BTK inhibitors

“BTK inhibitors are relatively safe drugs, and fortunately, most patients don’t have severe side effects,” Wang says.

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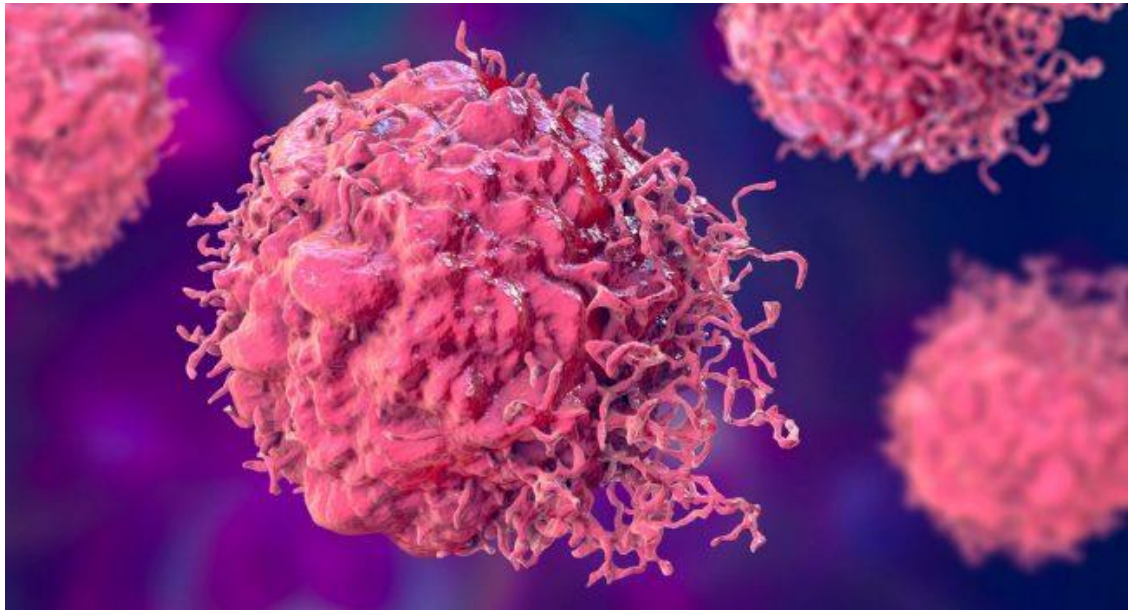
Introduction



- B cells are an important part of the immune system.
- One of their jobs is to neutralize the threat from a foreign invader known as a pathogen.
- They do this by producing an antibody that binds with the antigen on the threatening entity.

- When an antigen binds to a receptor on a B cell, the B-cell receptor signaling pathway is activated.

- Bruton’s tyrosine kinase (BTK) is an enzyme that’s critical to the activation of the B-cell receptor signaling pathway.

- BTK inhibitors are a type of drug that work to treat cancers caused by defective B cells, such as chronic lymphocytic leukemia CLL, B-cell lymphomas BCL, and Waldenström macroglobulinemia WM.

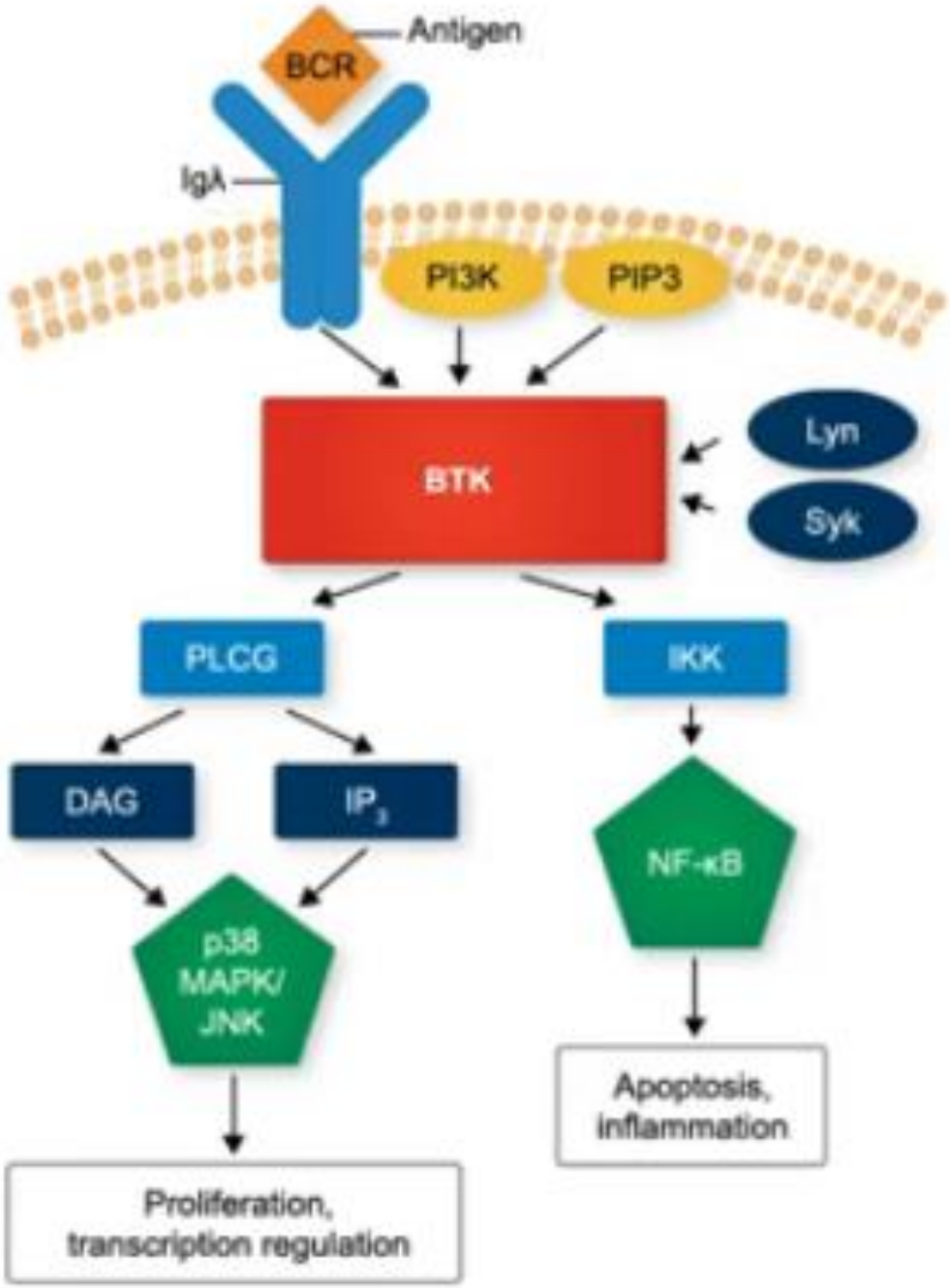
What is BTK?

