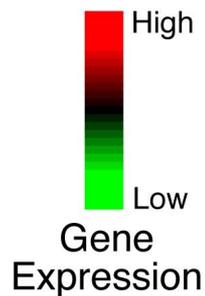
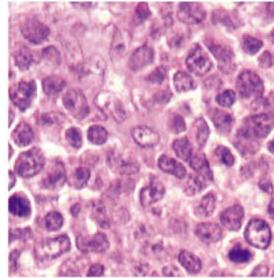
~23,000 new diagnoses/yr

~50% cure rate

~10,000 deaths/yr

Dissecting Cancer Into Molecularly and Clinically Distinct Subtypes by Gene Expression Profiling

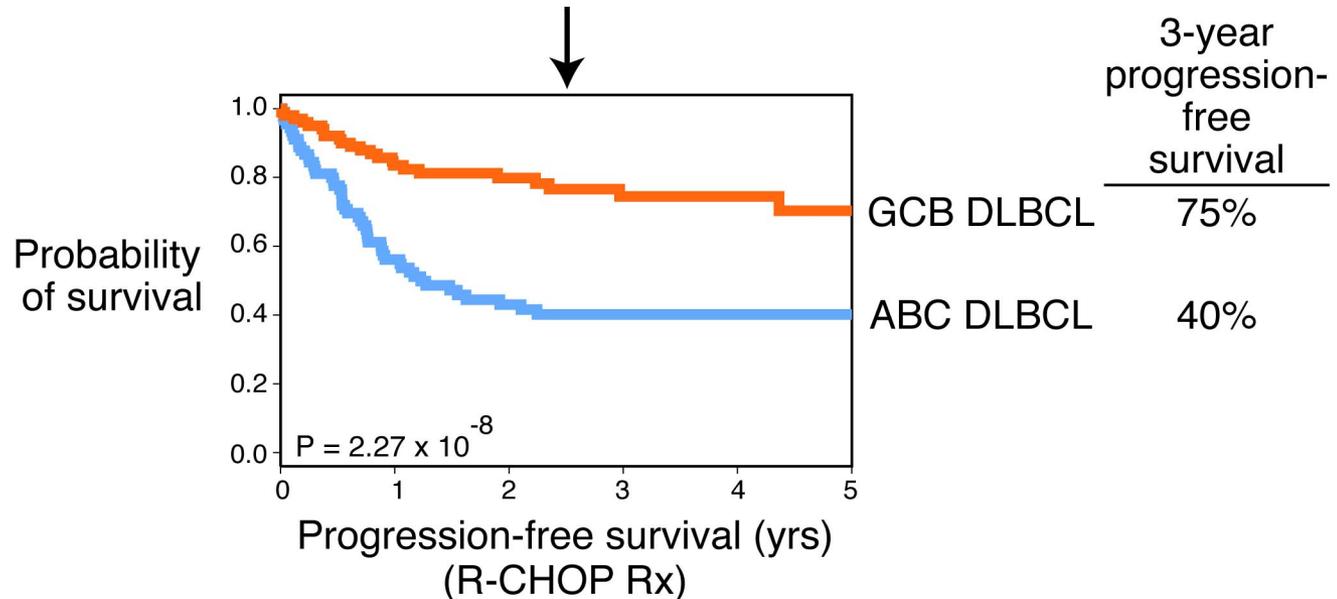
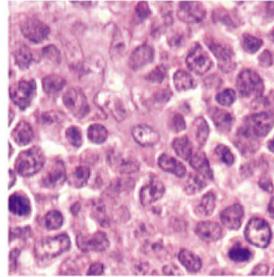
Diffuse Large B Cell
Lymphoma
(DLBCL)



Subtype-specific gene expression signatures

Dissecting Cancer Into Molecularly and Clinically Distinct Subtypes by Gene Expression Profiling

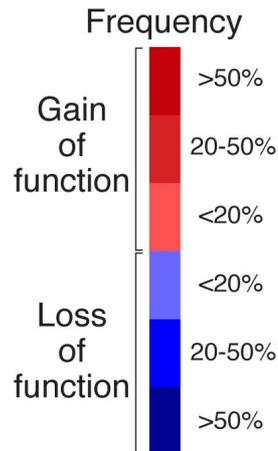
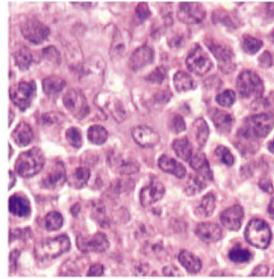
Diffuse Large B Cell
Lymphoma
(DLBCL)



Subtype-specific response
To chemotherapy

Dissecting Cancer Into Molecularly and Clinically Distinct Subtypes by Gene Expression Profiling

Diffuse Large B Cell Lymphoma (DLBCL)



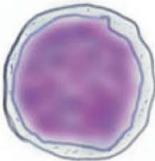
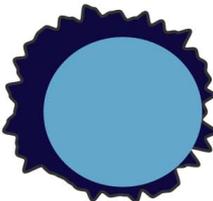
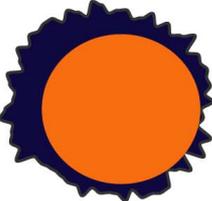
Activated B Cell-like DLBCL (ABC)	Germinal Center B Cell-like DLBCL (GCB)
MYD88 L265P*	BCL2 t(14;18)
CD79B*; CD79A*	EZH2*
SPIB amp	MEF2B*; MEF2C*
BCL2 amp	MDM2 amp
	miR-17-92 amp
	SGK1*
CDKN2A del	PTEN*/del
INK4a/ARF del	S1PR2*
TNFAIP3*/del	GNA13*
PRDM1*/del	TNFRSF14*/del
	FAS*/del

Subtype-specific genetic aberrations

Molecular Pathogenesis of Diffuse Large B Cell Lymphoma

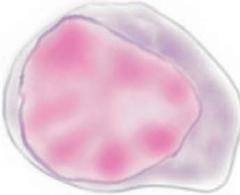
GCB DLBCL

ABC DLBCL



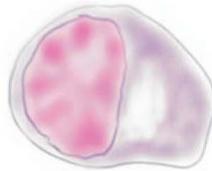
Germinal center B cell

NF- κ B \rightarrow IRF4

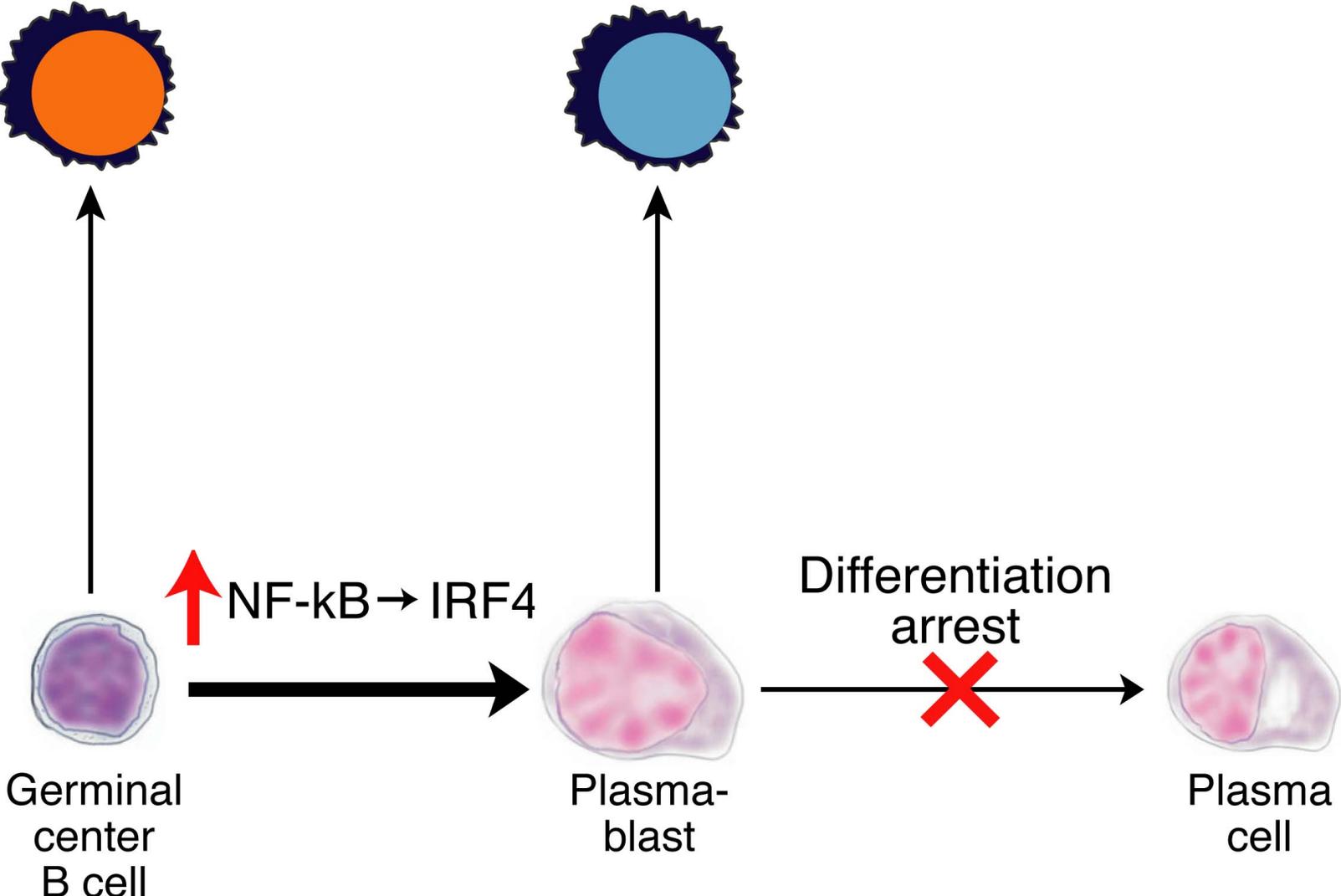


Plasma-blast

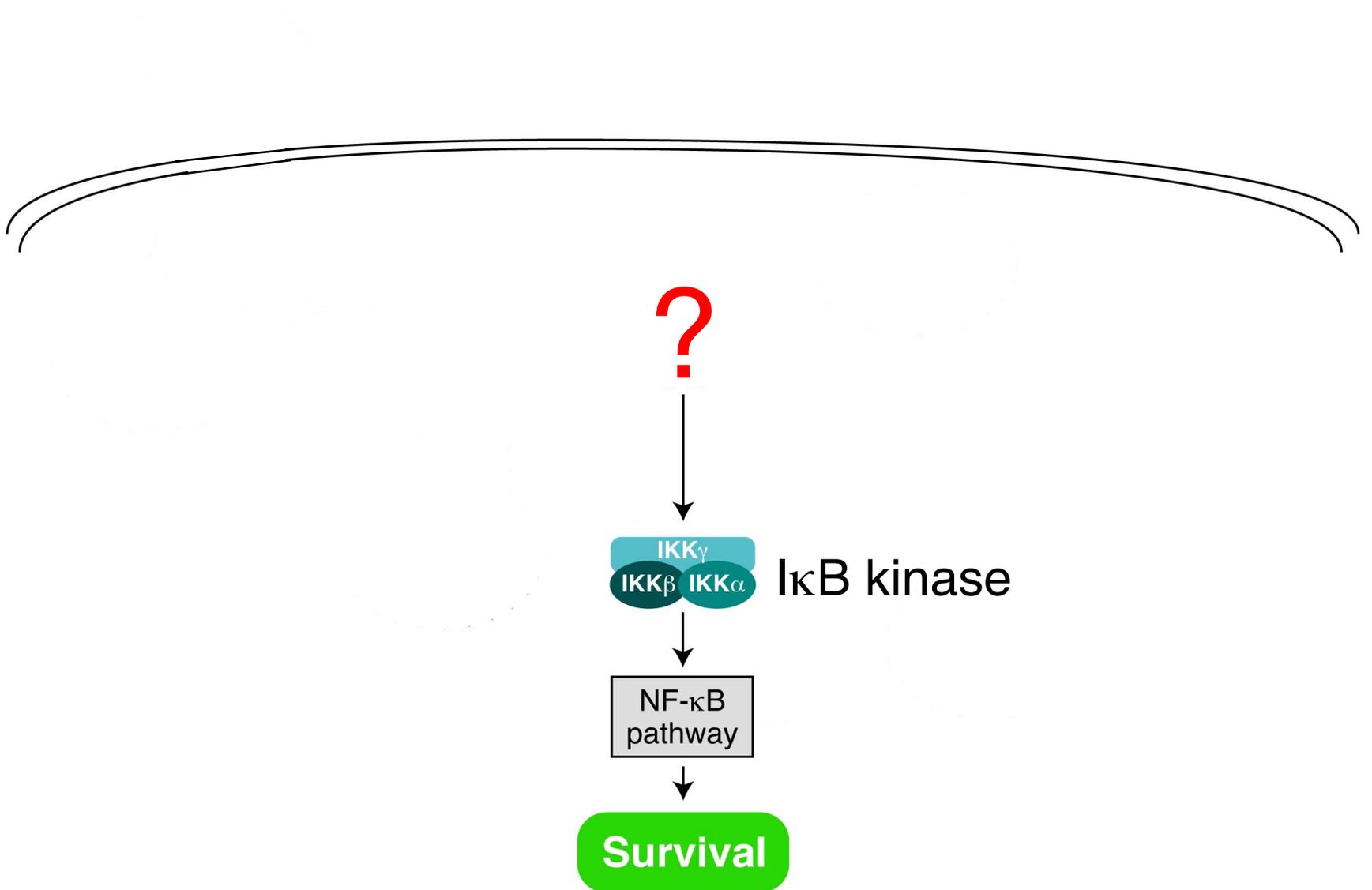
Differentiation arrest



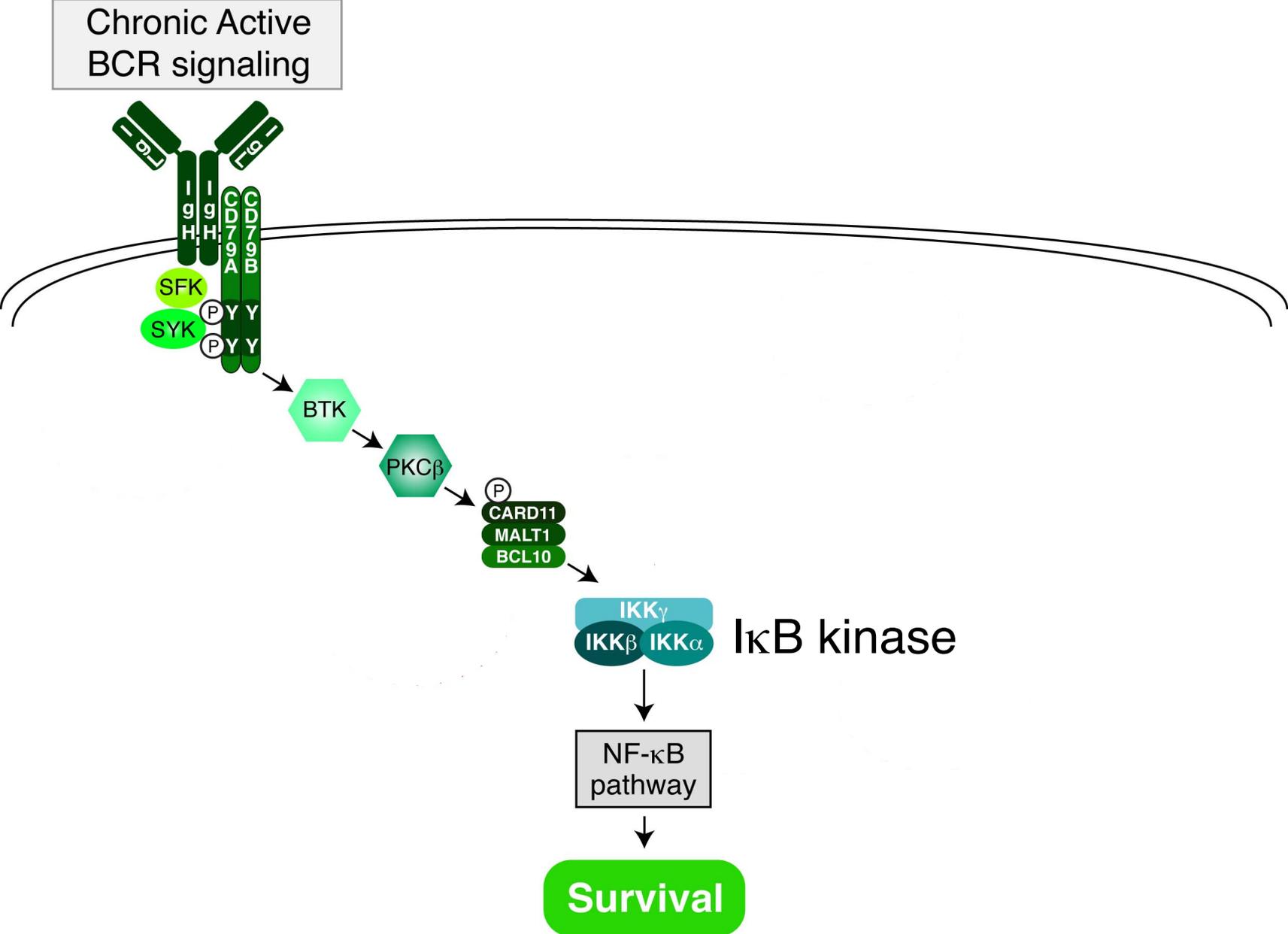
Plasma cell



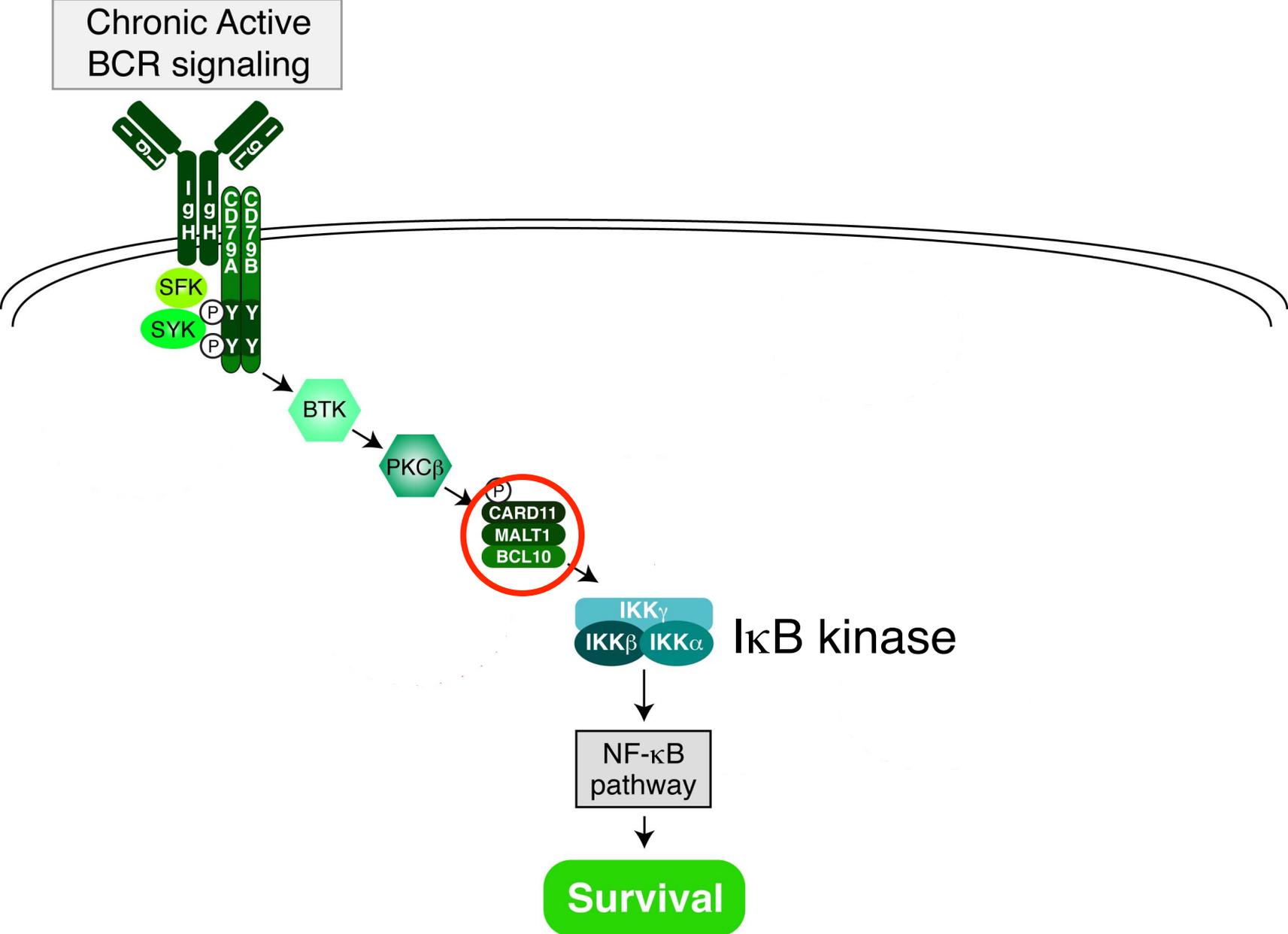
Oncogenic Activation of NF- κ B in ABC DLBCL