- Bruton's tyrosine kinase (abbreviated Btk or BTK), also known as tyrosine-protein kinase BTK, is a tyrosine kinase that is encoded by the BTK gene in humans.
- Bruton's tyrosine kinase was discovered in 1993 and is named for Ogden Bruton, who first described XLA in 1952
- BTK plays a crucial role in B cell development and should not be confused with Dennis Rader, who is also known as the BTK killer.
- BTK plays a crucial role in B cell development as it is required for transmitting signals from the pre-B cell receptor that forms after successful immunoglobulin heavy chain rearrangement.

Within the BCR Pathway

BTK is a valuable and effective drug

BTKis are highly effective in a variety of B cell cancer



BTKi Approvals in B-Cell Cancers

What limits the efficacy of BTKi therapy?

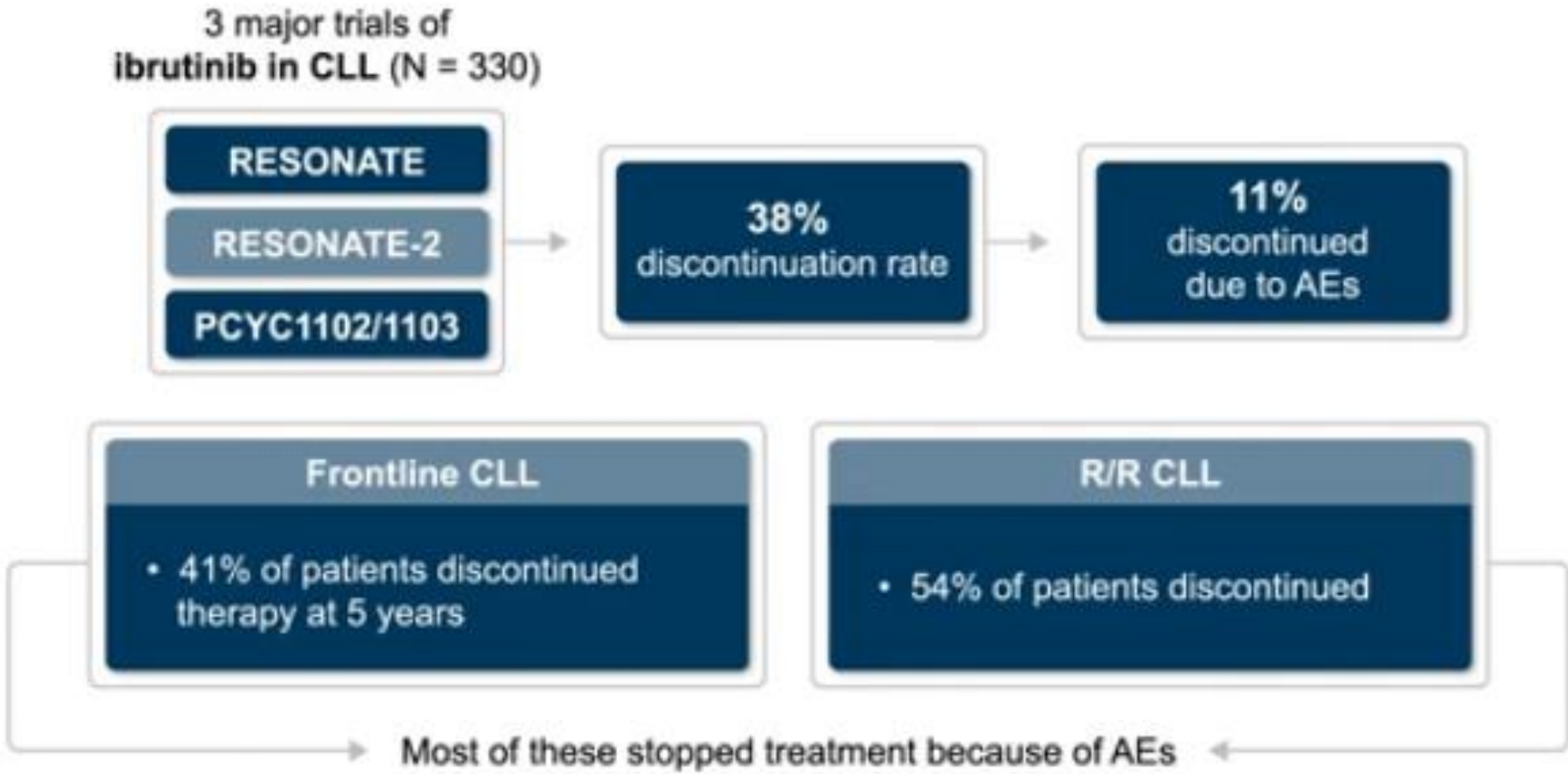
First-Generation BTK Inhibitor
Ibrutinib