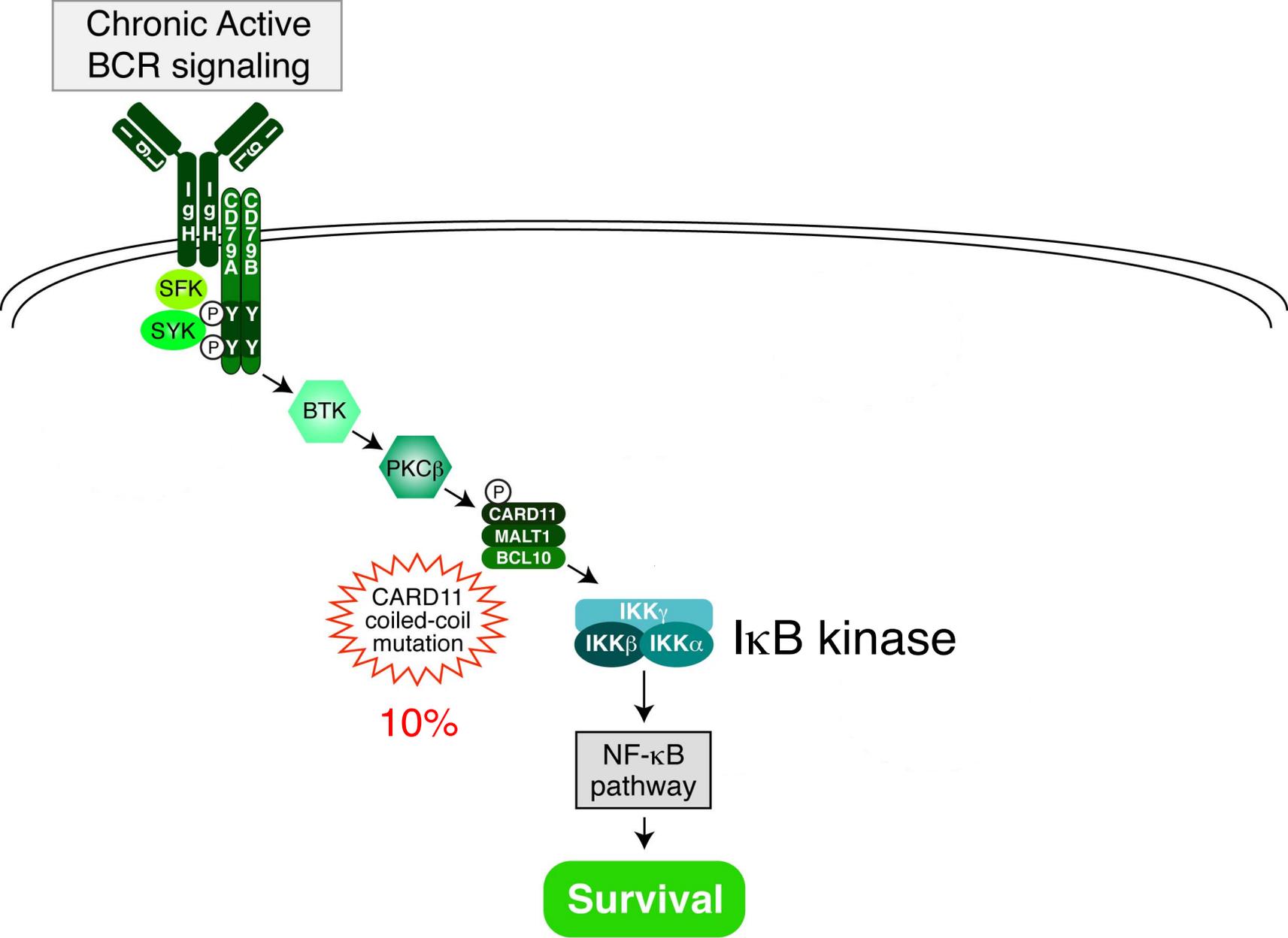
Chronic Active B Cell Receptor Signaling in ABC DLBCL



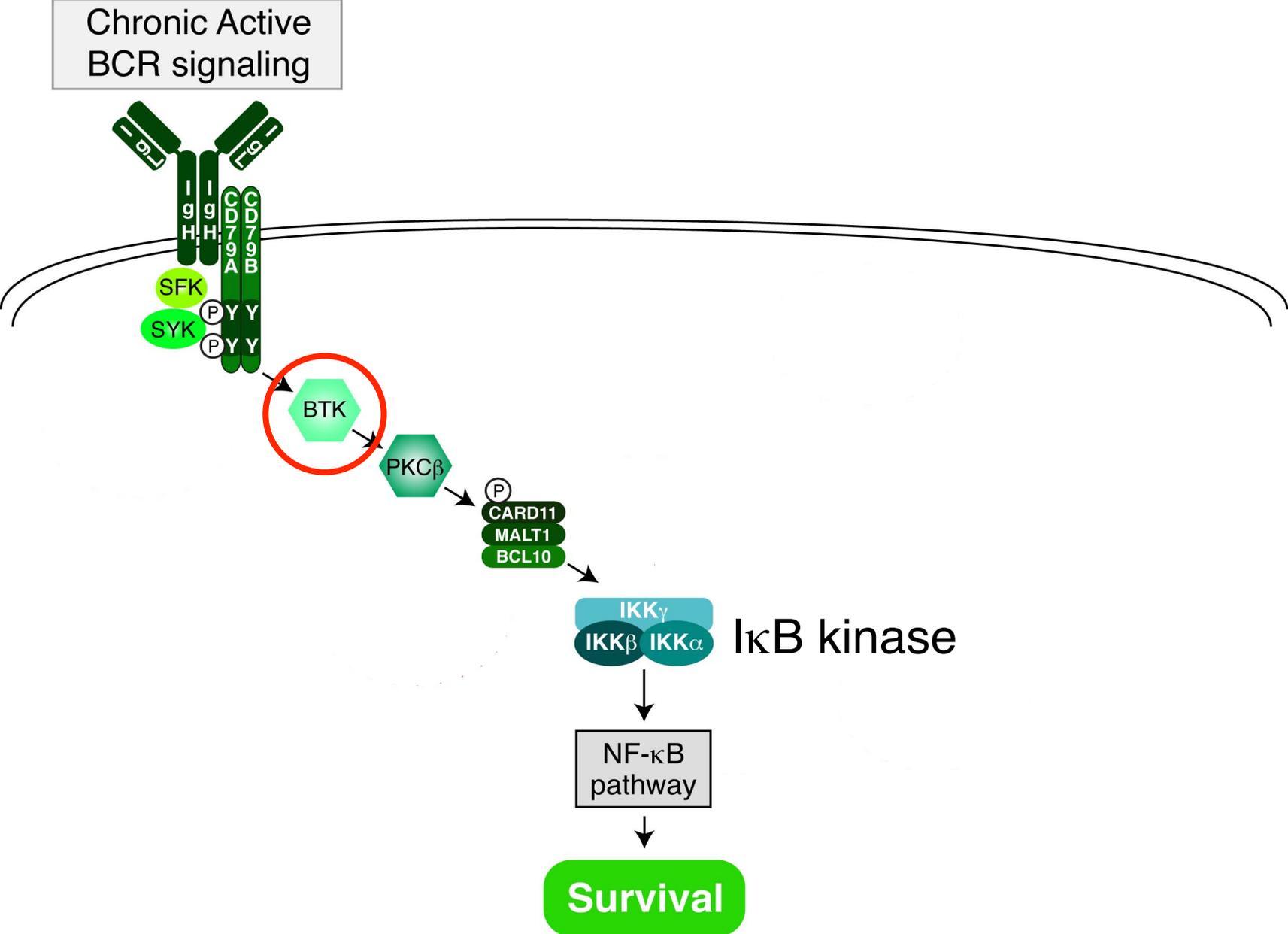
Chronic Active B Cell Receptor Signaling in ABC DLBCL



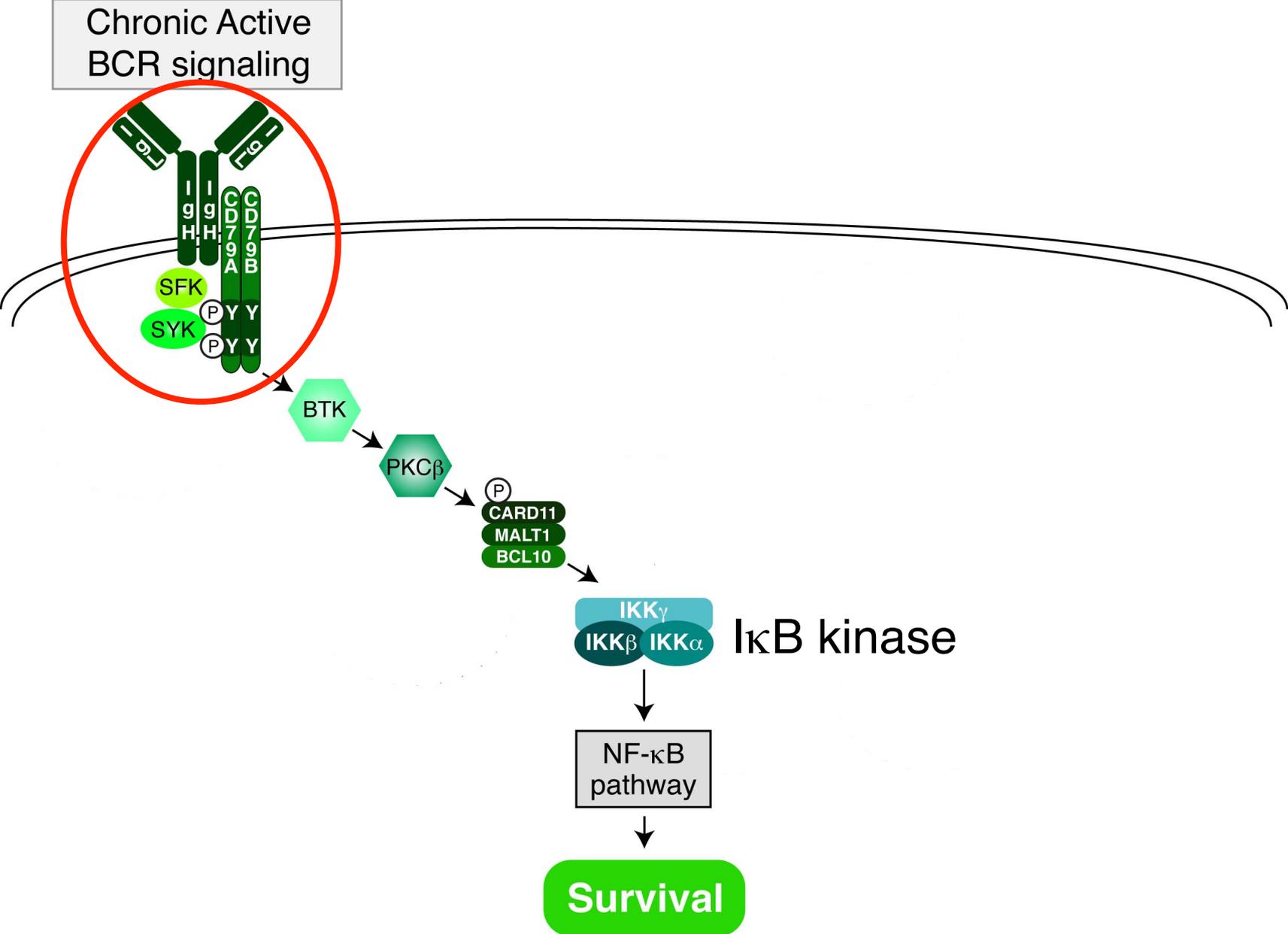
Chronic Active B Cell Receptor Signaling in ABC DLBCL



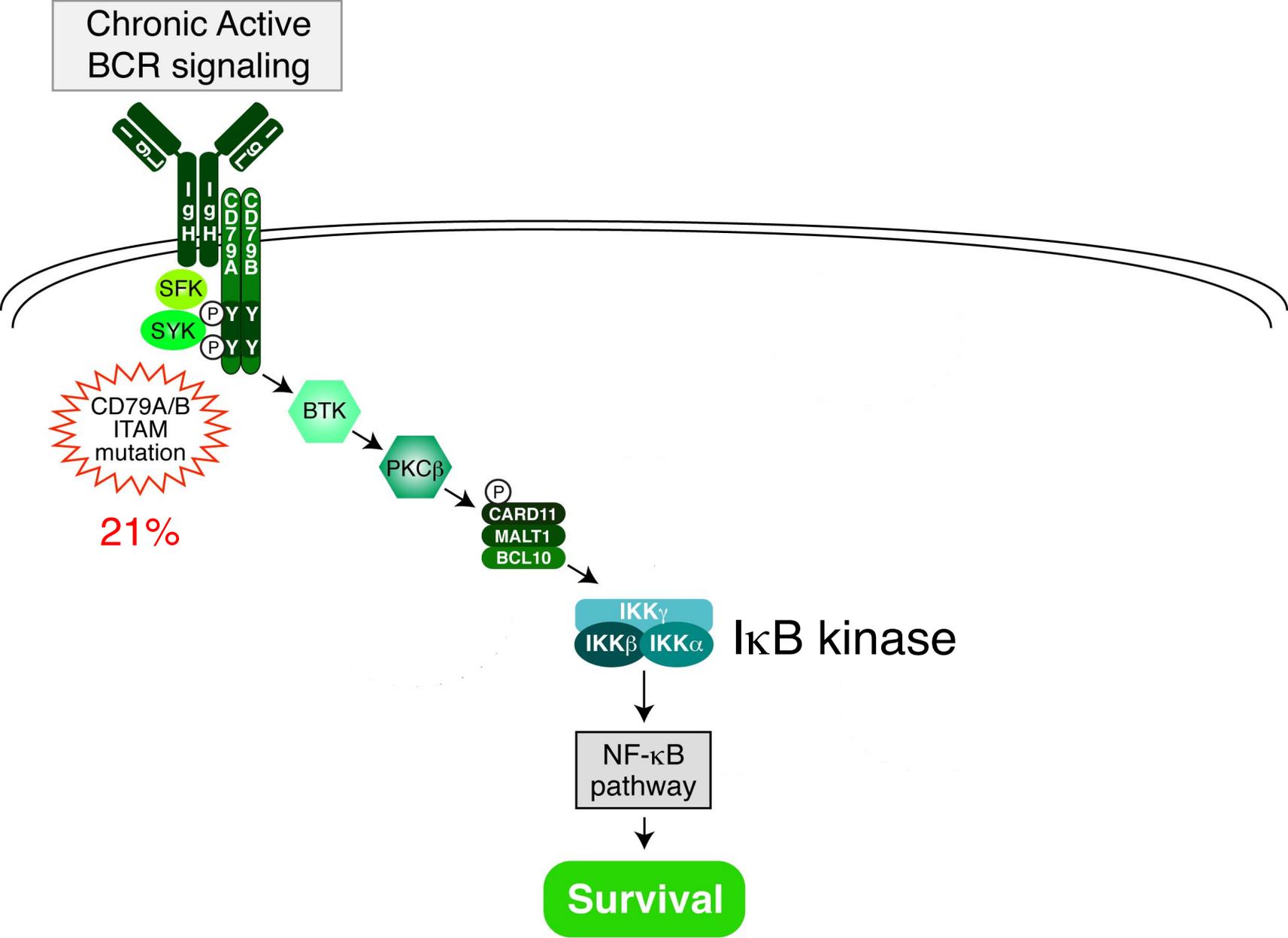
Chronic Active B Cell Receptor Signaling in ABC DLBCL



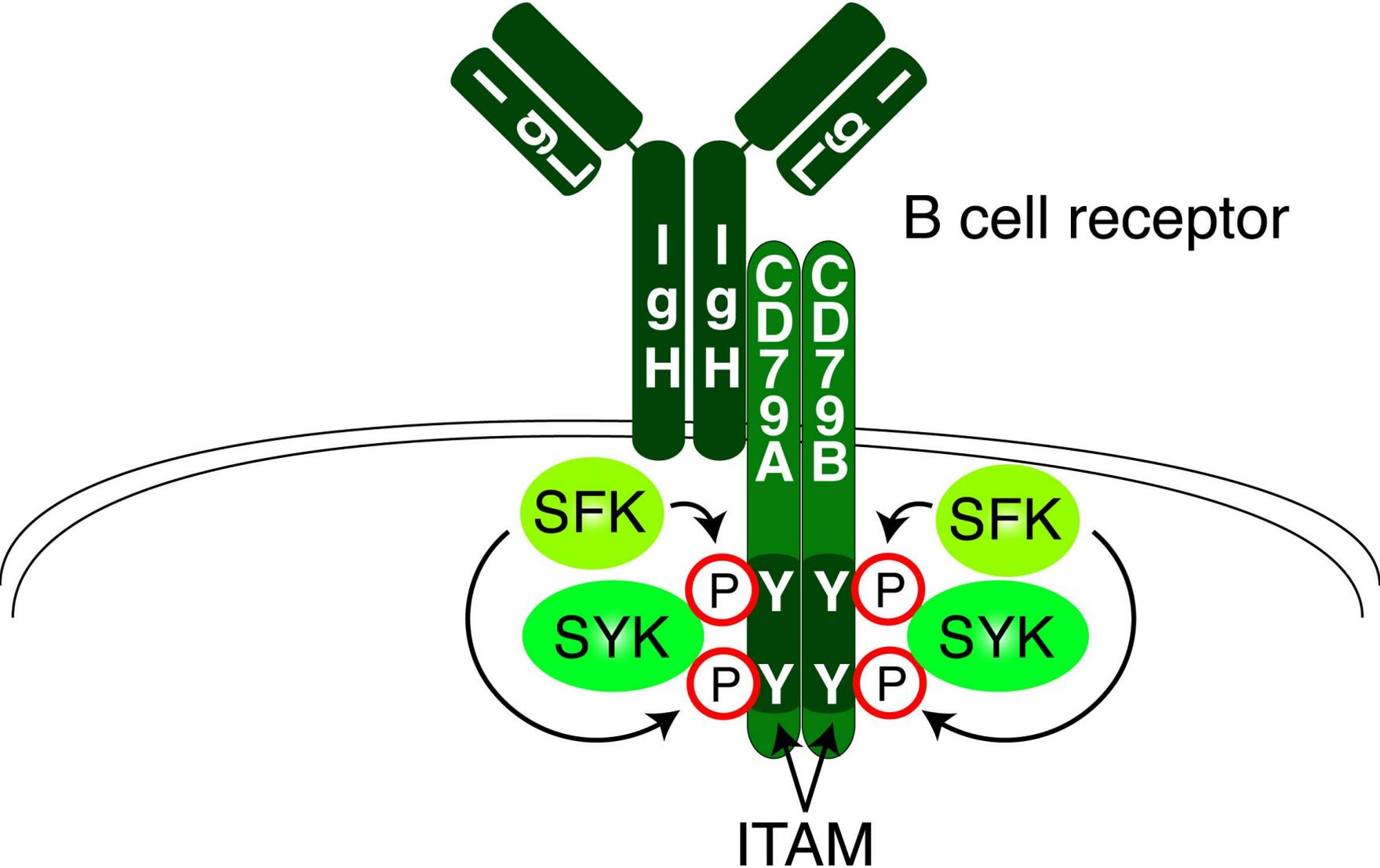
Chronic Active B Cell Receptor Signaling in ABC DLBCL



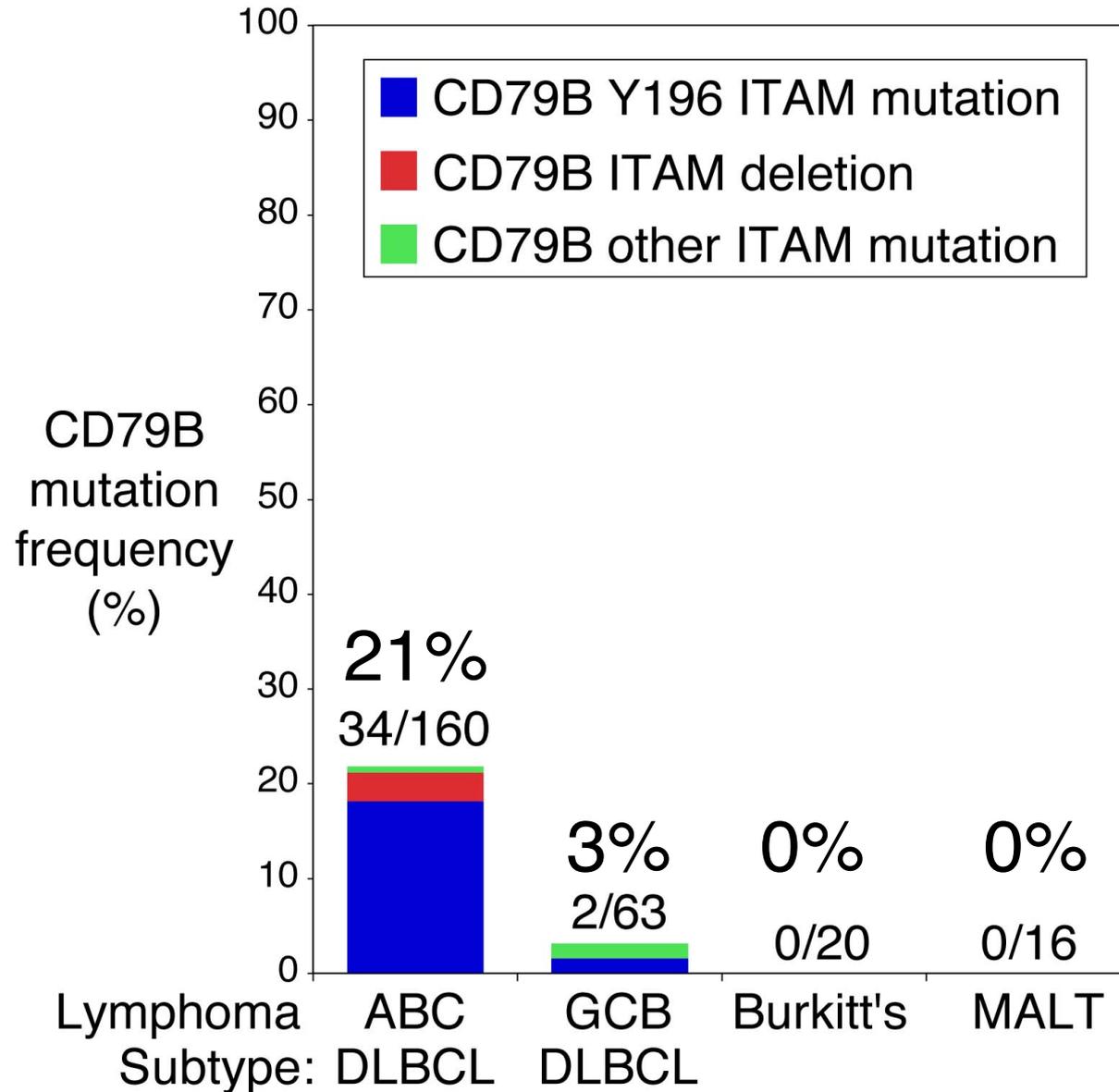
Chronic Active B Cell Receptor Signaling in ABC DLBCL