- Selective, covalent inhibitor of BTK[a,b]
  - Irreversibly binds to cysteine-481 in active site of BTK
  - Significant activity against other kinases
- Off-target kinases inhibited: Tec, EGFR, JAK3, ERBB2, ERBB4, ITK[c,d]
  - Platelet aggregation
  - Off-target binding associated with ibrutinib contributes to its side effects
    - AF, bleeding, diarrhea, rash

Second-Generation BTK Inhibitor
Acalabrutinib

- Irreversible BTK inhibitor[a]
  - Shares cysteine 481 binding site
  - Greater specificity for BTK vs other Tec-family kinases
  - Off-target kinases inhibited: ERBB4
  - Mean half-life approximately 1 hour
- In October 2017, acalabrutinib was granted US FDA approval for the treatment of adults with MCL who have received at least 1 prior therapy[b]

Drug	Binding	Current Phase
Evobrutinib	Covalent Irreversible	3
Tolebrutinib	Covalent Irreversible	3
Fenebrutinib	Noncovalent Reversible	3
BIIB091	Noncovalent Reversible	1


3 major trials of
ibrutinib in CLL (N = 330)
RESONATE
RESONATE-2
PCYC1102/1103
38%
discontinuation rate
11%
discontinued
due to AEs
Frontline CLL
• 41% of patients discontinued therapy at 5 years
R/R CLL
• 54% of patients discontinued
Most of these stopped treatment because of AEs

One real-world analysis showed that toxicity was the most common reason for discontinuation in patients who discontinued ibrutinib

Reason for Discontinuation, % (n)	Ibrutinib	Idelalisib
Toxicity	51 (73)	52 (18)
CLL progression	28 (40)	31 (11)
Radiation therapy	8 (11)	6 (2)
Cellular therapy (CAR-T or HCT)	2 (3)	0 (0)
Unrelated death/other	11 (16)	11 (4)

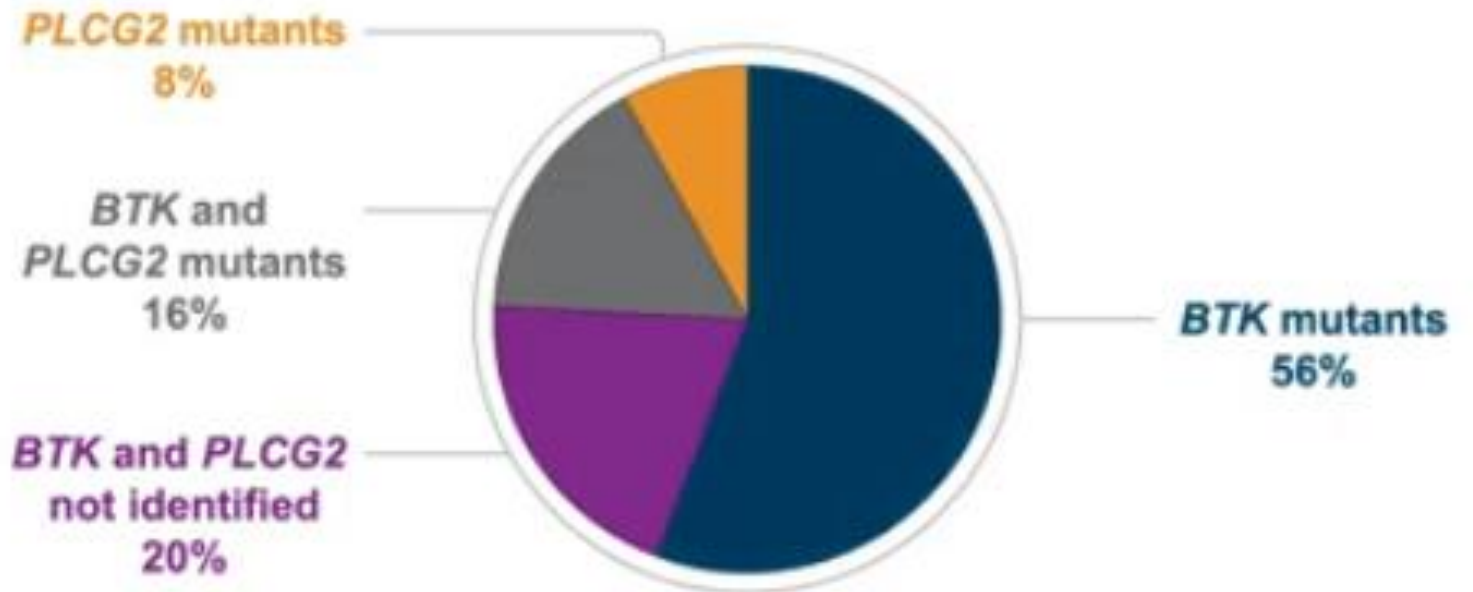
In another real-world CLL/SLL study (N = 616), 41% of patients discontinued ibrutinib (median follow-up of 17 months)

Most Common AEs Leading to Discontinuation

- Mutations in the BTK gene are implicated in the primary immunodeficiency disease X-linked agammaglobulinemia (Bruton's agammaglobulinemia); sometimes abbreviated to XLA and selective IgM deficiency.
- Patients with XLA have normal pre-B cell populations in their bone marrow but these cells fail to mature and enter the circulation.
- The Btk gene is located on the X chromosome (Xq21.3-q22).
- At least 400 mutations of the BTK gene have been identified. Of these, at least 212 are considered to be disease-causing mutations.

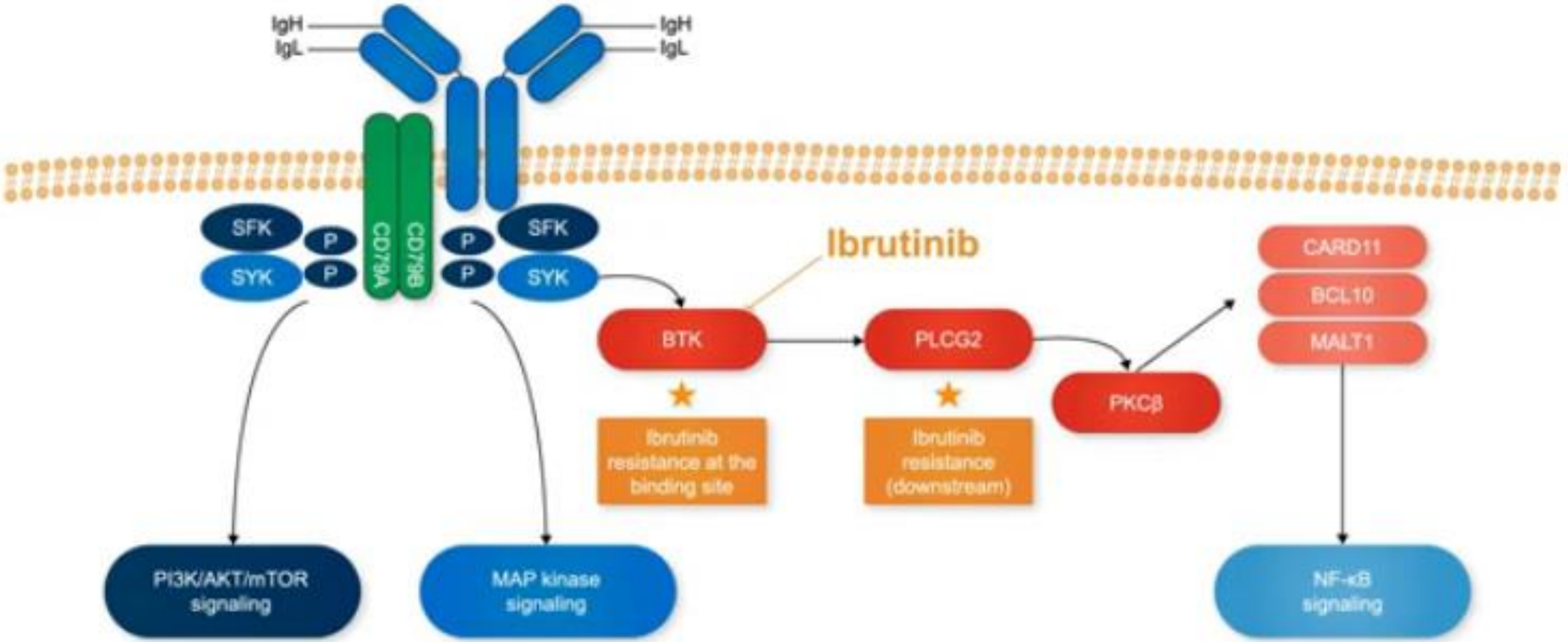
87% of CLL patients with progression had mutations at the *BTK* or *PLCG2* sites that were acquired at relapse