Critical Role of ITAM Motifs in B Cell Receptor Signaling

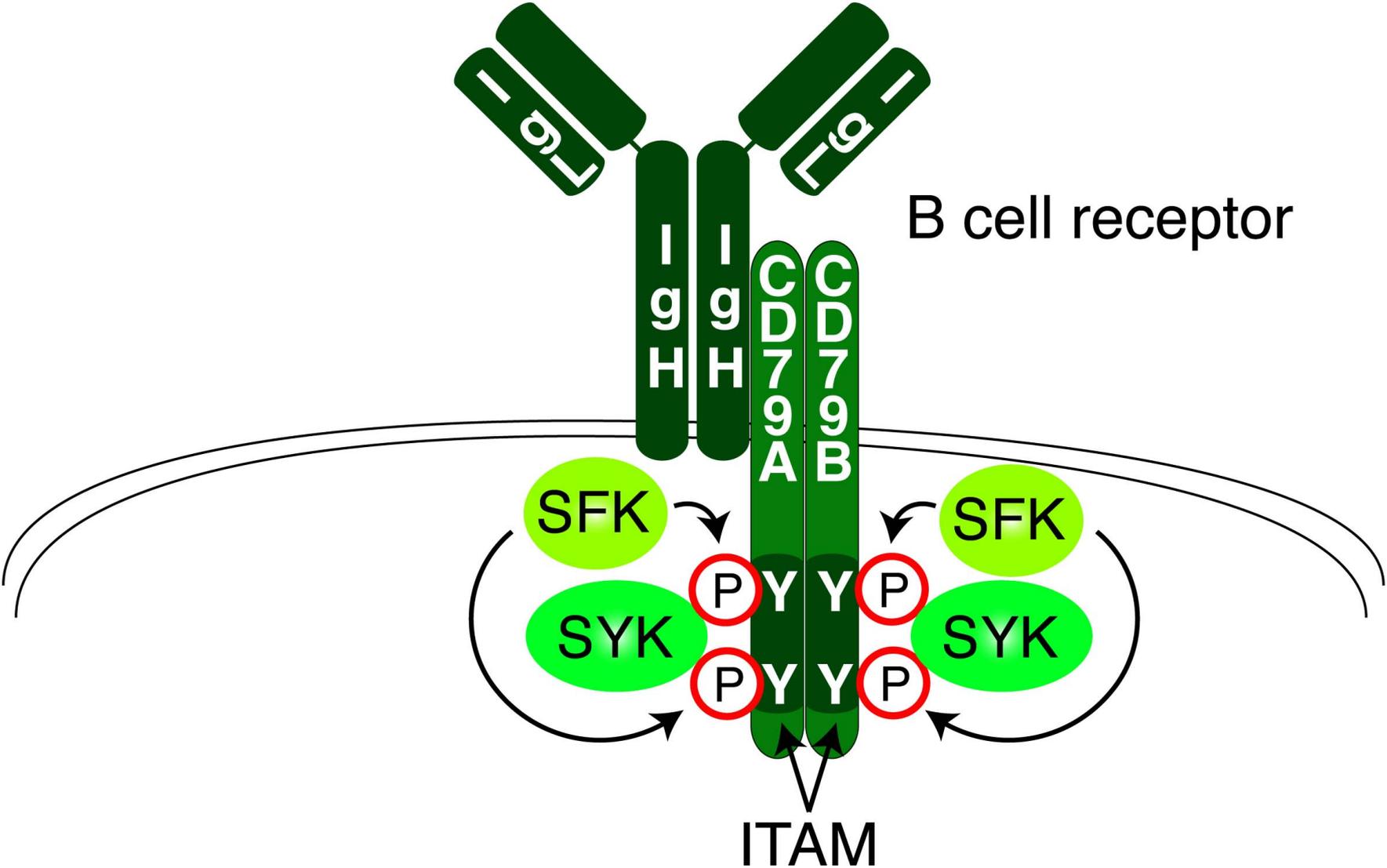


Preferential Mutation of CD79B in ABC DLBCL

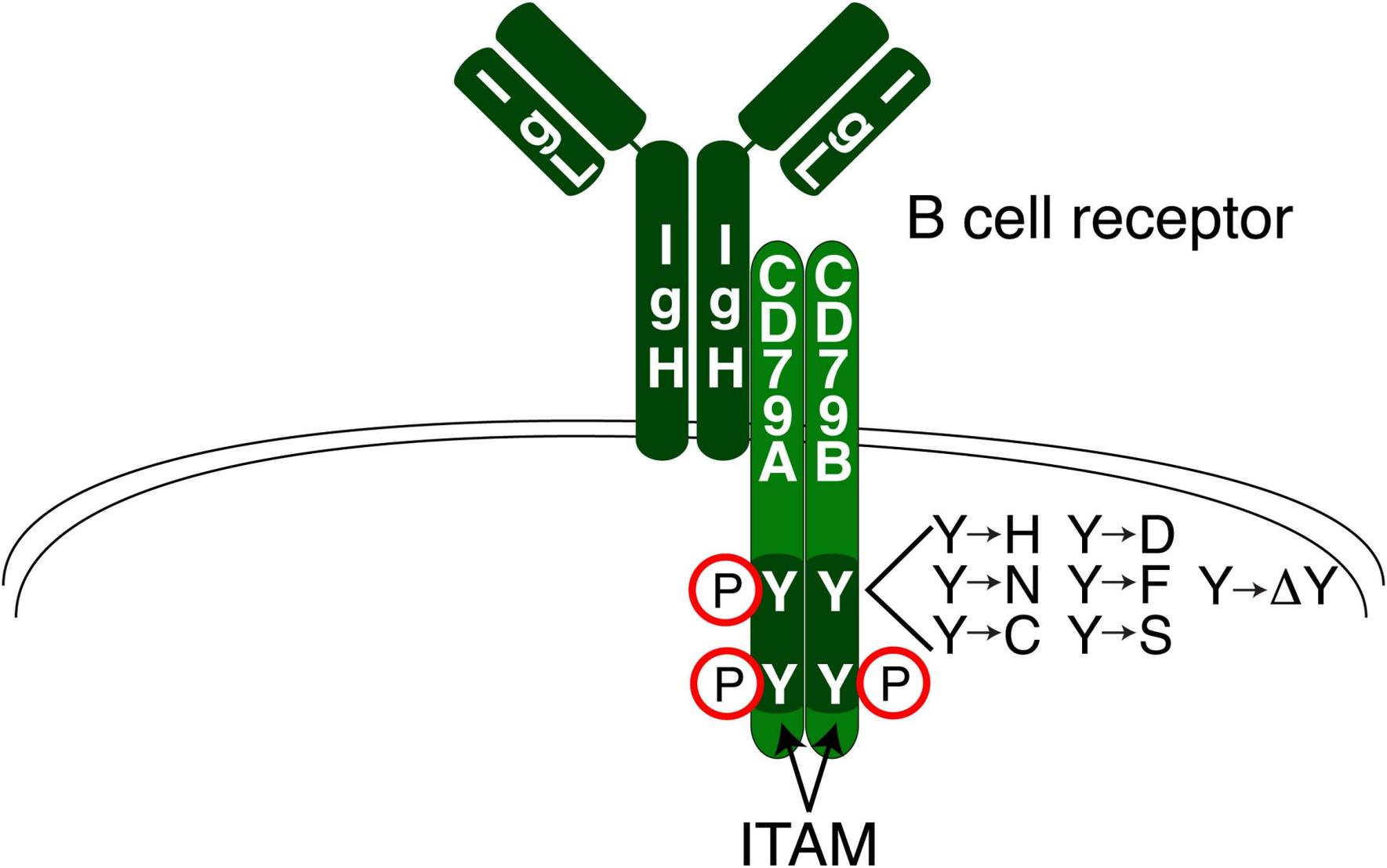


What Are the Functional Consequences of
CD79 Mutation in ABC DLBCL?

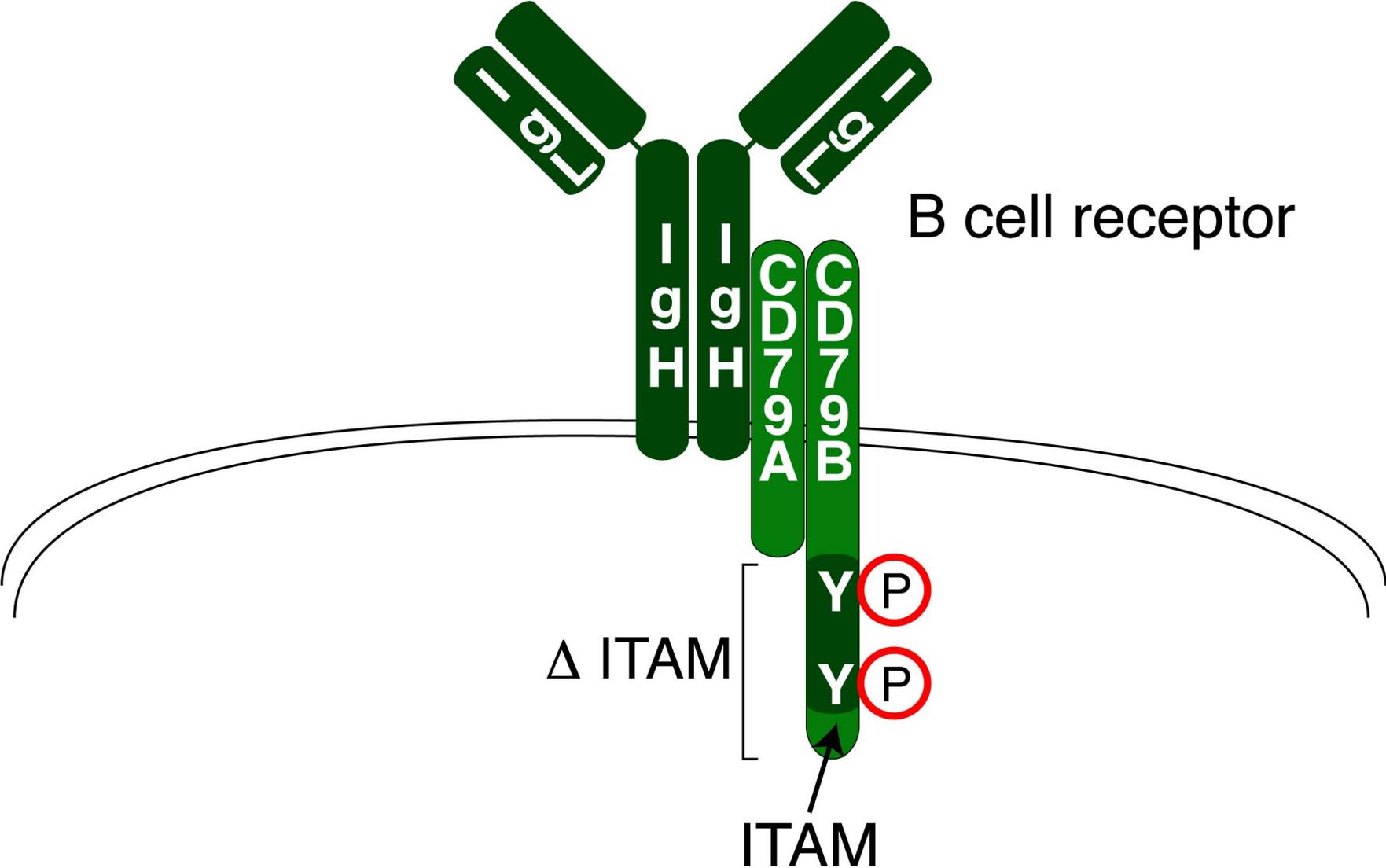
Critical Role of ITAM Motifs in B Cell Receptor Signaling



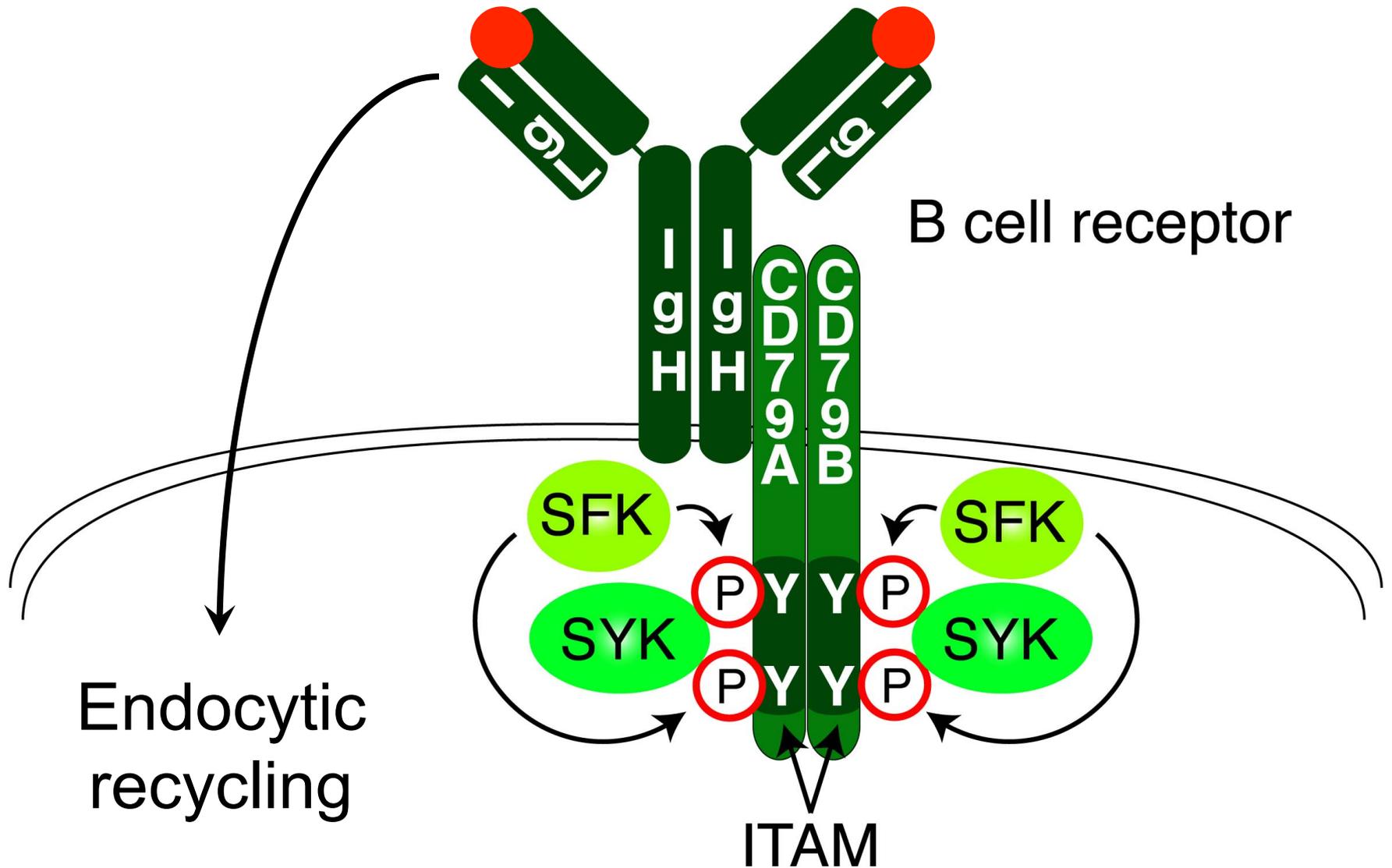
CD79B Mutations in ABC DLBCL Disrupt the ITAM Motif



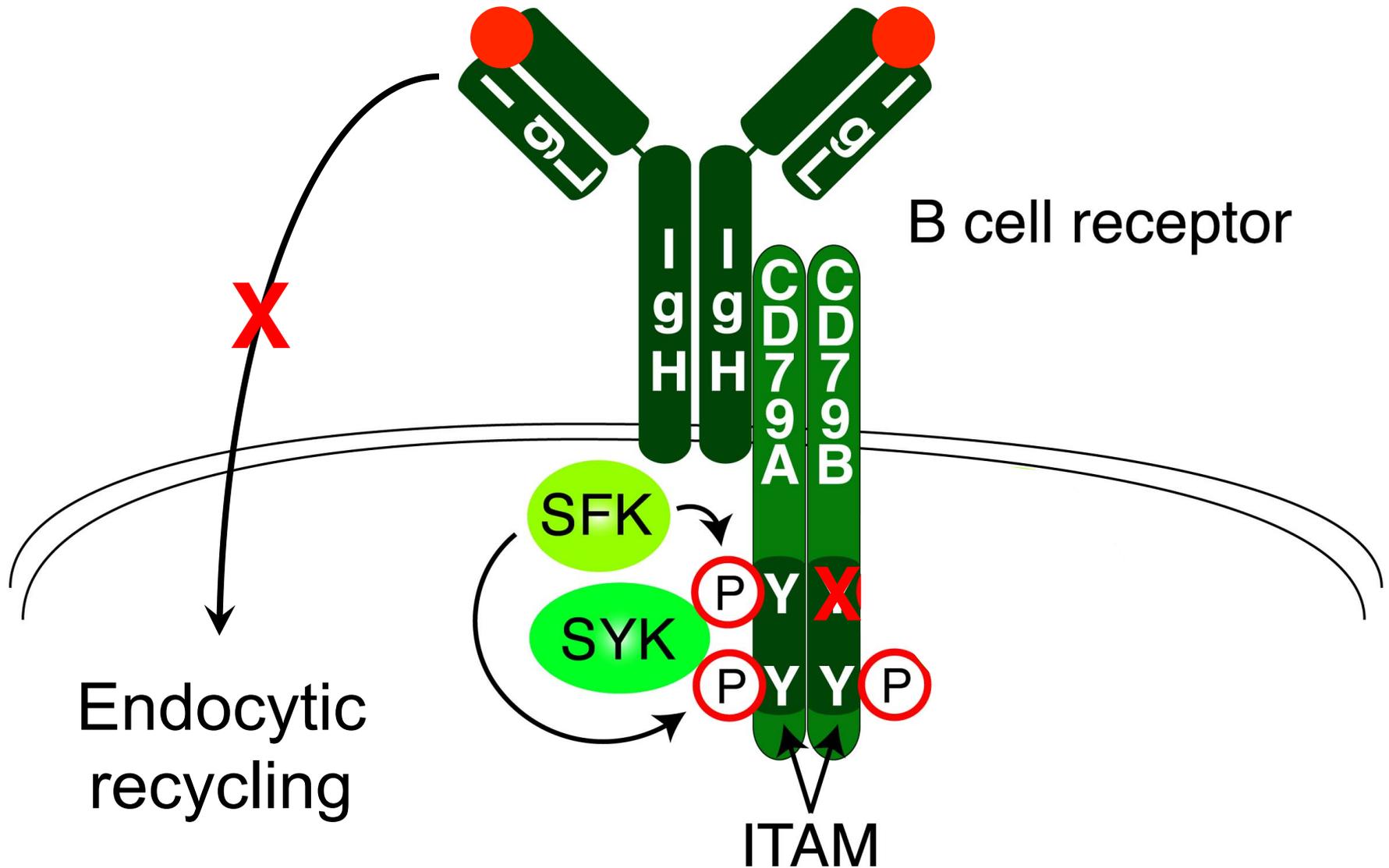
CD79A Deletions in ABC DLBCL Disrupt the ITAM Motif



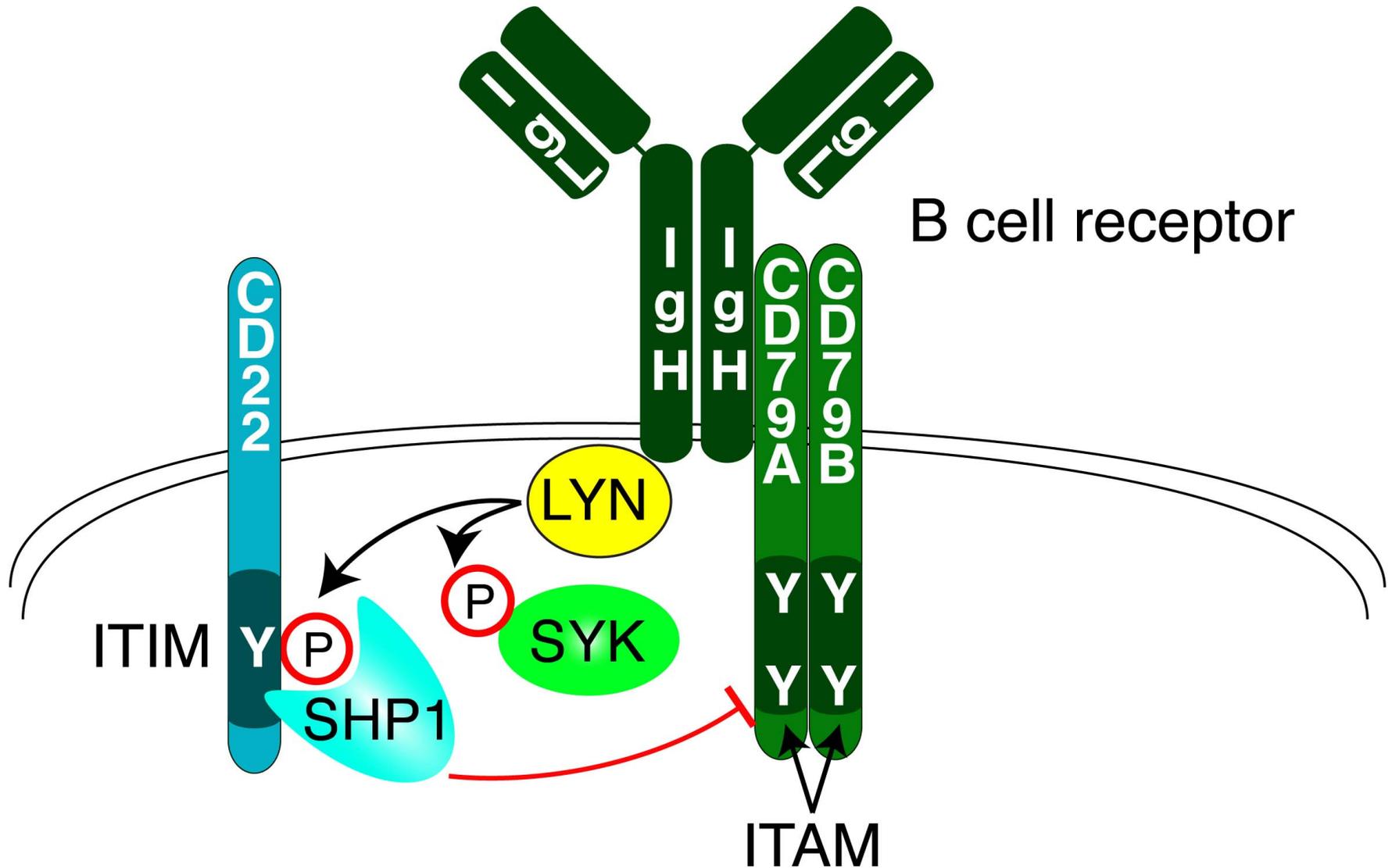
Antigenic Stimulate Promotes Endocytic Recycling of the B Cell Receptor



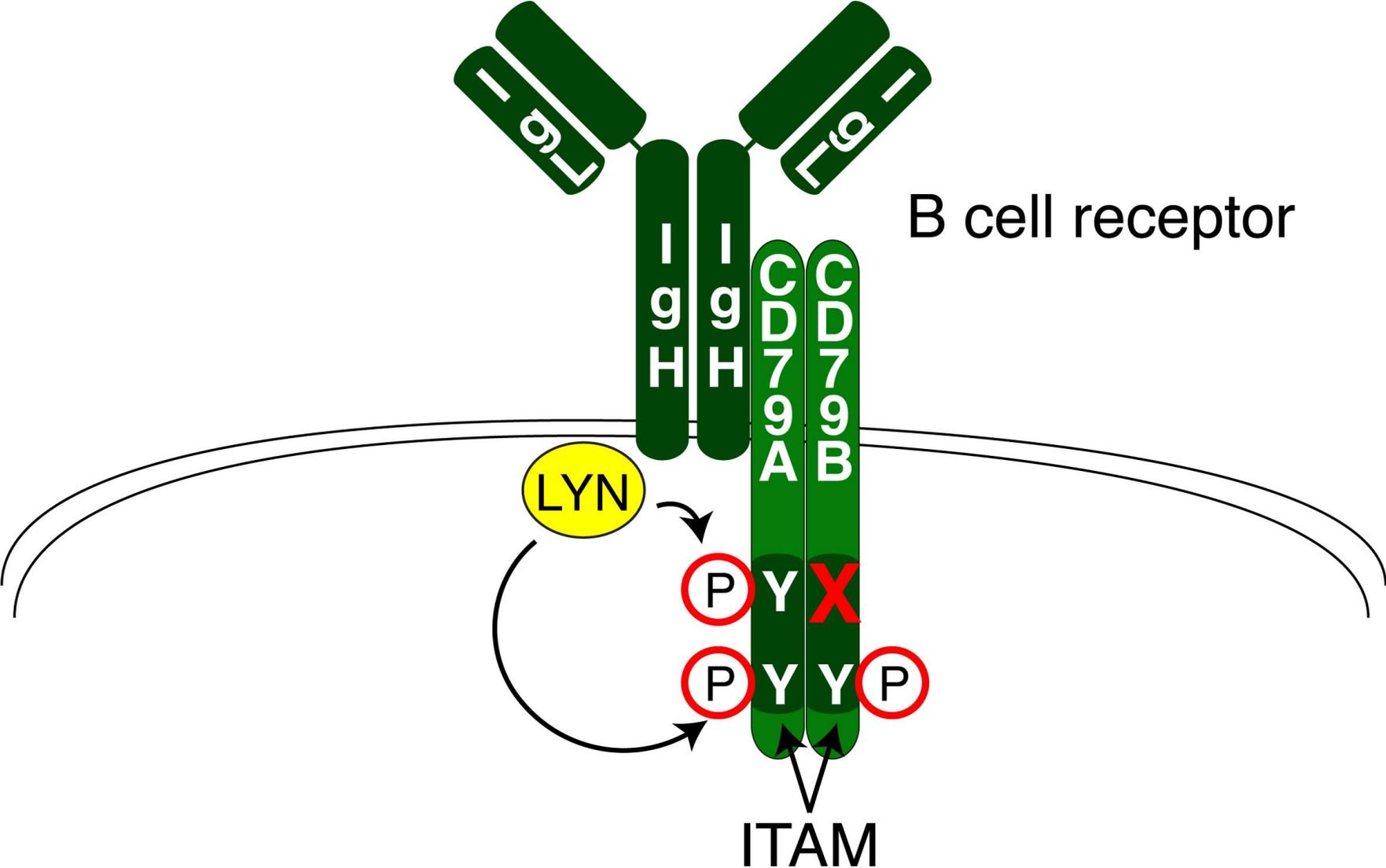
Lymphoma-derived CD79B Mutations Block Endocytic Recycling of the B Cell Receptor



LYN Attenuates B Cell Receptor Signaling



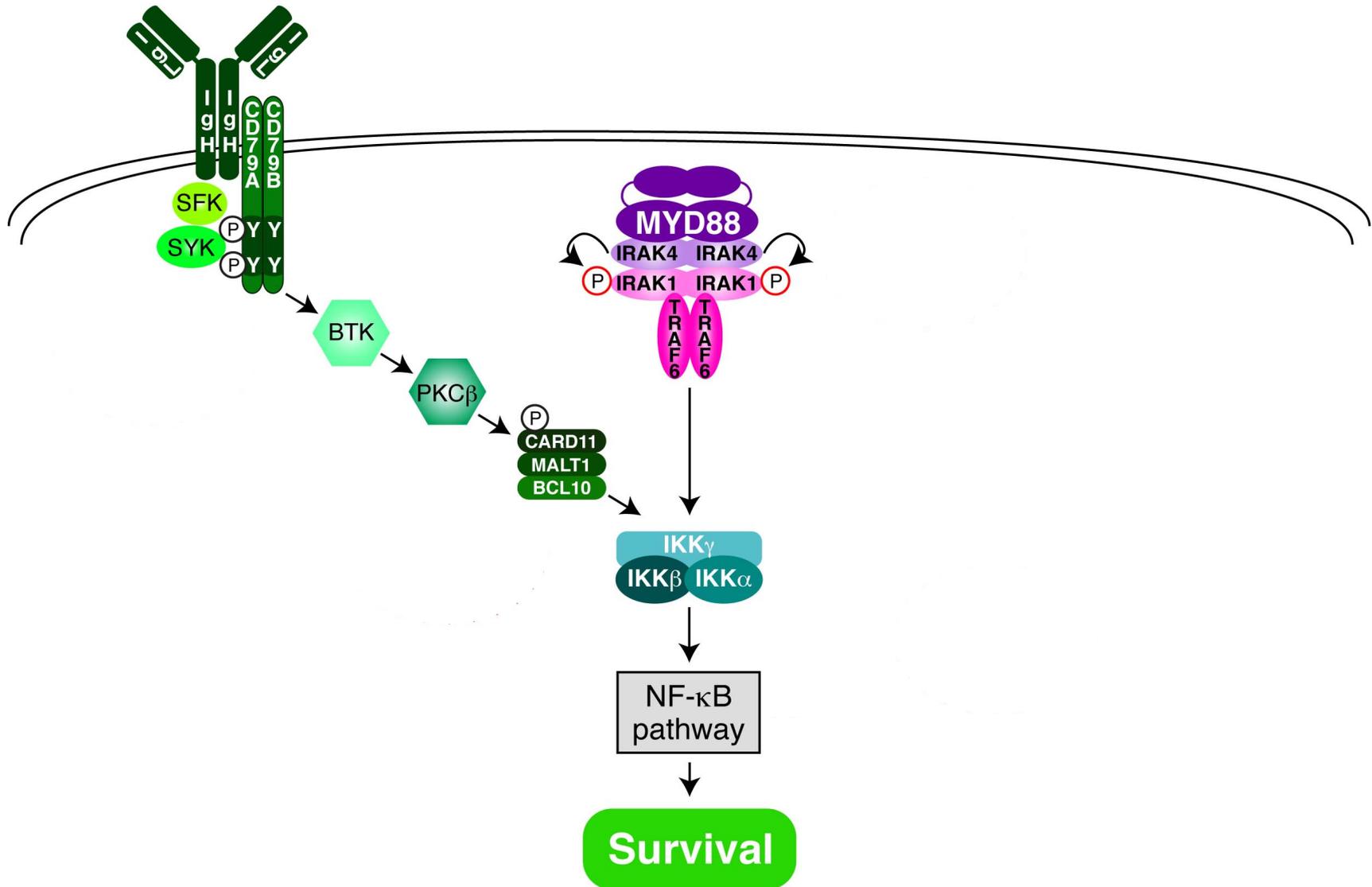
CD79B Mutants Decrease Negative Feedback by LYN



Constitutive MYD88 Signaling in ABC DLBCL

Chronic Active BCR signaling

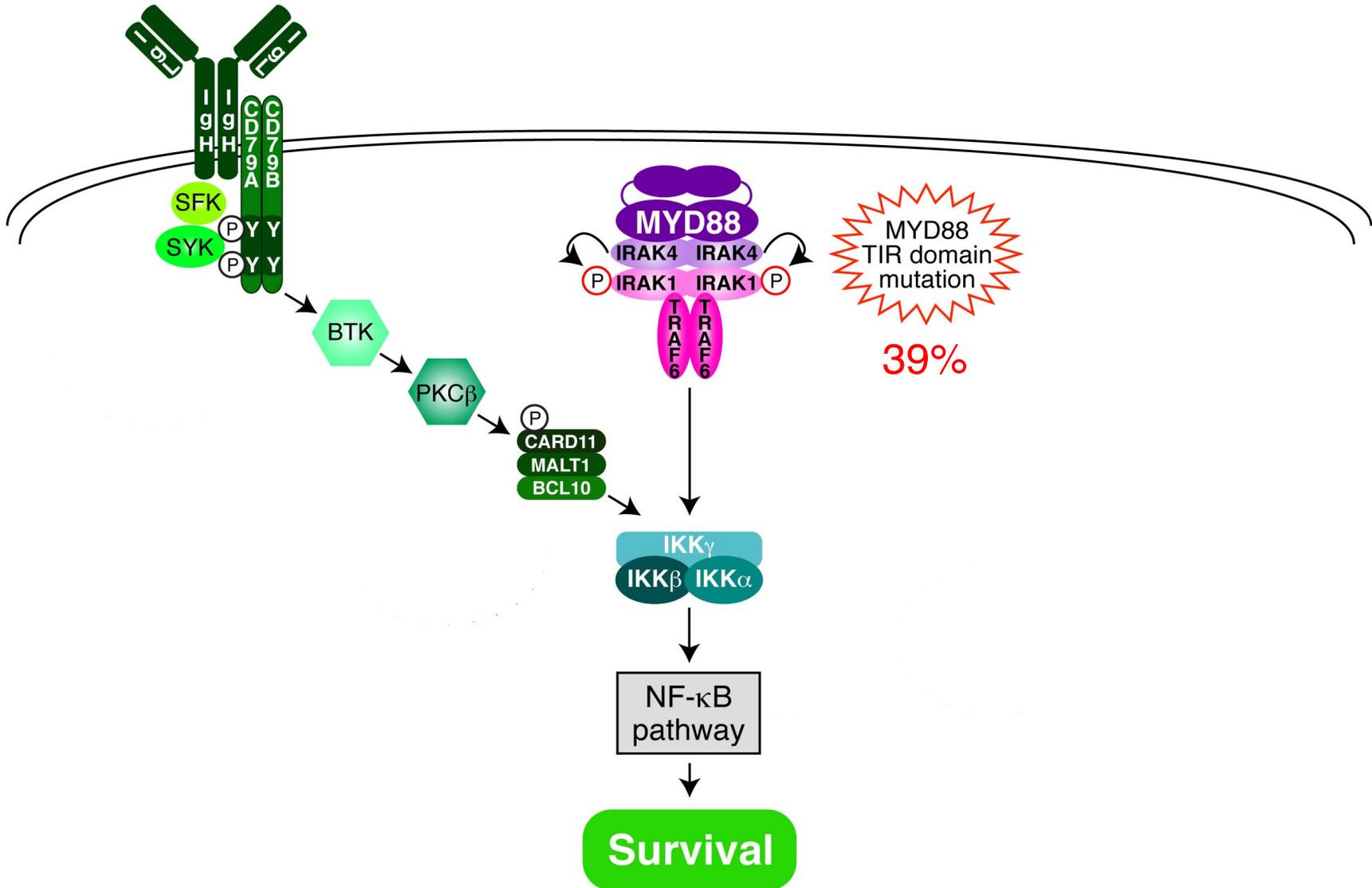
Constitutive MYD88 signaling



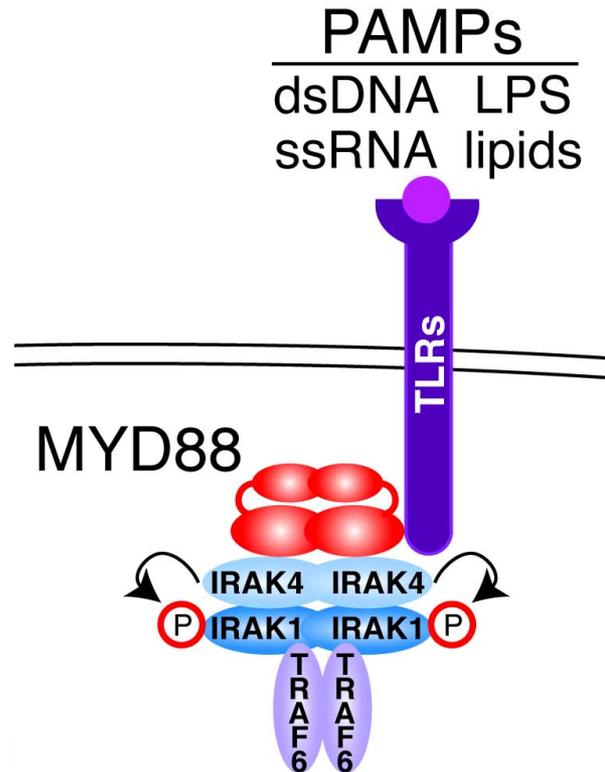
Constitutive MYD88 Signaling in ABC DLBCL

Chronic Active
BCR signaling

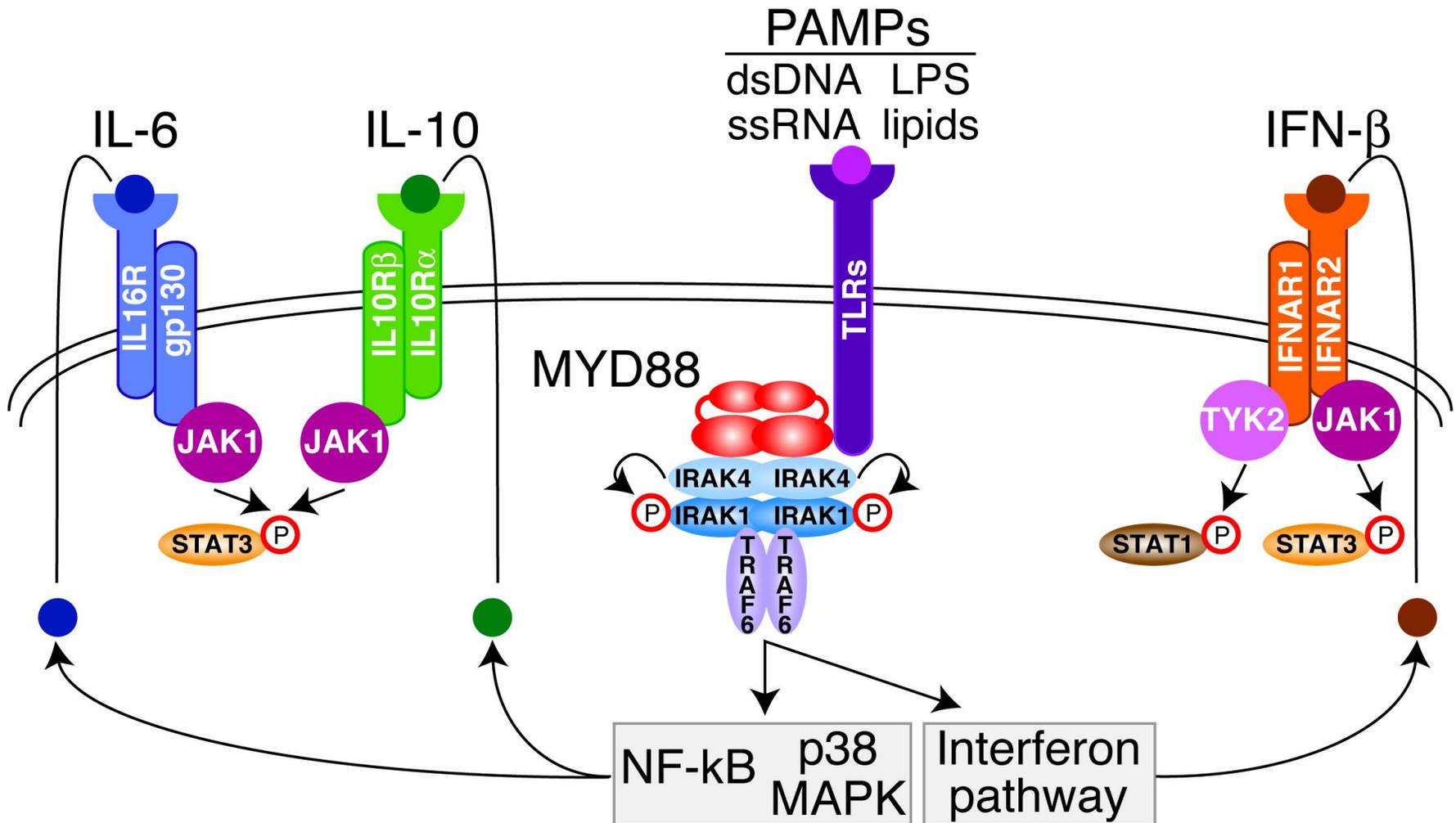
Constitutive
MYD88 signaling



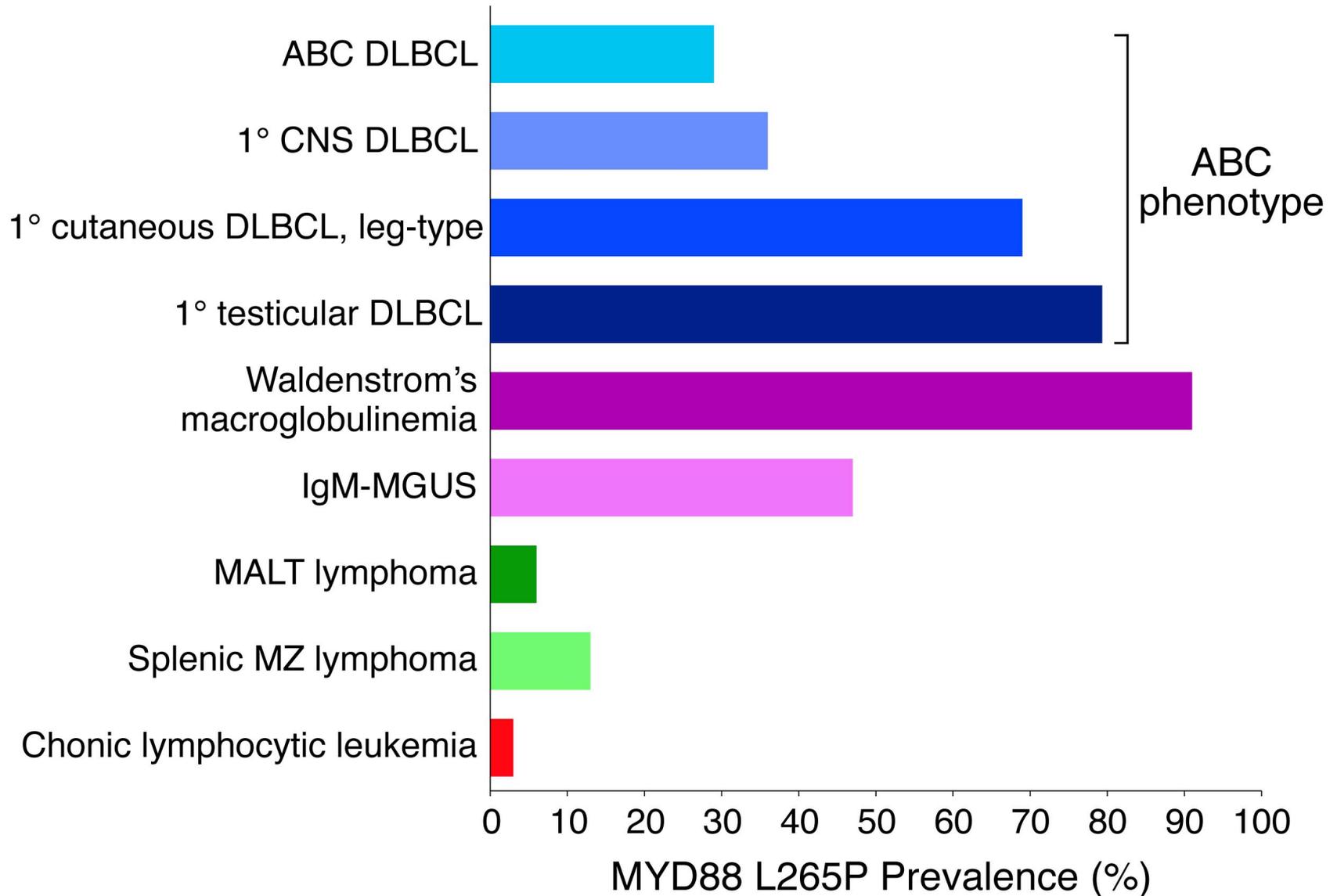
MYD88 is the Key Signaling Adapter Downstream of Toll-like Receptors