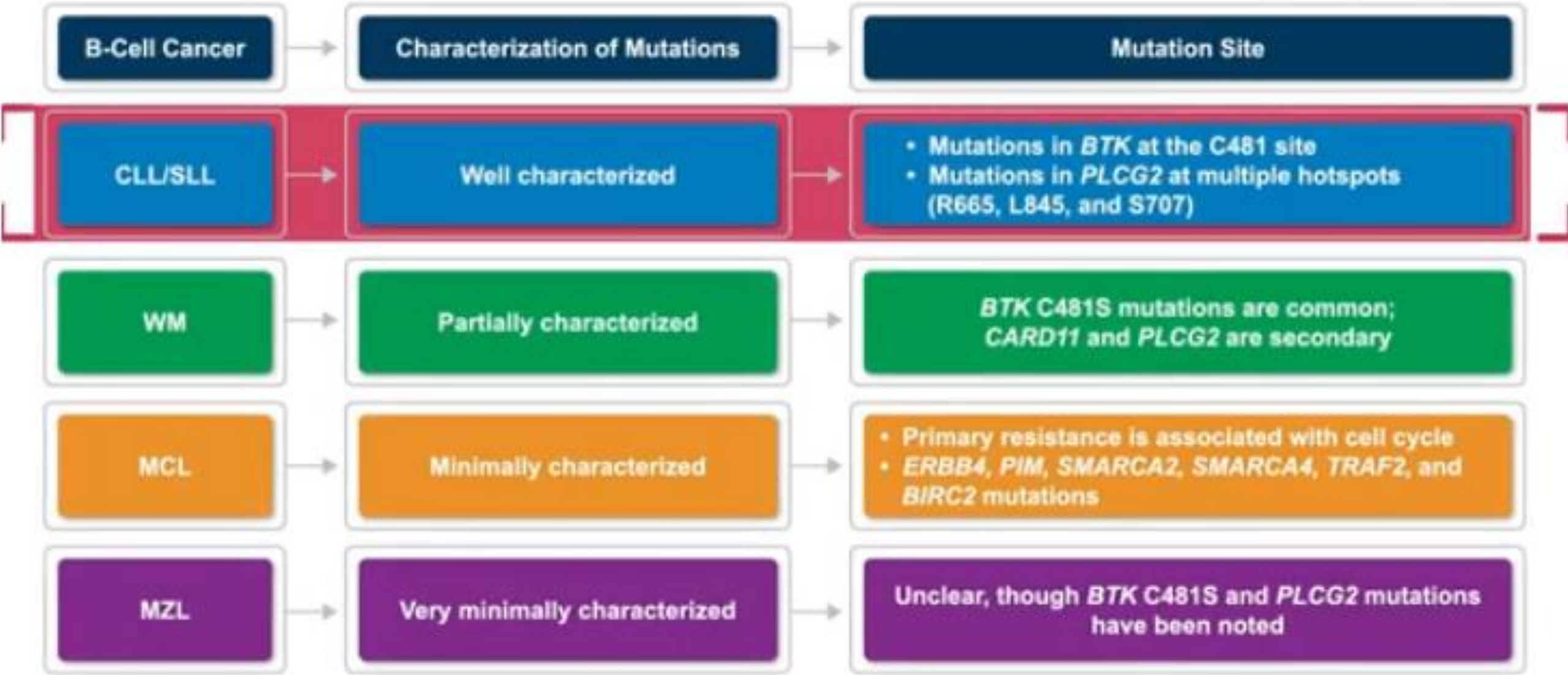
Ibrutinib-Acquired Resistance in Patients With Progressive CLL