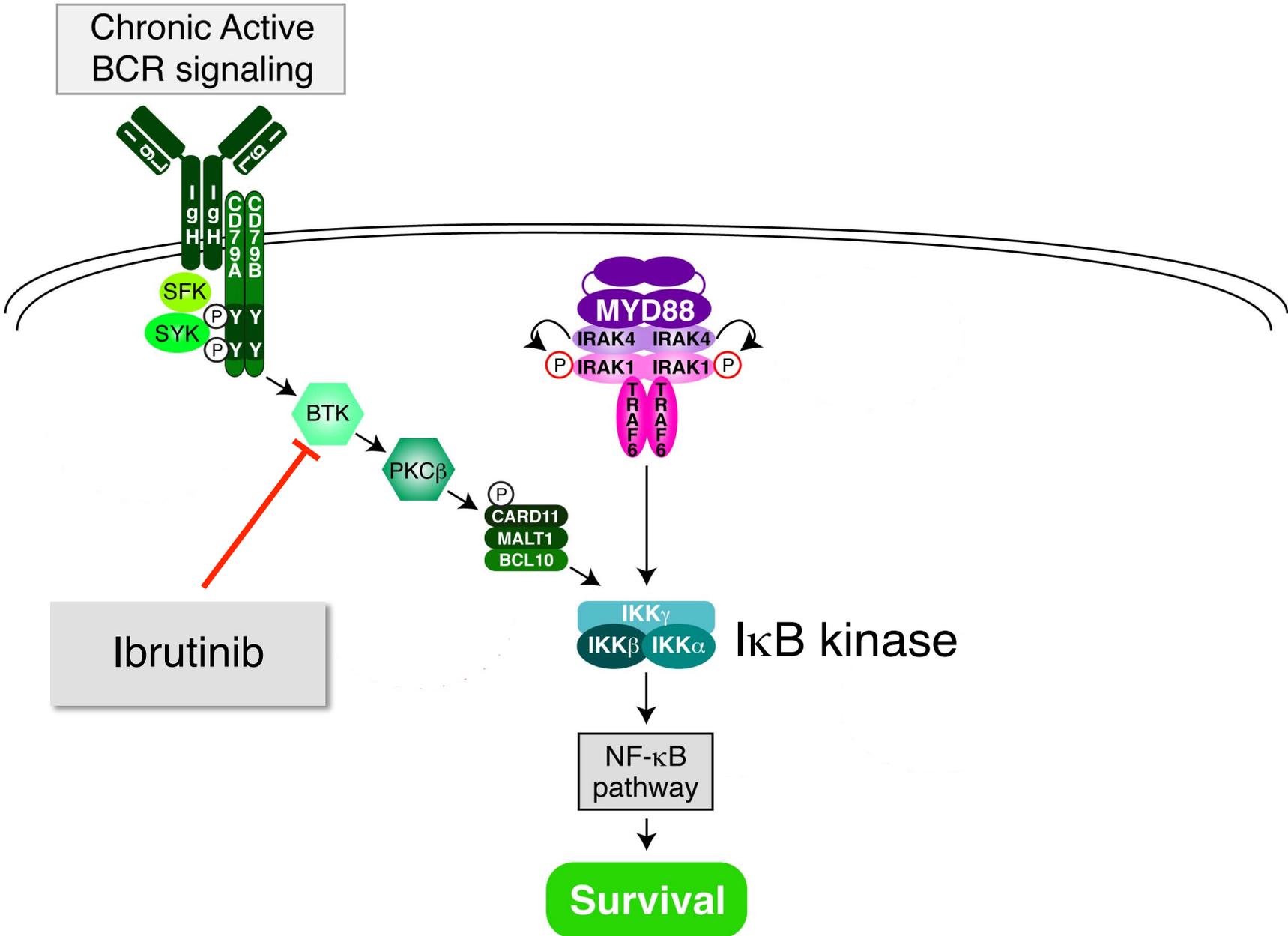
MYD88 is the Key Signaling Adapter Downstream of Toll-like Receptors



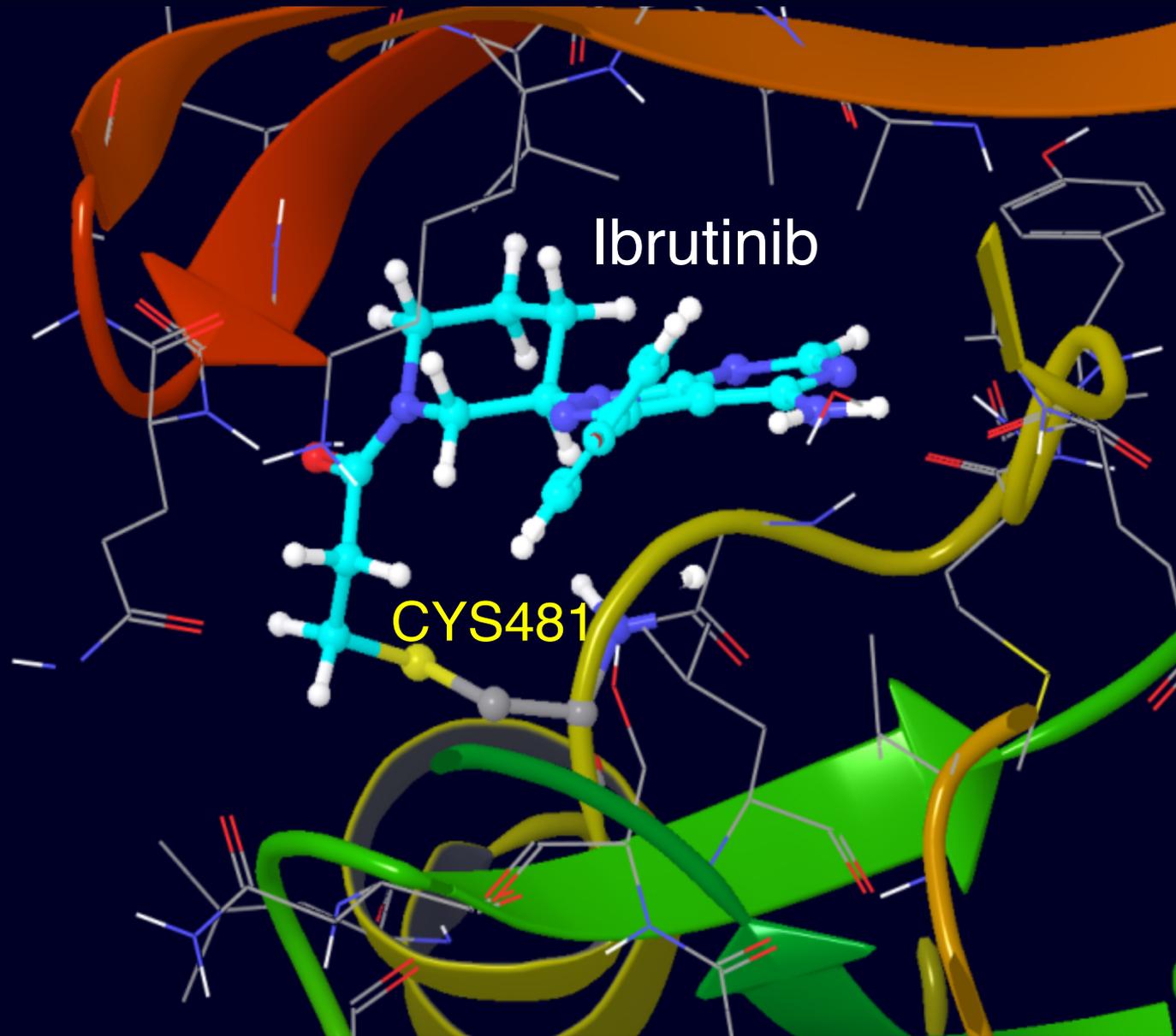
MYD88 L265P: A Frequent Oncogene in Diverse Lymphoma Malignancies



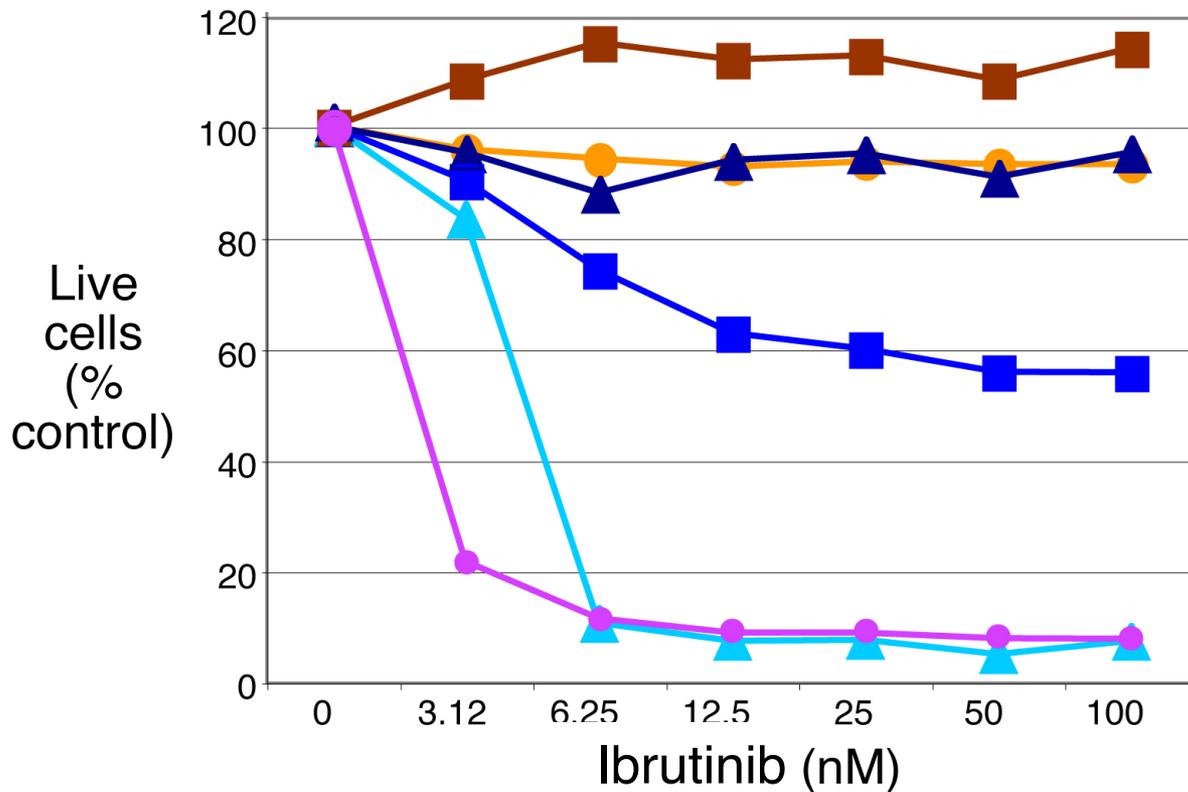
Blockade of BCR Signaling in ABC DLBCL with Ibrutinib



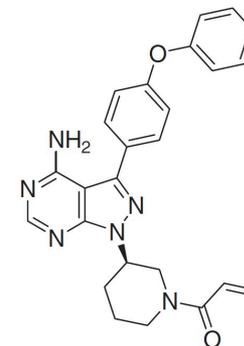
Ibrutinib Covalently Binds to the BTK Active Site



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



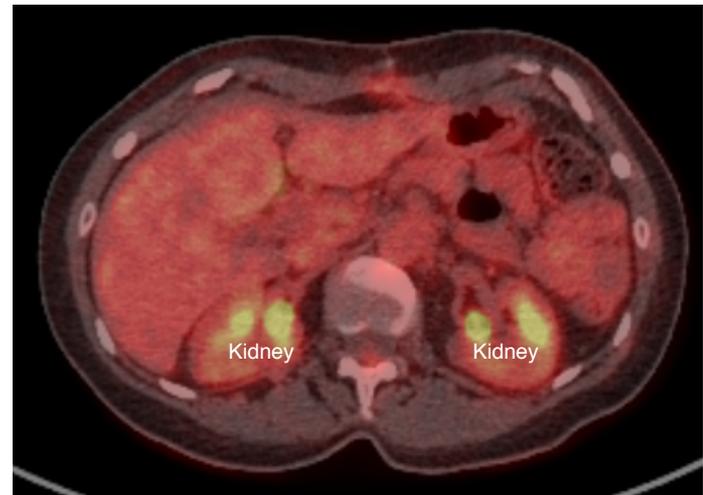
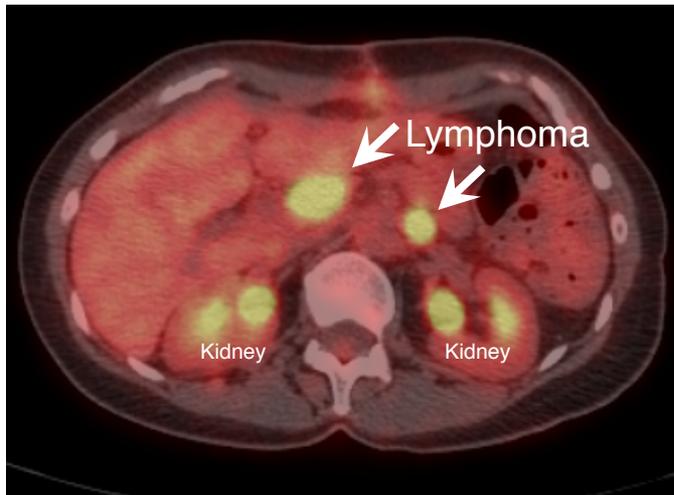
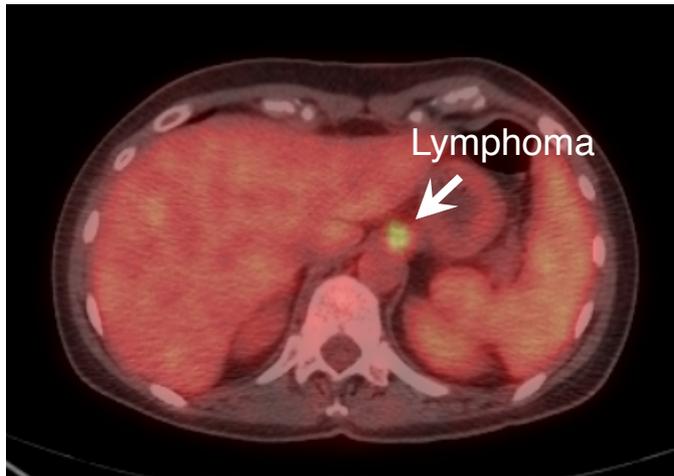
		CARD11 status
ABC DLBCL	OCI-Ly10	Mutant
	HBL1	WT
DLBCL	TMD8	WT
	OCI-Ly3	WT
GCB DLBCL	BJAB	WT
	OCI-Ly19	WT



Patient #2 on Ibrutinib Phase 1b Trial in Relapsed/refractory DLBCL

- ❖ 52 year old female
ABC DLBCL
- ❖ CD79B Y196C mutations
- ❖ Relapse following 2 prior chemotherapies
 - DA-EPOCH-R + Campath CR and relapse
 - DA-EPOCH-R CR and relapse
- ❖ Single agent treatment with Ibrutinib
- ❖ Complete response at week 8 by CT and PET scan

PET/CT Scan of Patient #2 With ABC DLBCL Before and On Treatment With Ibrutinib



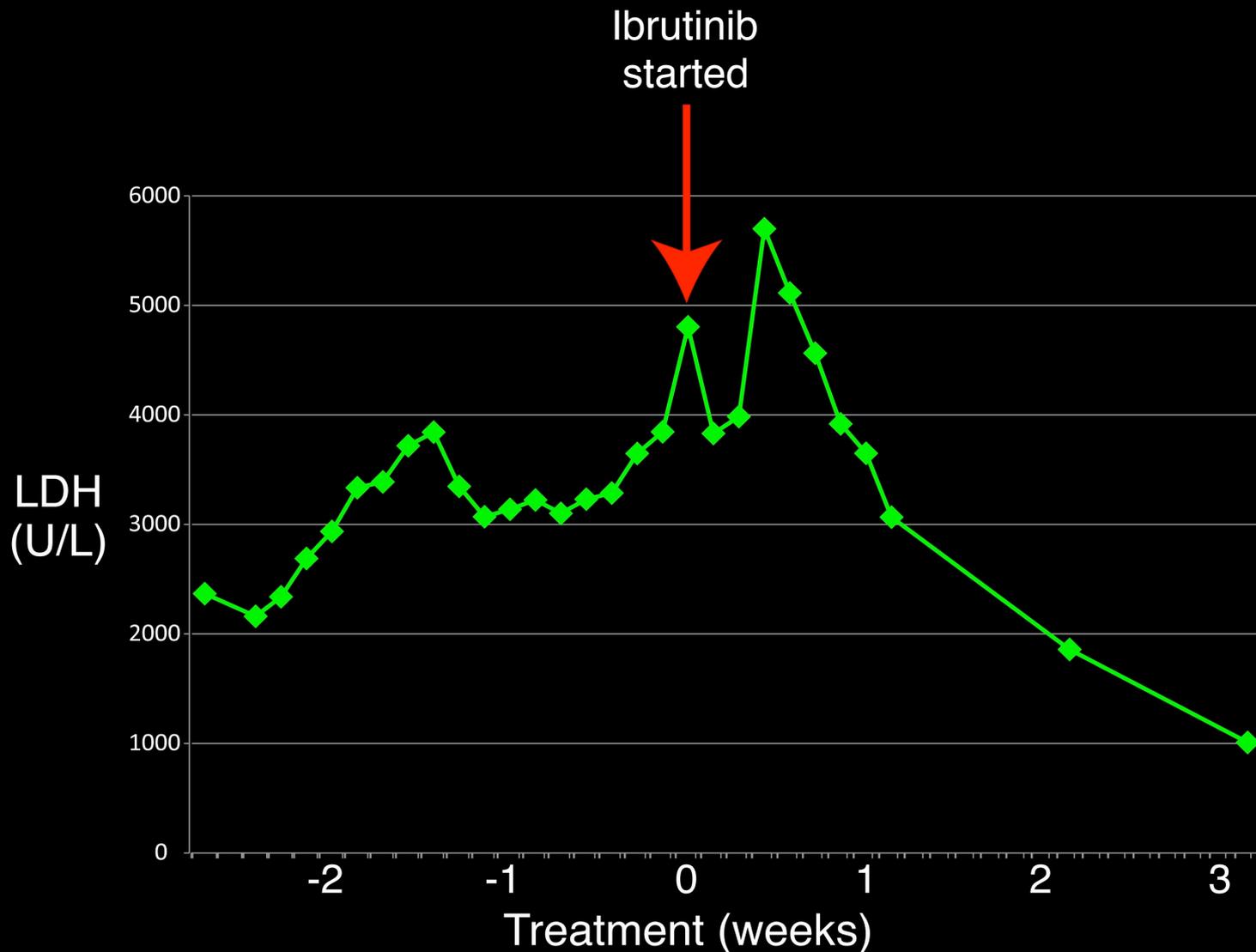
Before Rx

On Rx: week 8
Complete Response

Patient #9 on Pilot Trial of Ibrutinib (PCI-32765) 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 Treatment with Ibrutinib (PCI-32765)



Partial Remission of ABC DLBCL in Patient #3 on Pilot Trial of Ibrutinib (PCI-32765)



Before Rx



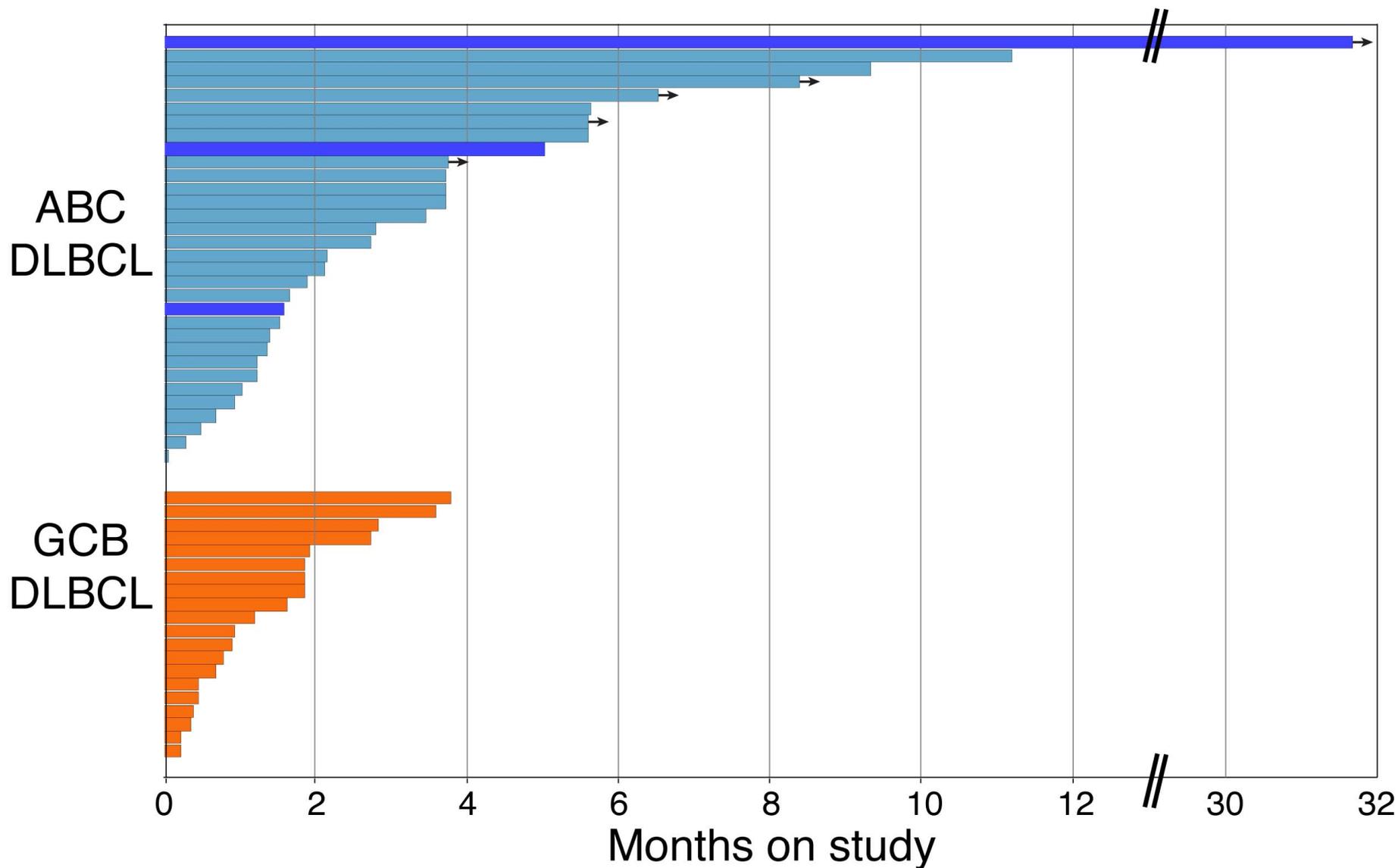
On Rx: week 3

Phase 2 Clinical Trial of Ibrutinib in Relapsed/refractory DLBCL

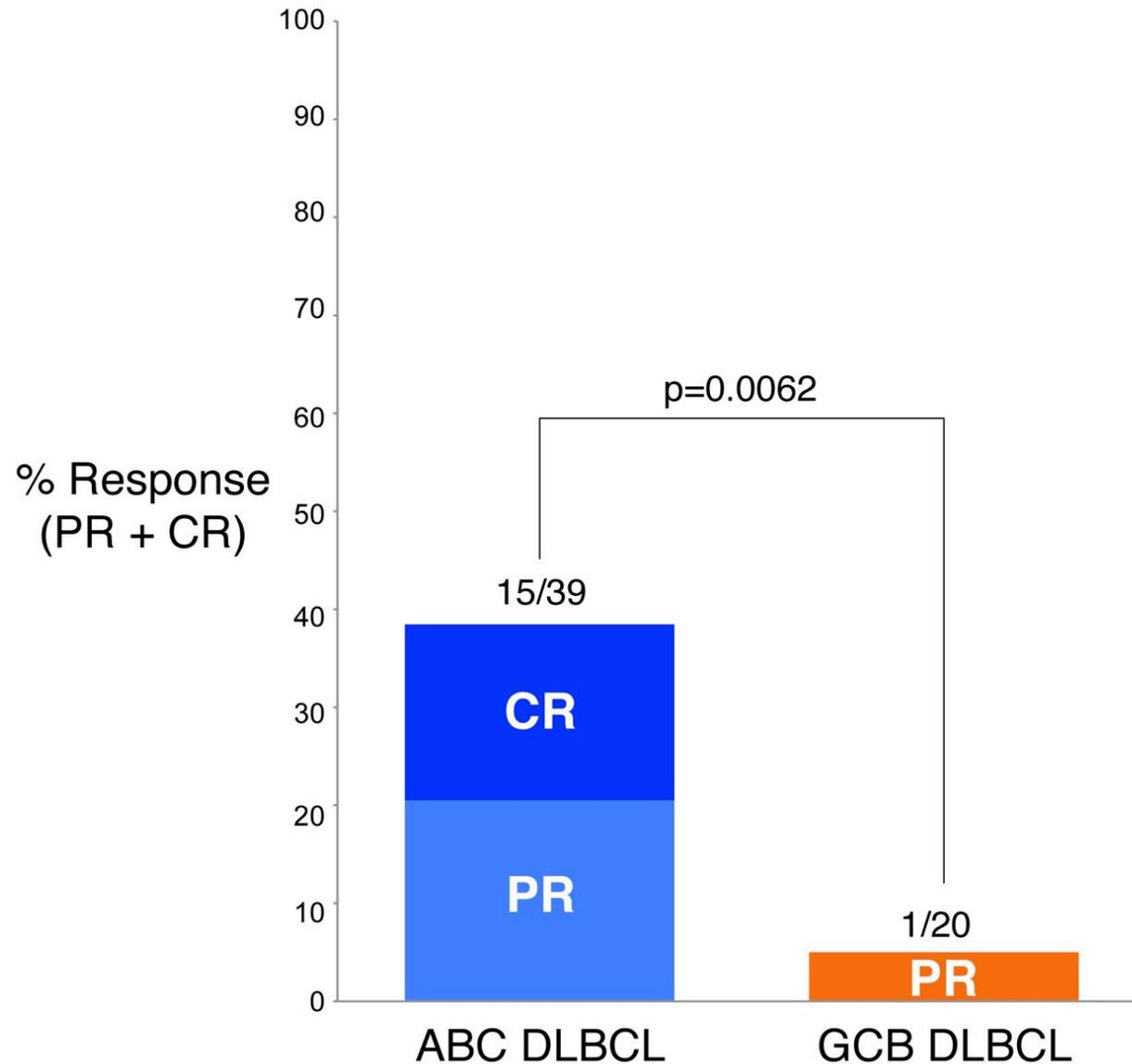
❖ Multicenter phase 2 trial

- 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

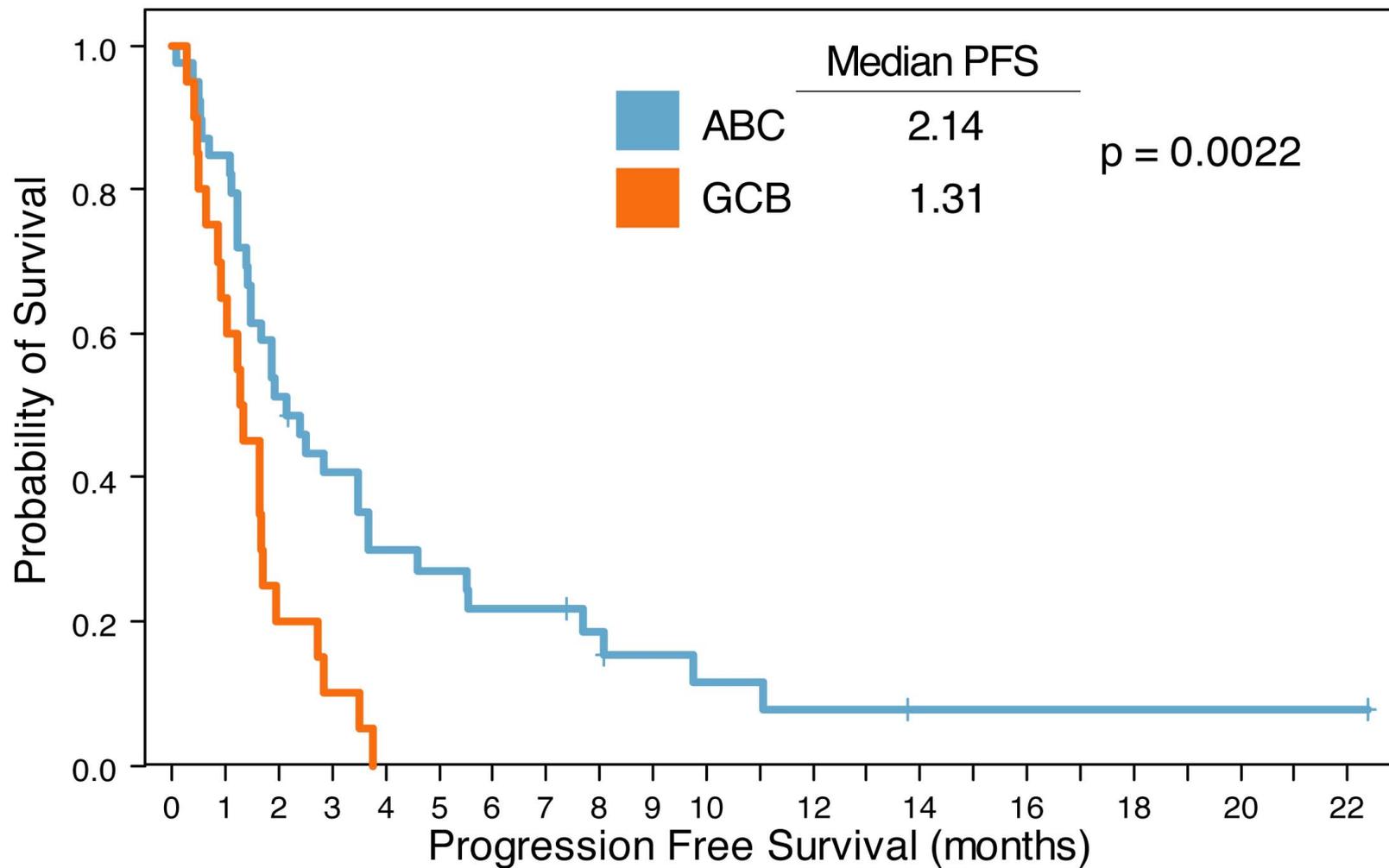
Ibrutinib Extends Life in Relapsed/Refractory ABC DLBCL



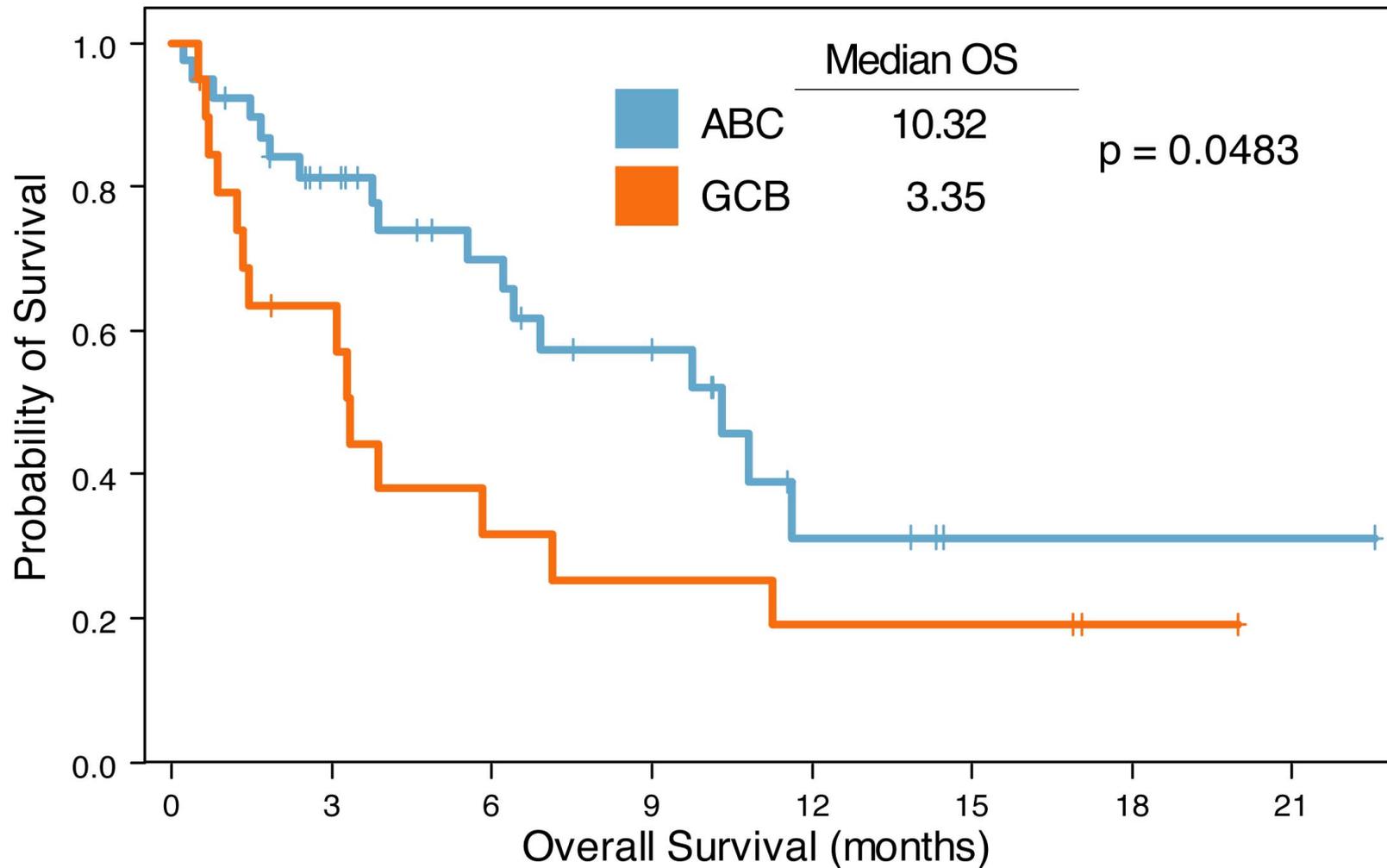
Ibrutinib is Preferentially Active in ABC DLBCL



Ibrutinib Extends Progression-free Survival in Relapsed/Refractory ABC DLBCL

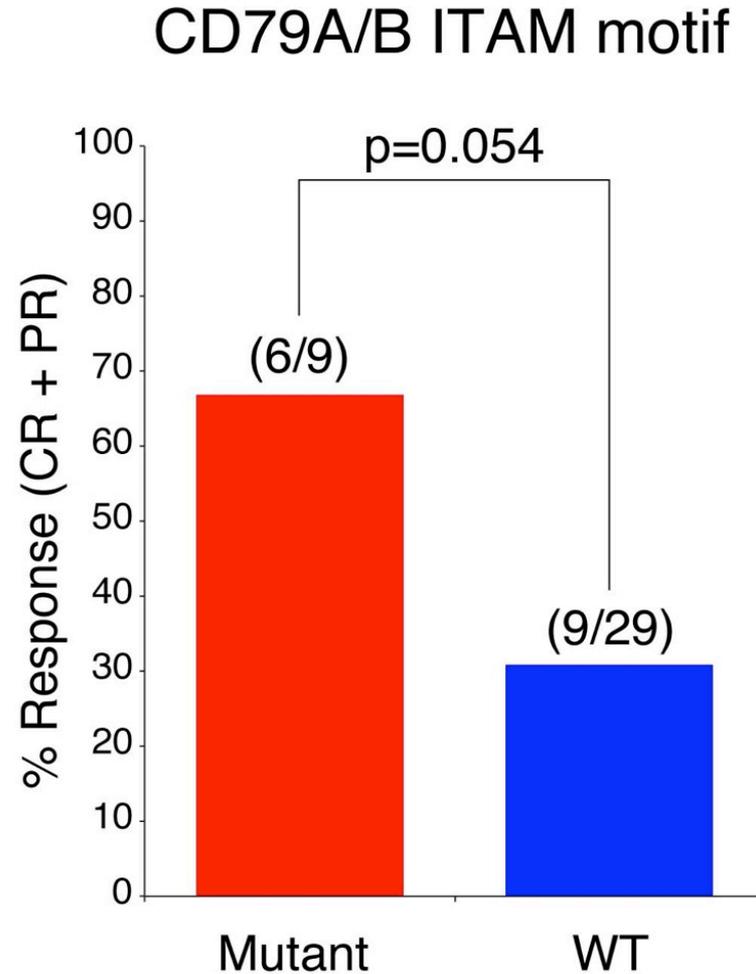


Ibrutinib Extends Overall Survival in Relapsed/Refractory ABC DLBCL



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

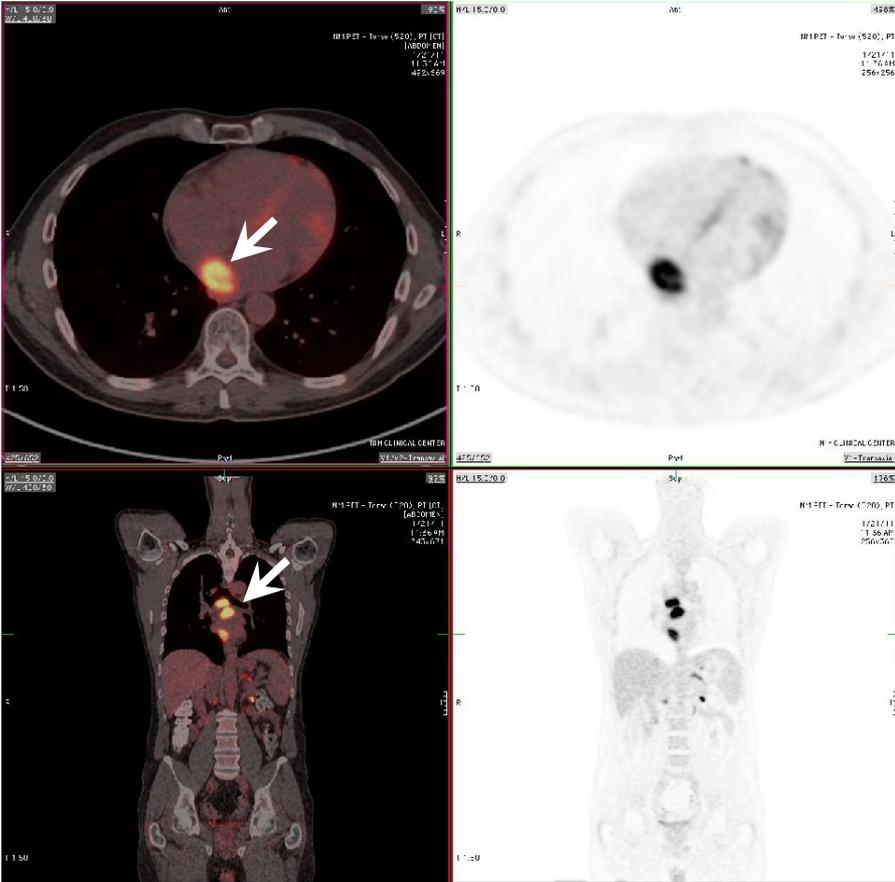
Influence of B Cell Receptor and MYD88 Pathway Mutations on Ibrutinib Response in ABC DLBCL



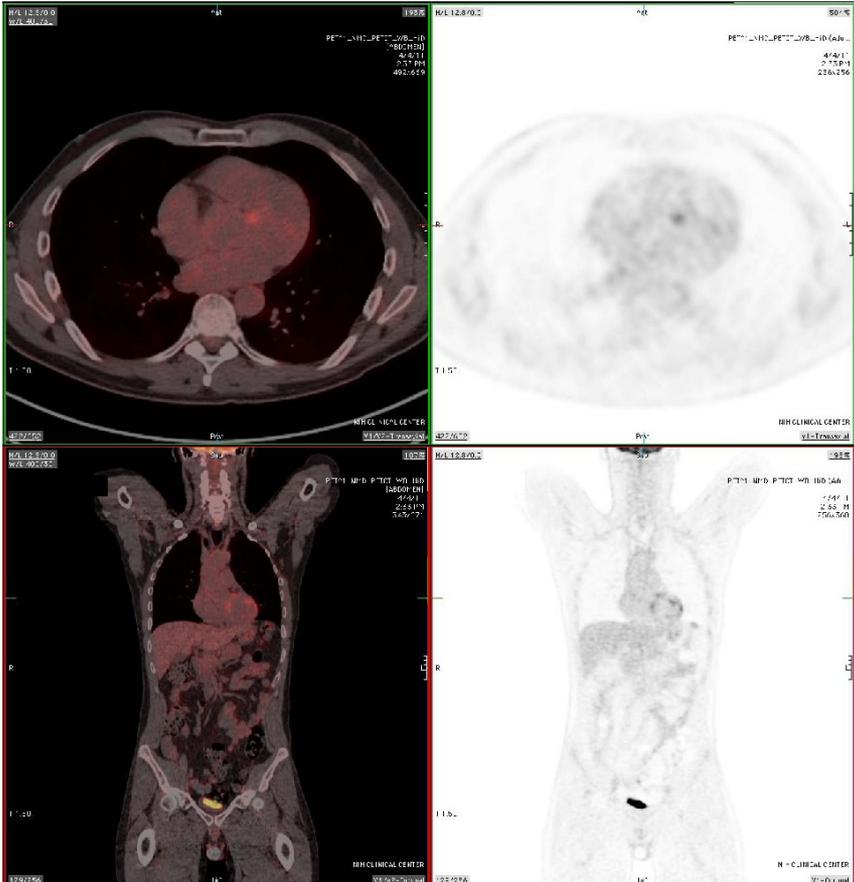
Patient #3 on Pilot Trial of Ibrutinib in Relapsed/refractory ABC DLBCL

- ❖ 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

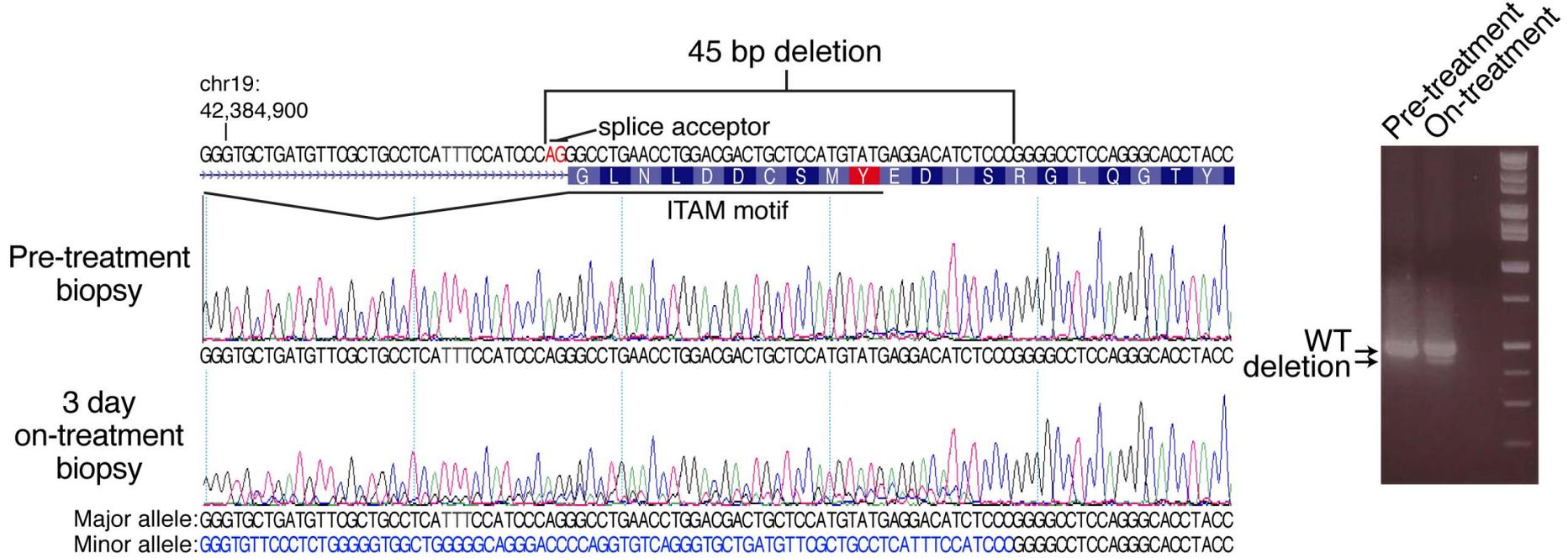


Before Rx



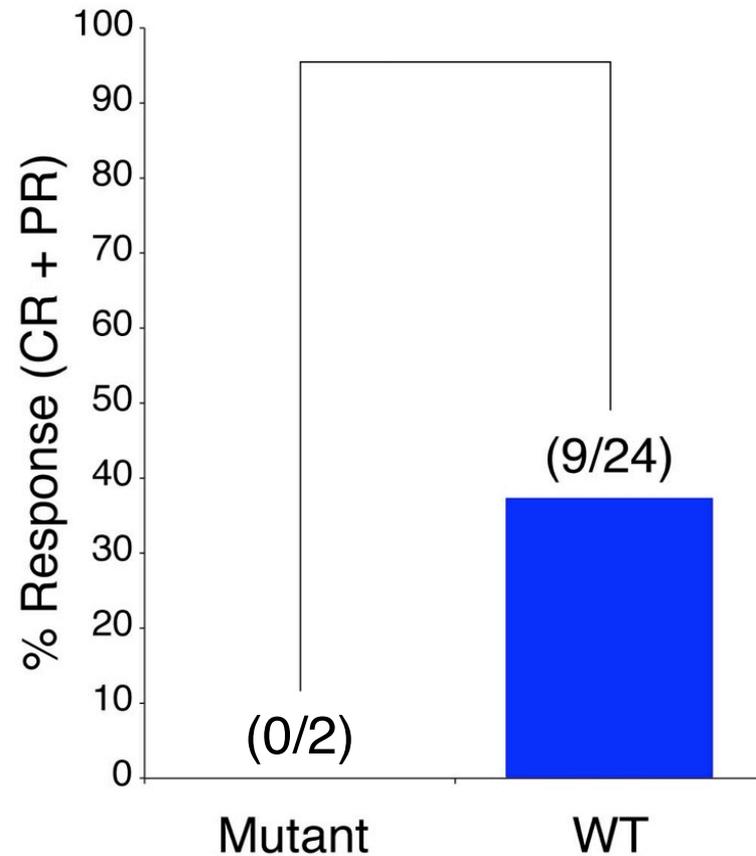
On Rx: week 10

Enrichment for a CD79A ITAM Mutation During Treatment of ABC DLBCL With Ibrutinib