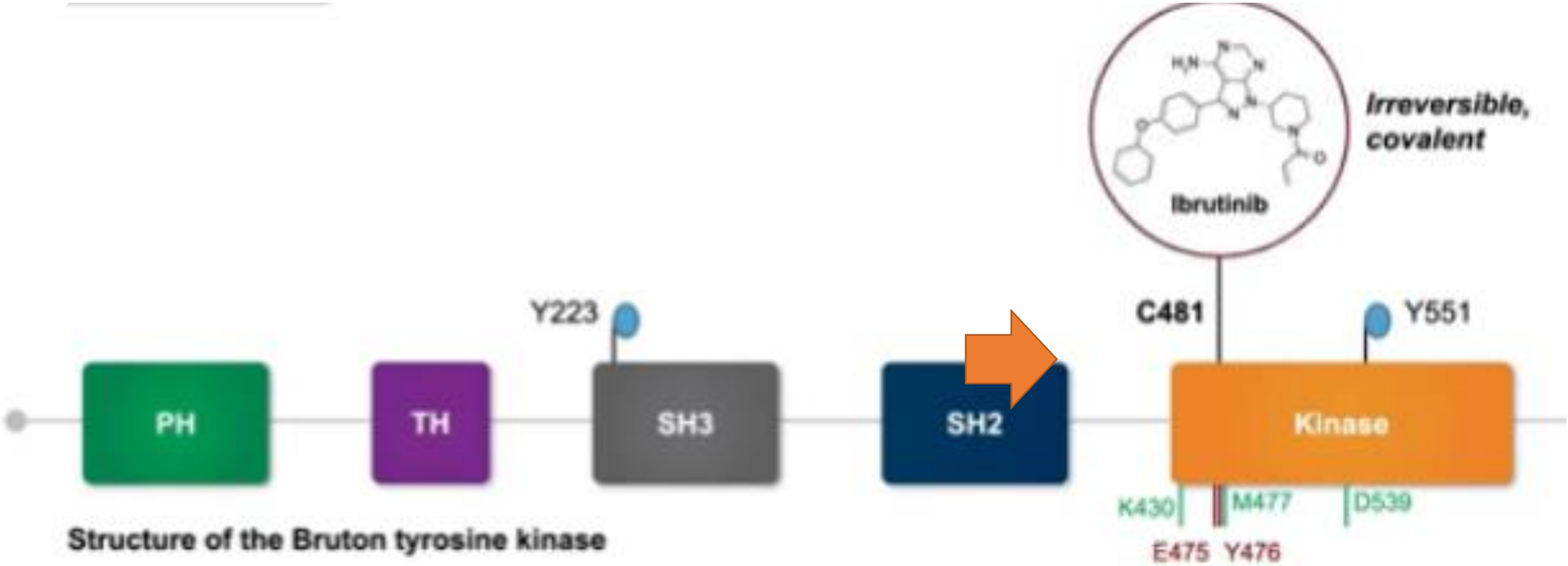


***BTK* C481 mutations prevent covalent BTK inhibitors from effective target inhibition**

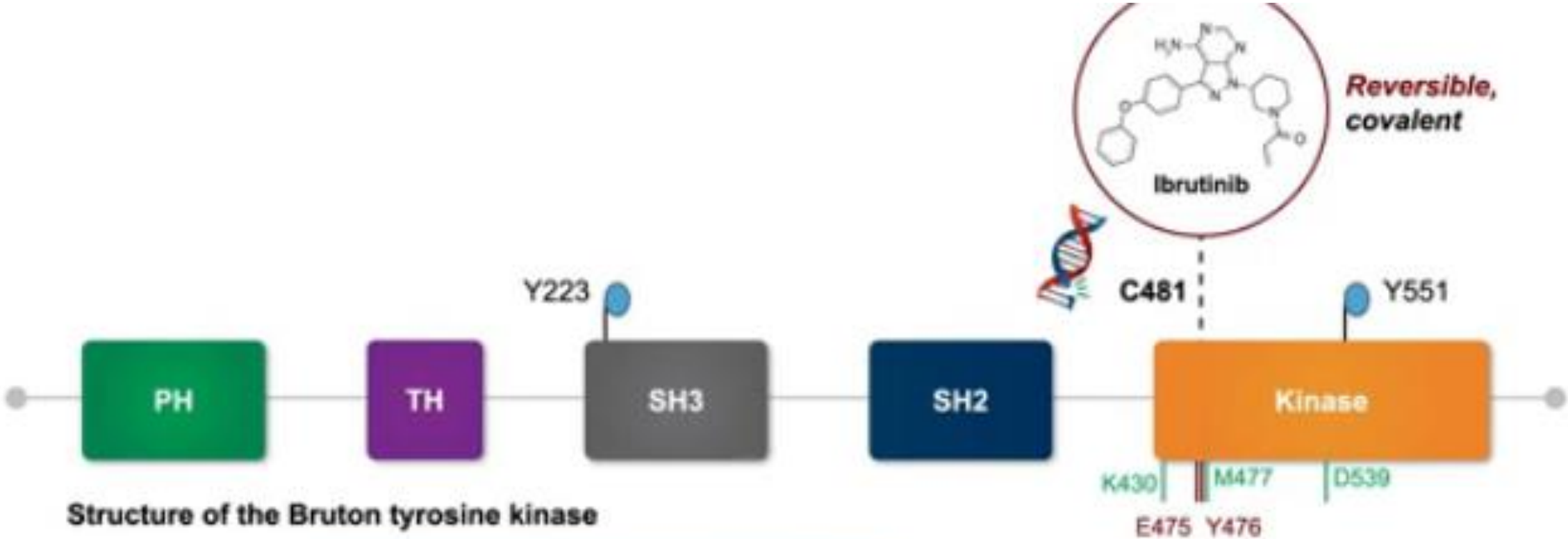
BTK signaling




B-Cell Cancer
Characterization of Mutations
Mutation Site
CLL/SLL
Well characterized
• Mutations in BTK at the C481 site
• Mutations in PLCG2 at multiple hotspots (R665, L845, and S707)
WM
Partially characterized
BTK C481S mutations are common; CARD11 and PLCG2 are secondary
MCL
Minimally characterized
• Primary resistance is associated with cell cycle
• ERBB4, PIM, SMARCA2, SMARCA4, TRAF2, and BIRC2 mutations
MZL
Very minimally characterized
Unclear, though BTK C481S and PLCG2 mutations have been noted