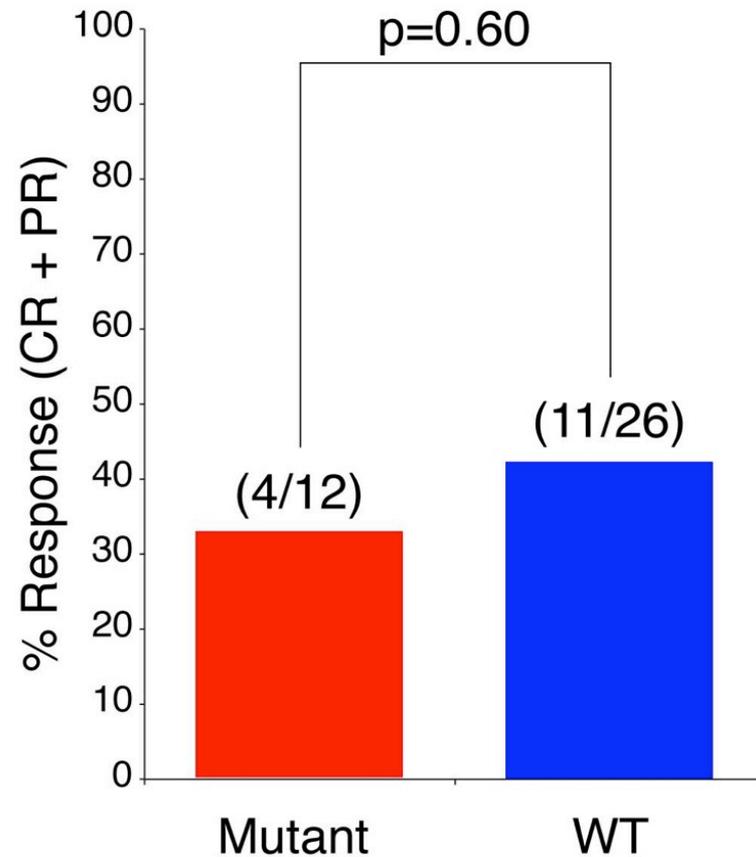
Influence of B Cell Receptor and MYD88 Pathway Mutations on Ibrutinib Response in ABC DLBCL

CARD11 coiled-coil domain



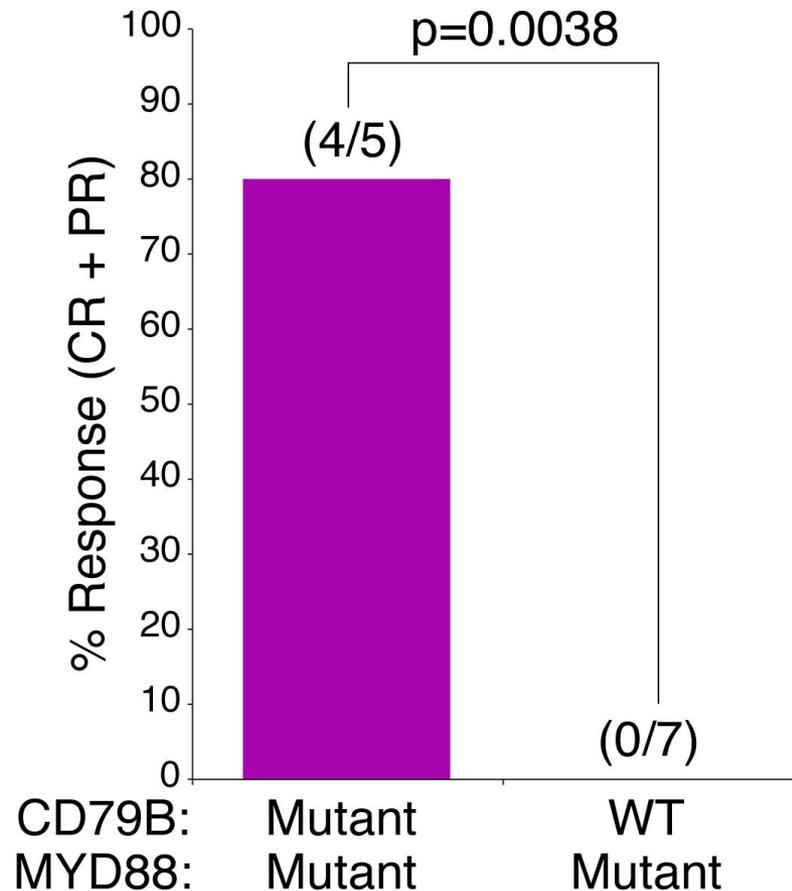
Influence of B Cell Receptor and MYD88 Pathway Mutations on Ibrutinib Response in ABC DLBCL

MYD88 TIR domain



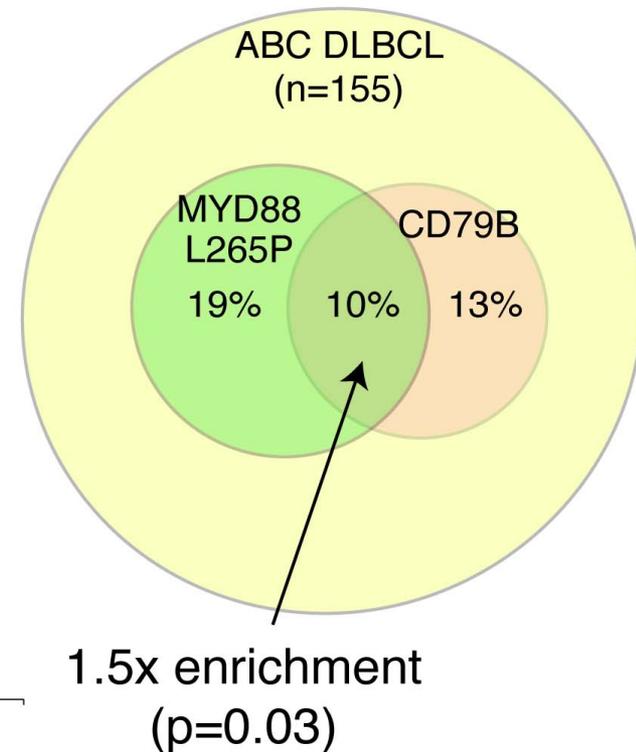
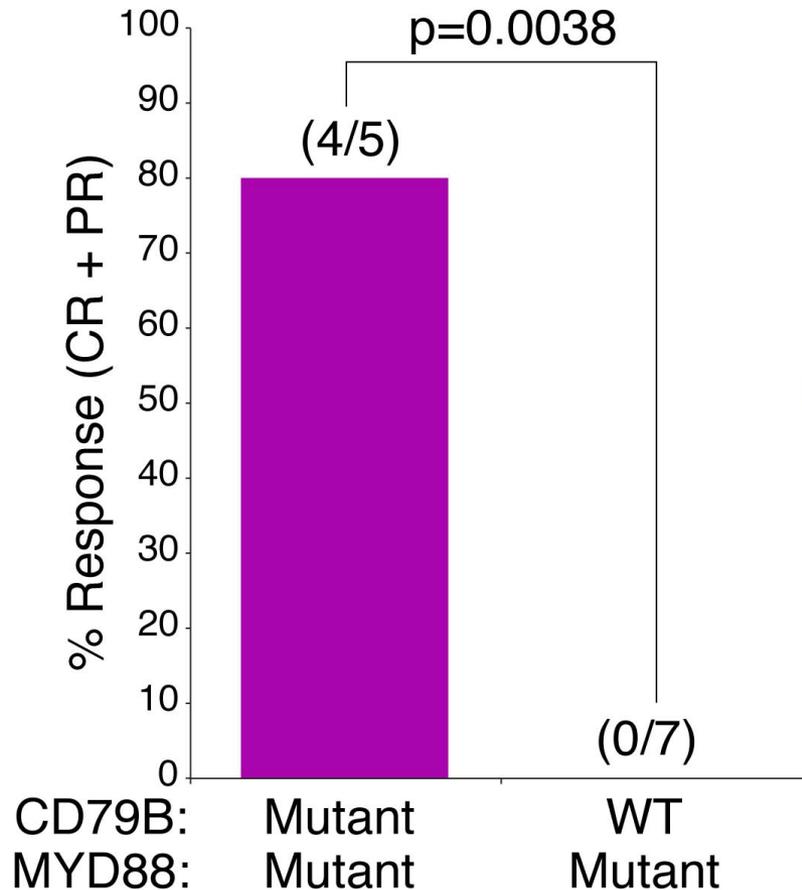
Influence of B Cell Receptor and MYD88 Pathway Mutations on Ibrutinib Response in ABC DLBCL

MYD88 TIR domain vs.
CD79A/B ITAM motif



Influence of B Cell Receptor and MYD88 Pathway Mutations on Ibrutinib Response in ABC DLBCL

MYD88 TIR domain vs.
CD79A/B ITAM motif

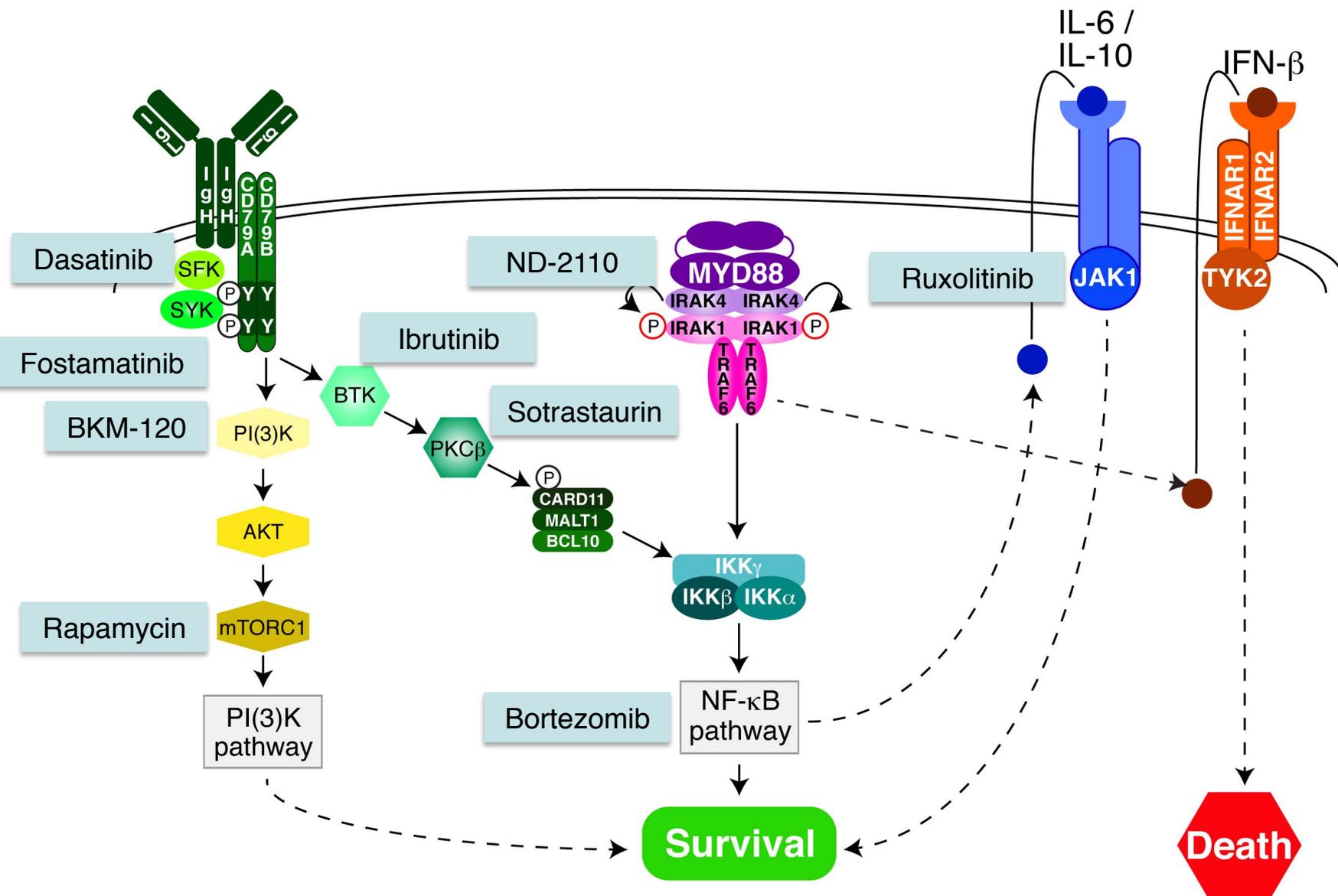


Drugs That Target Oncogenic Pathways in ABC DLBCL

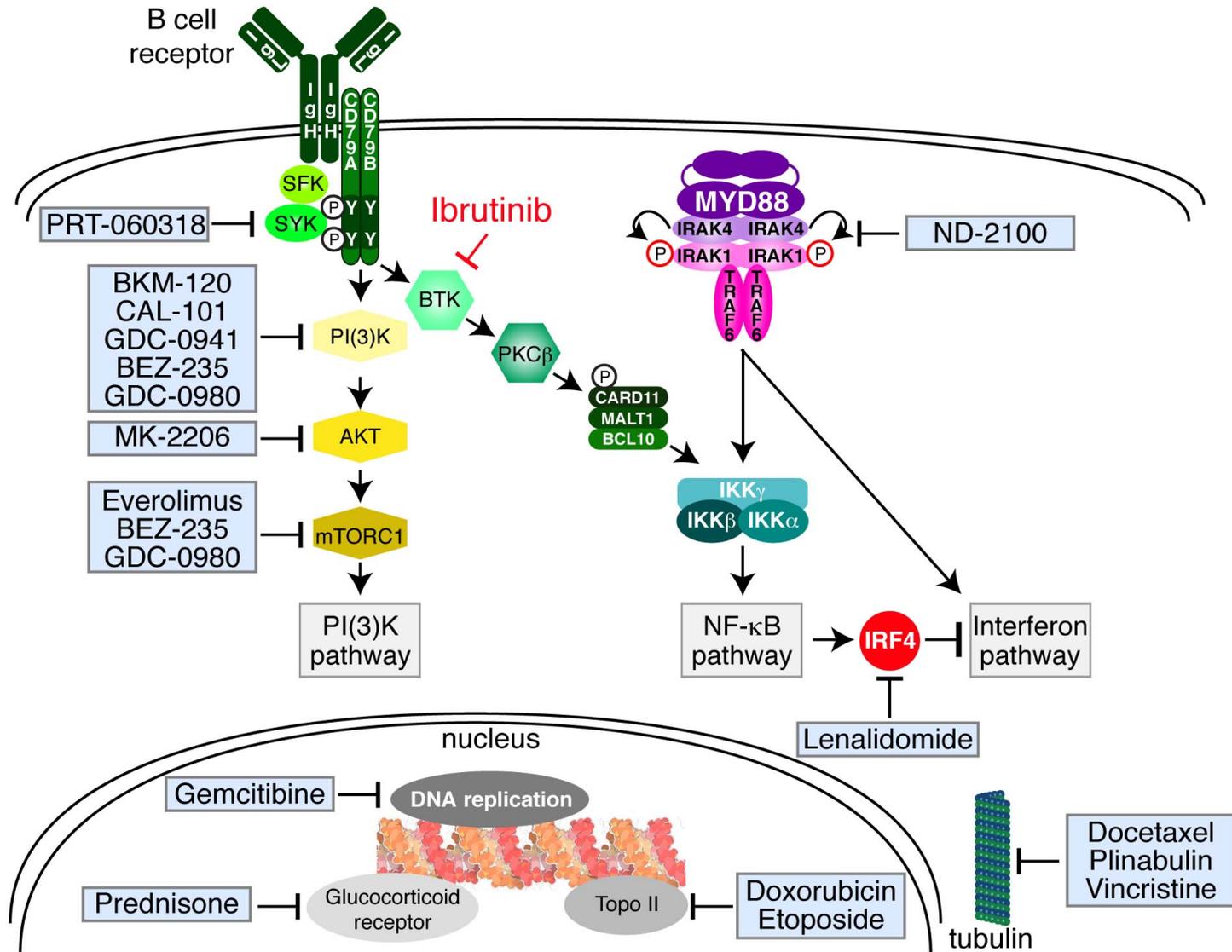
Chronic Active
BCR signaling

Constitutive
MYD88 signaling

Constitutive
cytokine signaling



Drugs Targeting Many Pathways Synergize With Ibrutinib in Killing ABC DLBCL Cells

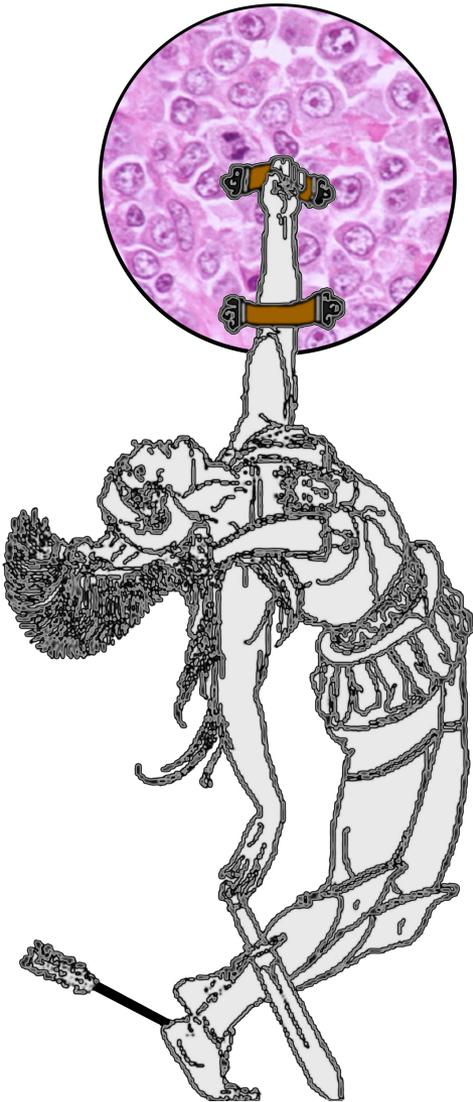


Targeted Therapy of ABC DLBCL

- ❖ Ibrutinib, a selective irreversible BTK inhibitor, induced a high response rate in relapsed/refractory ABC DLBCL

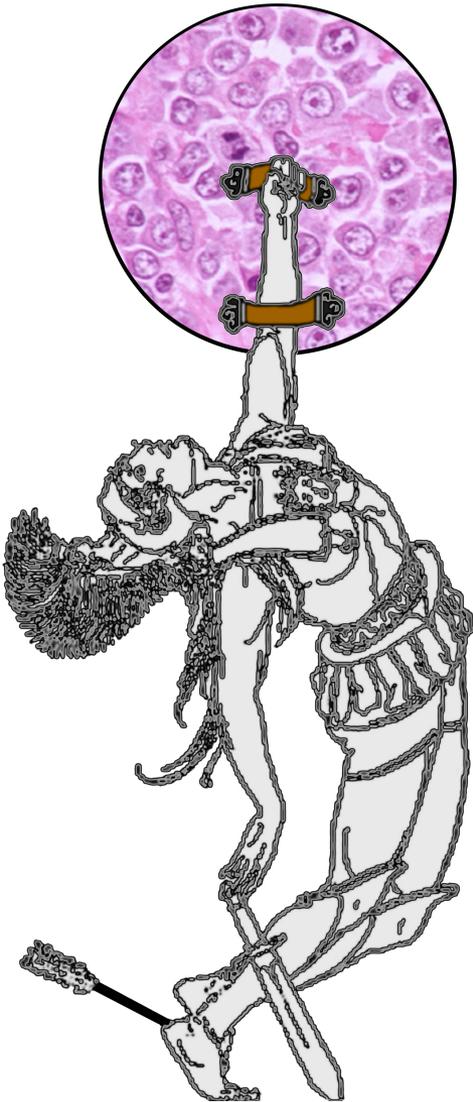


Targeted Therapy of ABC DLBCL



- ❖ Ibrutinib, a selective irreversible BTK inhibitor, induced a high response rate in relapsed/refractory ABC DLBCL
- ❖ CD79B mutant tumors responded frequently to ibrutinib, indicating that ibrutinib inhibits chronic active BCR signaling in ABC DLBCL

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Targeted Therapy of ABC DLBCL



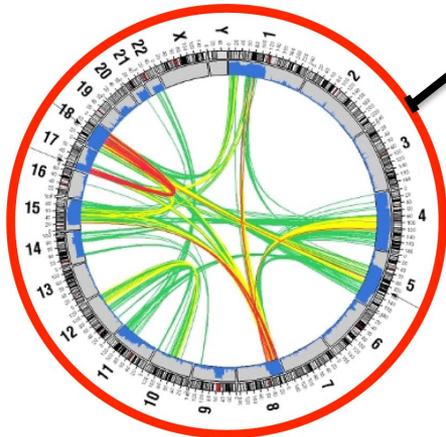
- ❖ Ibrutinib, a selective irreversible BTK inhibitor, induced a high response rate in relapsed/refractory ABC DLBCL
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- ❖ Ibrutinib synergizes with multiple targeted agents and chemotherapy in killing ABC DLBCLs
- ❖ Rational drug combinations hold promise in ABC DLBCL

Structural Genomics

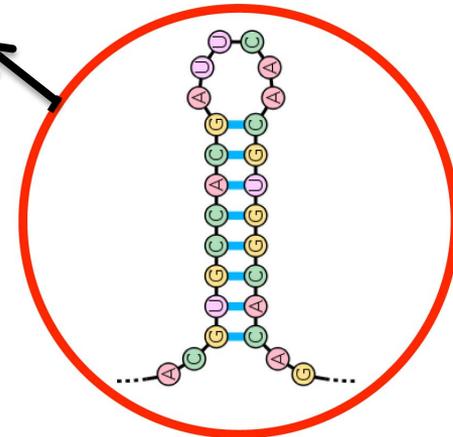
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GCTAAGGTGCGACTC
AGCGTACCAGATA
TTATAGATACAC
TTGTGTC



Essential cancer pathways



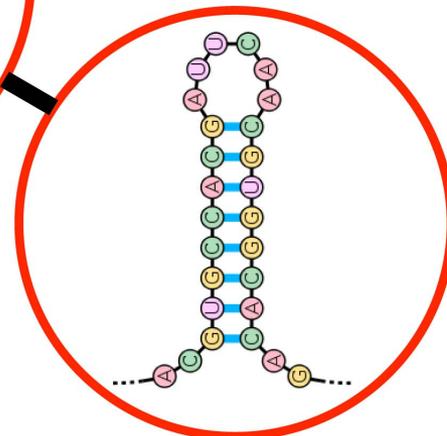
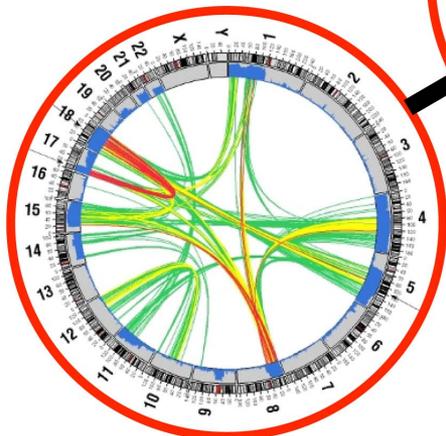
Computational Genomics



Functional Genomics

Structural Genomics

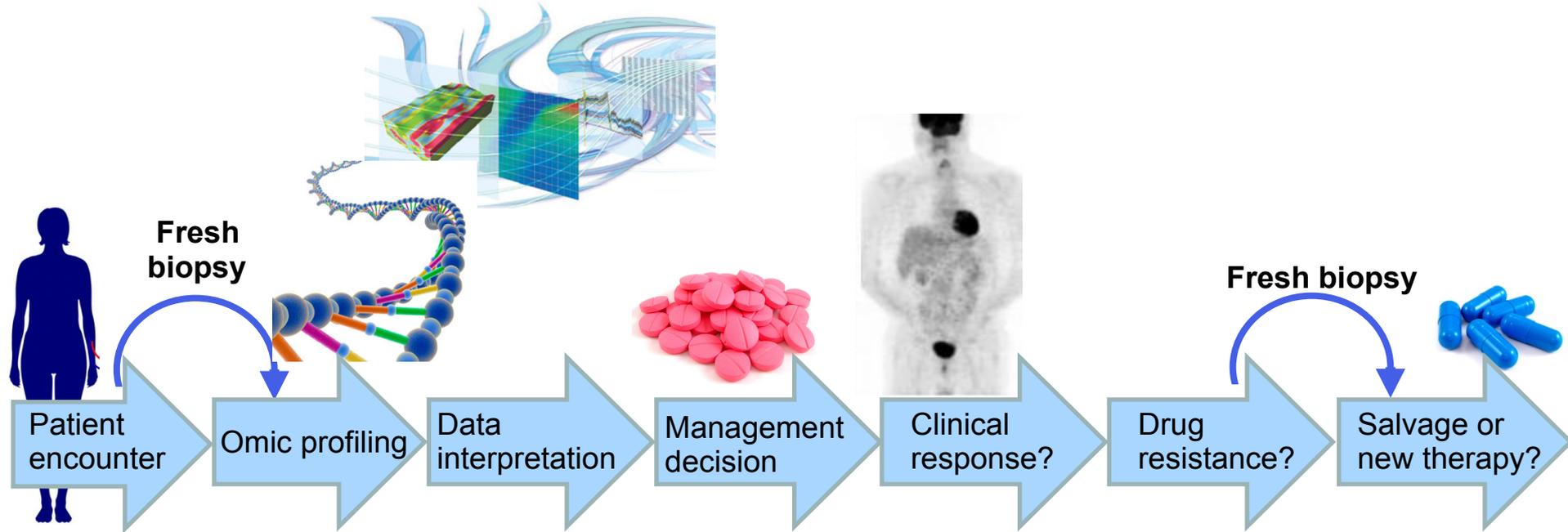
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AGCCAGAGAGAGAT
GCCAAACACACCCAT
GCTAAGGTGCGACTC
AGCGTACCAGATA
TTATAGATACAC
TTGTGTC



Computational Genomics

Functional Genomics

The Engine of Precision Cancer Medicine



Acknowledgements

Metabolism Branch, CCR, NCI

BCR Signaling

Eric Davis
Ryan Young

MYD88

Vu Ngo

Ibrutinib Trial

Wyndham Wilson
Yandan Yang
Sameer Jhavar
Art Shaffer
Ryan Young
Roland Schmitz

Laboratory of Pathology, CCR, NCI

Stefania Pittaluga

LLMPP consortium members

Biometric Research Branch, NCI

George Wright

Frederick National Laboratory, NCI

Jason Lih
Mickey Williams

Pharmacyclics

Jesse McGreivy

Lori A. Kunkel

Sriram Balasubramanian

Mei Cheng

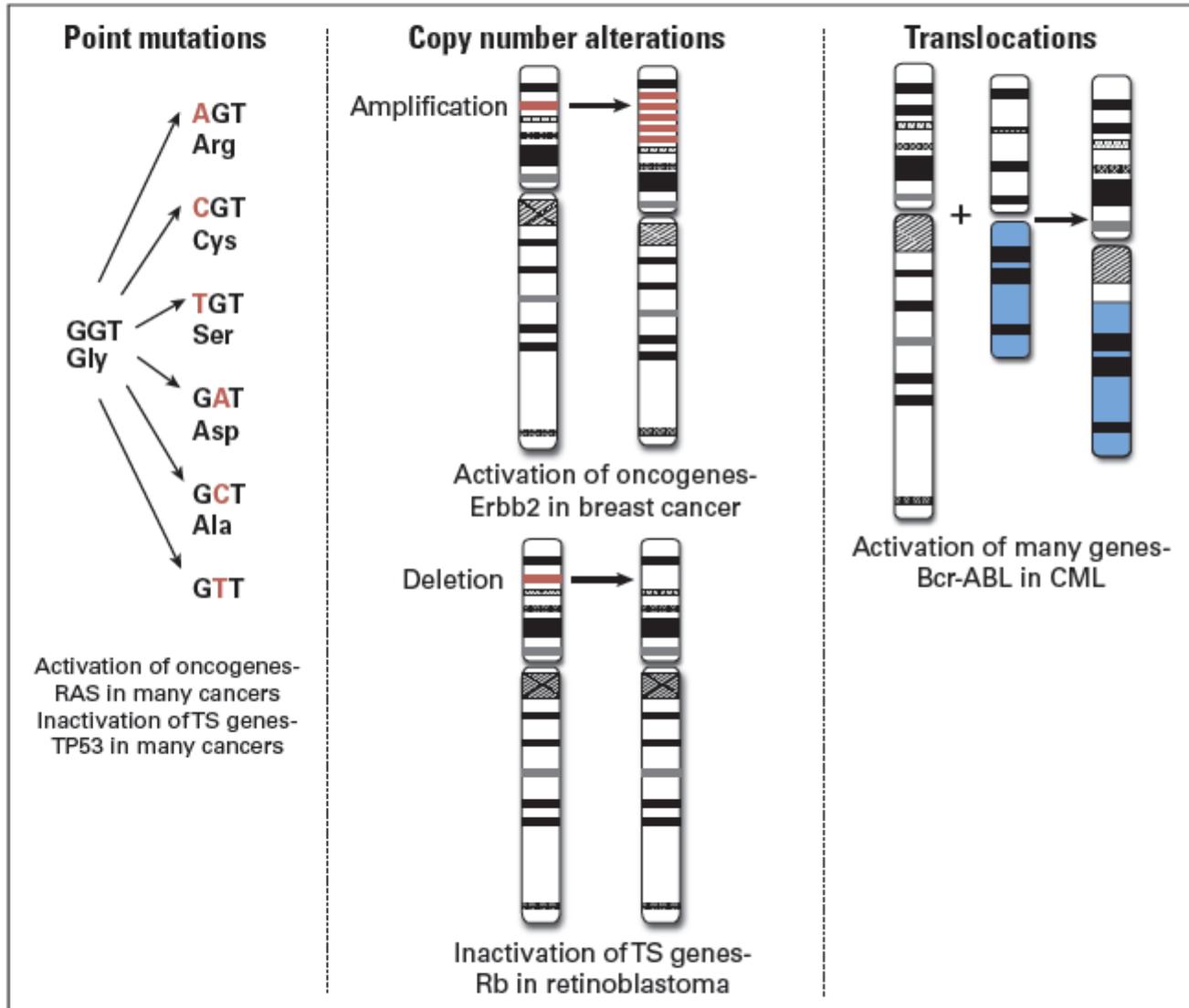
Davina Moussa

Joseph J. Buggy

J&J

Deb Ricci

Major Categories of Tumor Genomic Alterations



Initial genome sequencing and analysis of multiple myeloma

Michael A. Chapman^{1†}, Michael S. Lawrence¹, Jonathan J. Keats^{2,3}, Kristian Cibulskis¹, Carrie Sougnez¹, Anna C. Schinzel⁴, Christina L. Harview¹, Jean-Philippe Brunet¹, Gregory J. Ahmann^{2,3}, Mazhar Adli^{1,5}, Kenneth C. Anderson^{3,4}, Kristin G. Ardlie¹, Daniel Auclair^{3,6}, Angela Baker⁷, P. Leif Bergsagel^{2,3}, Bradley E. Bernstein^{1,5,8,9}, Yotam Drier^{1,10}, Rafael Fonseca^{2,3}, Stacey B. Gabriel¹, Craig C. Hofmeister^{3,11}, Sundar Jagannath^{3,12}, Andrzej J. Jakubowiak^{3,13}, Amrita Krishnan^{3,14}, Joan Levy^{3,6}, Ted Liefeld¹, Sagar Lonial^{3,15}, Scott Mahan¹, Bunmi Mfuko^{3,6}, Stefano Monti¹, Louise M. Perkins^{3,6}, Robb Onofrio¹, Trevor J. Pugh¹, S. Vincent Rajkumar^{3,16}, Alex H. Ramos¹, David S. Siegel^{3,17}, Andrey Sivachenko¹, A. Keith Stewart^{2,3}, Suzanne Trudel^{3,18}, Ravi Vij^{3,19}, Douglas Voet¹, Wendy Winckler¹, Todd Zimmerman^{3,20}, John Carpten⁷, Jeff Trent⁷, William C. Hahn^{1,4,8}, Levi A. Garraway^{1,4}, Matthew Meyerson^{1,4,8}, Eric S. Lander^{1,8,21}, Gad Getz¹ & Todd R. Golub^{1,4,8,9}

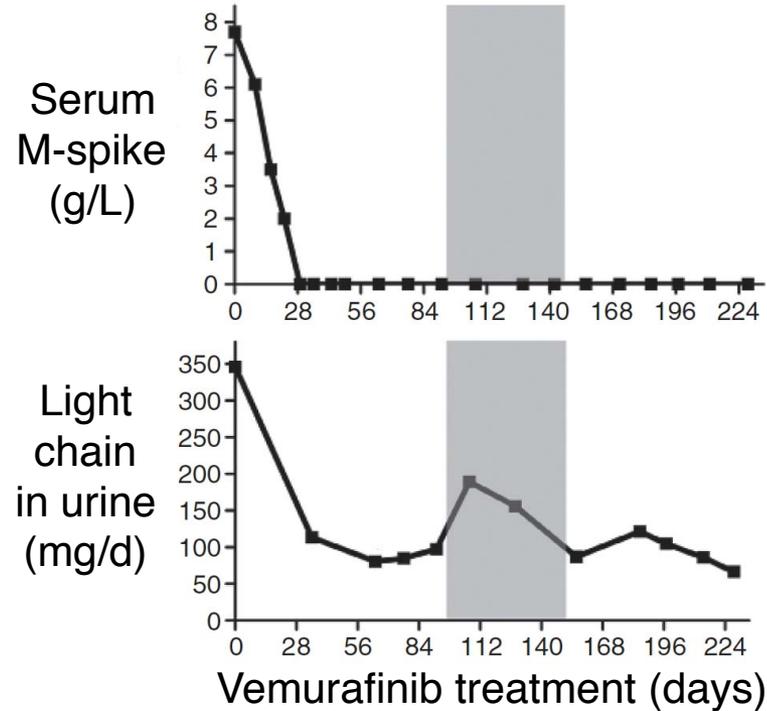
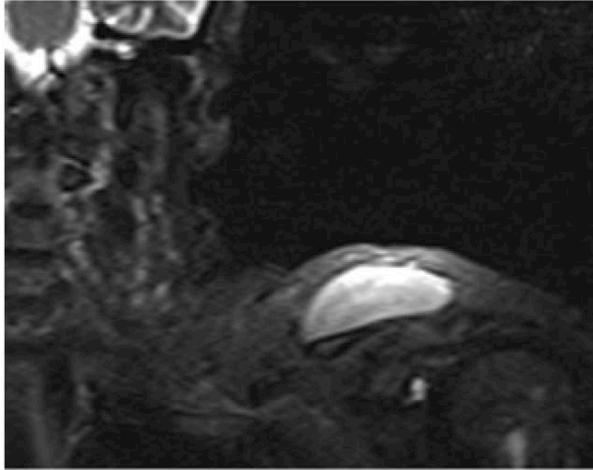
BRAF mutations in 4% of primary multiple myeloma cases

V600E – 2.5%

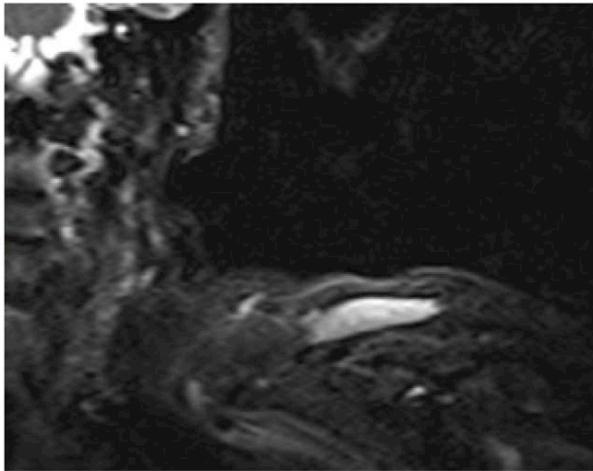
K661N – 1.9%

Response of Multiple Myeloma With BRAF V600E To Vemurafinib

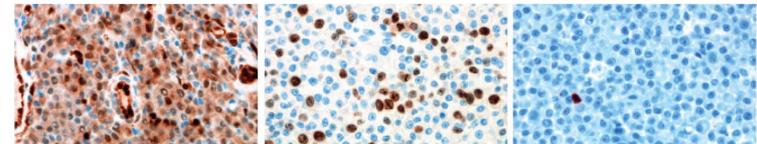
Baseline



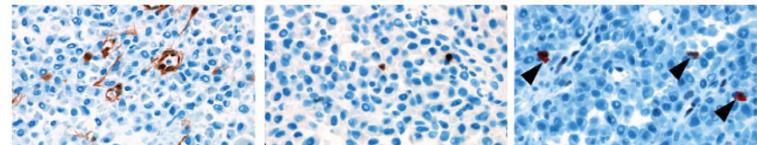
Vemurafinib day 28



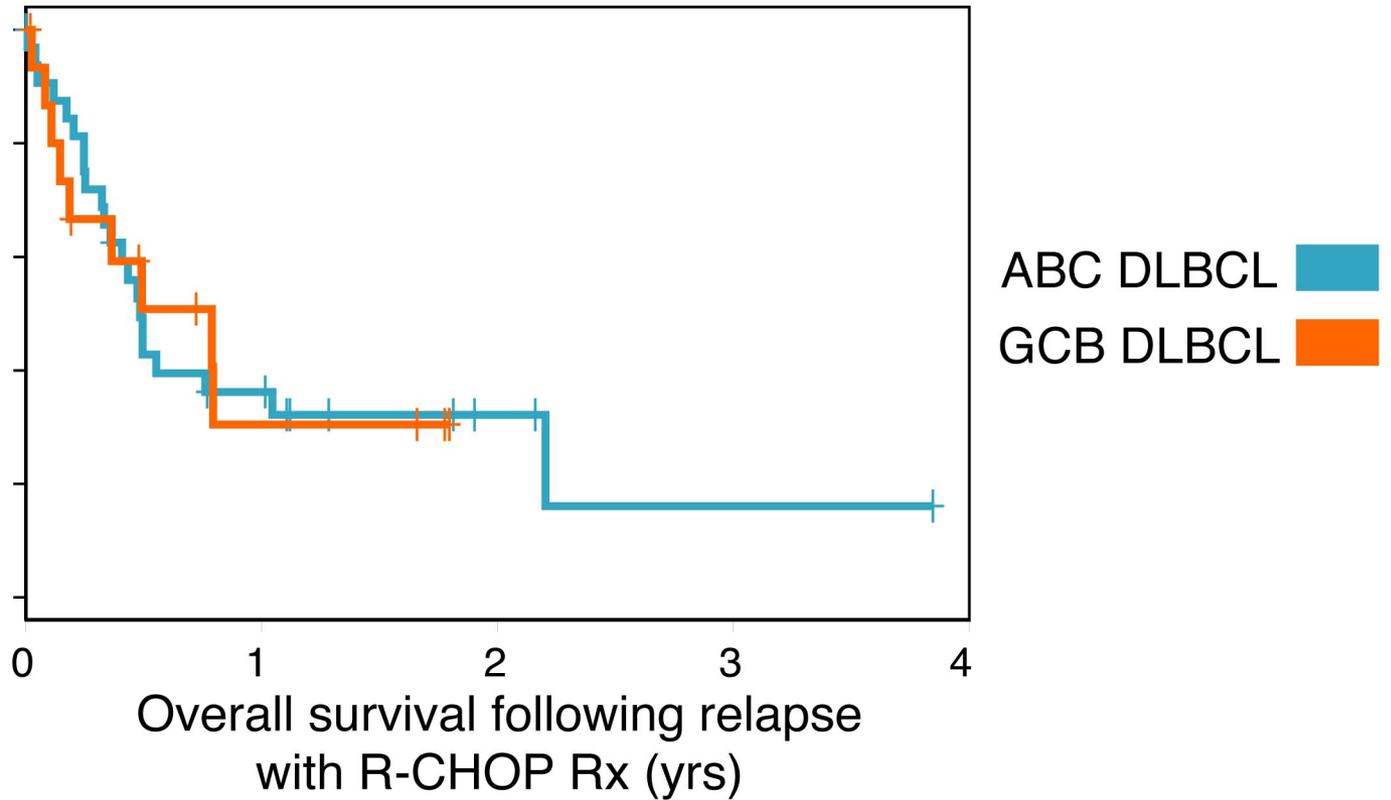
Baseline



Vemurafinib day 28

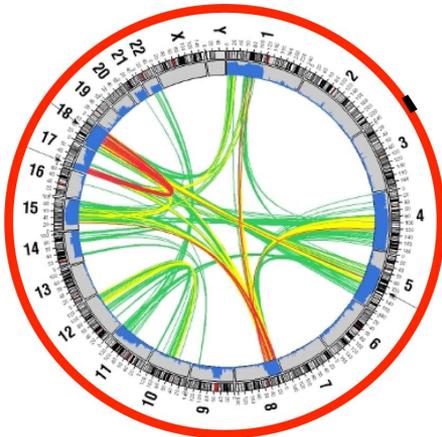


Patients with ABC and GCB DLBCL Who Relapse Following R-CHOP Therapy Have Equivalent Overall Survival Following Relapse

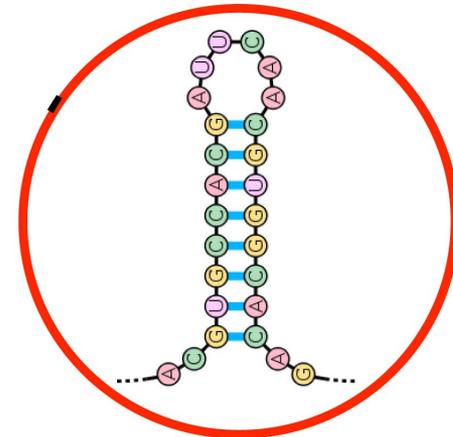


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AGCTGCT
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GCCAAACACACCCAT
GCTAAGGTGCGACTC
AGCGTACCAGATA
TTATAGATACAC
TTGTGTG



Computational Genomics



Functional Genomics