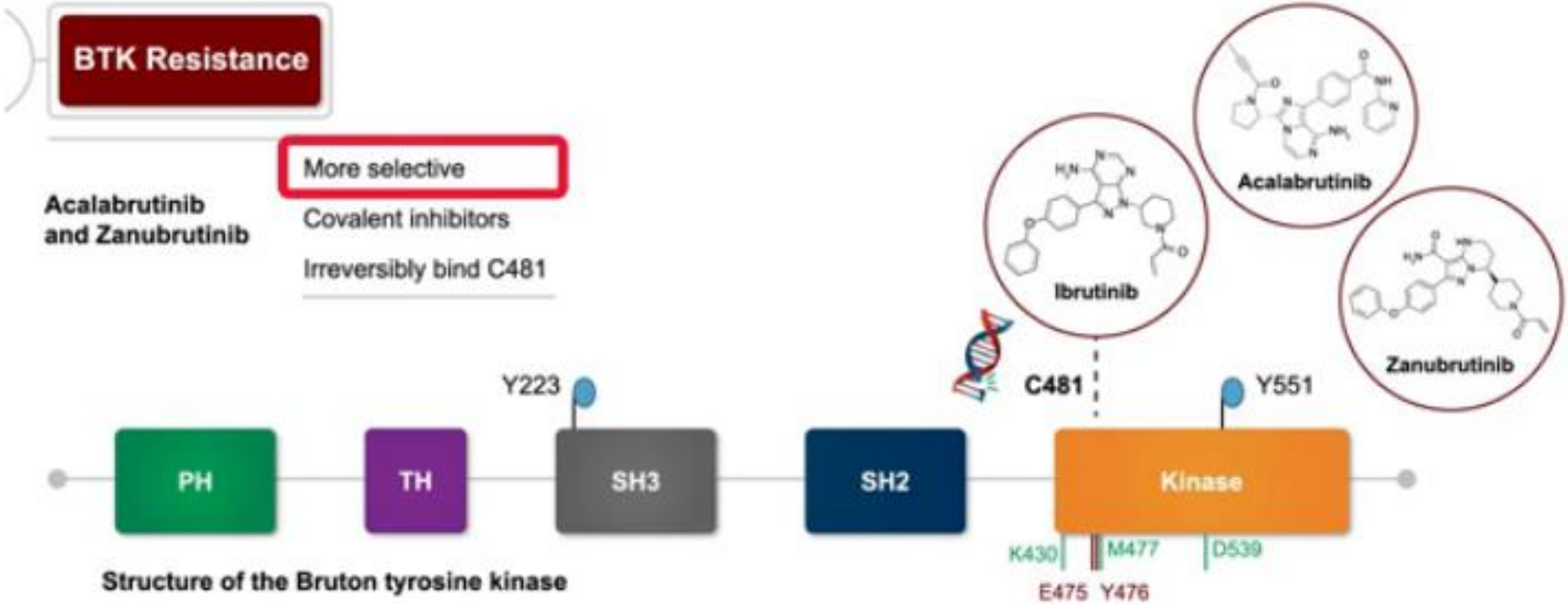
Structure of the Bruton tyrosine kinase



Structure of the Bruton tyrosine kinase

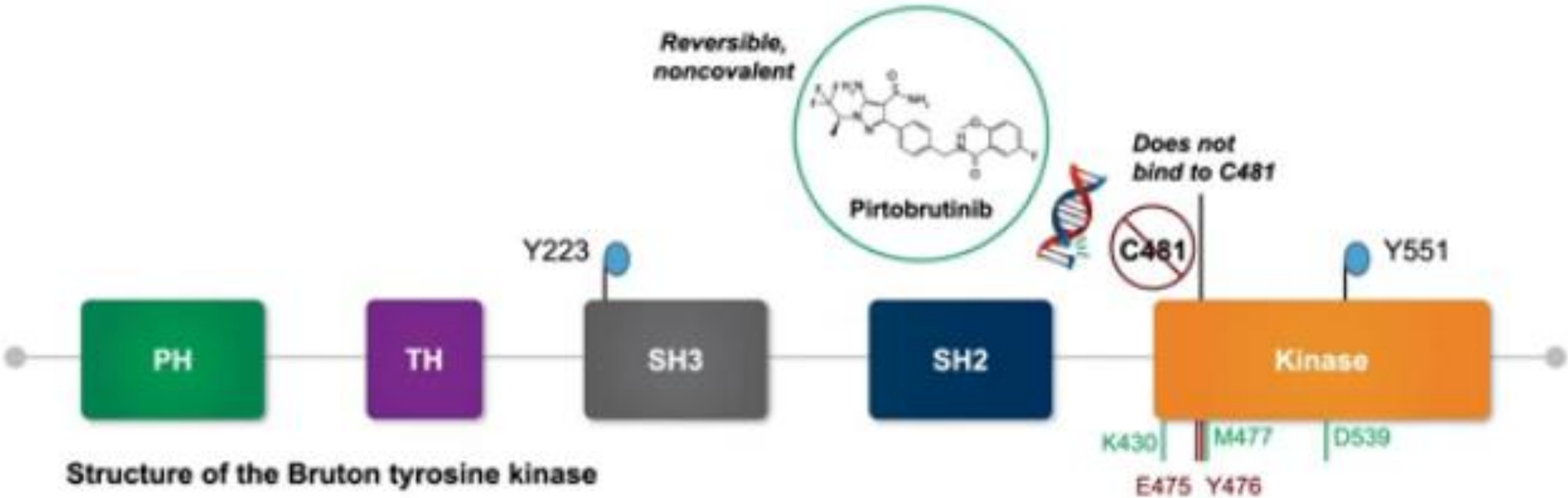
↓ in binding efficiency

Results in resistance and allows for an ↑ in BTK enzymatic activity



disease progression

Diminish the efficacy of all covalent BTKi



Structure of the Bruton tyrosine kinase

Pirtobrutinib	Can reversibly inhibit BTK
	Can overcome BTK resistance in patients who have not responded to other BTK inhibitors
	Blocks ATP binding site of BTK

	CLL/SLL	MCL	MZL	WM
Ibrutinib	Approved	Approved (second-line therapy)	Approved (second-line therapy)	Approved
Acalabrutinib	Approved	Approved (second-line therapy)	Phase 1/2	Phase 2
Zanubrutinib	Phase 3 (SEQUOIA)	Approved (second-line therapy)	Approved	Approved
Pirtobrutinib	Phase 3 (NCT04666038)	Phase 3 (NCT04662255)	Phase 2	Phase 2

Novel, noncovalent BTK inhibitors have efficacy in patients progressing on prior covalent BTK inhibitor therapy (BRUIN)

The toxicity profile of noncovalent agents appears to be different than that of covalent irreversible inhibitors

- **BRUIN-MCL-321:** pirtobrutinib versus ibrutinib, acalabrutinib, or zanubrutinib in R/R BTK-naïve MCL

Noncovalent BTK inhibitors can overcome resistance mutations in patients who have not responded to irreversible covalent BTK inhibitors

The potential of noncovalent agents to offer better efficacy than covalent BTK inhibitors is being explored in phase 3 trials

Patient population	Therapeutic regimen	Phase	Efficacy
R/R CLL	Ibrutinib	Ib/II	ORR (71%), PR(20%)
R/R CLL	Ibrutinib	III	ORR (63%)
TN CLL	Ibrutinib	Ib/II	ORR (85%), CR(26%)
TN CLL	Ibrutinib	III	ORR (86%), CR(4%)
R/R MCL	Ibrutinib	II	ORR (68%), CR(21%)
R/R MCL	Ibrutinib	III	ORR (72%), CR(19%)
R/R WM	Ibrutinib	II	ORR(91%), Major response (73%)
R/R ABC-DLBCL	Ibrutinib	II	ORR (37%)
R/R CLL	Ibrutinib-Rituximab	II	ORR (95%), CR(8%)
R/R CLL	Ibrutinib-bendamustine-rituximab	III	ORR (83%), CR(10%)
R/R MCL	Ibrutinib-Rituximab	II	ORR (88%), CR(44%), PR(44%)
R/R CLL	Acalabrutinib	I/II	ORR(95%)
R/R	Acalabrutinib	II	ORR (81%), CR (40%), PR(41%)
R/R CLL	ONO/GS-4059	I	ORR(96%)
R/R MCL	ONO/GS-4059	I	ORR(92%)
R/R non-GCB DLBCL	ONO/GS-4059	I	ORR(92%)
R/R CLL	BGB-3111	I	ORR(90%)
R/R MCL	BGB-3111	I	ORR(80%)

Combination	Disease	Model	Rationale	Effect
γ-secretase inhibitors (crucial protease in Notch signaling)	CLL	CLL patient cells	NOTCH1 signaling is related to resistance to therapy in B-CLL.	Combination therapy showed enhanced cytotoxicity and reduced CXCR4 expression and functions (response to SDF-1α)
Histone Deacetylase (HDACs) Inhibitor	CLL	- MCL cell line - mice engrafted with TCL-1 splenocytes	HDACs increase transcription of miRNA that repress BTK	HDAC induced increase in target miRNA and a decrease in BTK RNA; combination exhibited higher cytotoxicity than either drug alone; reduction of p-BTK and total BTK protein.
Anti-CD19 CAR T Cells (CART19)	MCL	MCL Xenograph model	Efficient B cell depletion	Long-term remission in 80–100% of mice (treated with CART19 only: 0–20% of mice)
Ethacridine (Poly(ADP-ribose) glycohydrolase inhibitor)	AML	SCID mice injected s.c. with OCI-AML2 cells	Result of a drug screening	High decrease of OCI-AML2 cell growth (more than with either drug alone). Suggested mechanism: increased intracellular ROS production in cells treated with combination.
ND-2158 (IRAK4 inhibitor)	ABC-DLBCL	- ABC-DLBCL cell lines OCI-Ly10 and TMD8 - OCI-Ly10 xenografts	MYD88-IRAK4 signaling is important for ABC- DLBCL viability	Combination was more effective than ND-2158 alone in inhibiting IKK activity, enhancing apoptosis, and blocking tumor growth in mice.
PU-H71 (Binds to tumor enhanced HSP90 complexes)	ABC-DLBCL	DLBCL cell lines (HBL-1 and TMD8)	teHSP90 complexes are associated with tumor survival.	PU-H71 disrupts teHSPP90 (but not house-keeping fractions associated with HSP90). Synergistic effect, with ~ 95% tumor growth inhibition; decreased NF-kB activity
TP-0903 (AXL inhibitor)	CLL	Patient CLL cells prior to or after ibrutinib therapy	AXL contributes to oncogenic survival in CLL.	TP-093 disrupts the activity of AXL; Induction of cell-death in a dose-dependent fashion
B-PAC-1 (pro-caspase activating compound)	CLL	B cells from patients on ibrutinib therapy	B-PAC activates caspases dimers	Induced cytotoxicity in leukemic cells
Carfilzomib (proteasome inhibitor)	CLL	Primary CLL patient samples MEC-1 and MEC2 cell lines	Upregulation of pro-apoptotic transcription factor CHOP	Combination showed an additive cytotoxic effect; Carfilzomib induced a pro-apoptotic response involving Noxa, MCL-1, Bax, and

“Once they’re linked, they don’t let go,” Because they share the same binding mechanism, if one drug doesn’t work for a patient, neither will the others.

“This opens the door to another option, even if a patient has received another BTK inhibitor,” .