

This is a copy of a chat between Claude and Lars S. Content may include unverified or unsafe content

(i) that do not represent the views of Anthropic. Shared snapshot may contain attachments and data not displayed here.

Report

Ls What genes can cause resistance to ibrutinib in chronic lymphocytic leukemia, and what alternative drugs can target them?

I'll search for information about genes associated with ibrutinib resistance in CLL and potential alternative therapies.

L get_variant_evidence

L get_variant_evidence

Now let me search for drug interactions targeting BTK and PLCG2:

L get_drug_interactions_for_gene_list

Let me also search for evidence on pirtobrutinib specifically for C481S resistance:

L get_variant_evidence

Based on the CIViC and DGIdb databases, here's what's known about ibrutinib resistance in CLL:

Genes Associated with Ibrutinib Resistance in CLL

1. BTK (Bruton's Tyrosine Kinase)

The most common resistance mechanism involves mutations in **BTK**, the direct target of ibrutinib:

- **BTK C481S** - The most frequent resistance mutation. Studies found this mutation in 5/6 patients with acquired ibrutinib resistance ([EID:436](#), [PMID:24869598](#)). In a larger study of 308 CLL patients, 8/9 BTK mutations identified were C481S ([EID:1770](#), [PMID:26182309](#)). This mutation disrupts the cysteine residue where ibrutinib covalently binds.

- **BTK T316A** - A less common mutation in the SH2 domain that also confers resistance ([EID:1985](#), [PMID:27626698](#)).

2. PLCG2 (Phospholipase C Gamma 2)

Mutations in **PLCG2**, which acts downstream of BTK in B-cell receptor signaling, can bypass BTK inhibition entirely. Variants like N571S and D1140E have been associated with resistance ([PMID:32232486](#)).

Alternative FDA-Approved BTK Inhibitors

Drug	Mechanism	Notes
Pirtobrutinib	Non-covalent (reversible) BTK inhibitor	Specifically designed to retain activity against C481S-mutant BTK; approved for relapsed/refractory CLL
Zanubrutinib	Covalent BTK inhibitor	More selective than ibrutinib; may have improved tolerability
Acalabrutinib	Covalent BTK inhibitor	More selective than ibrutinib
Tirabrutinib	Covalent BTK inhibitor	Approved in some regions

Key point: Covalent inhibitors like zanubrutinib and acalabrutinib share the same binding mechanism as ibrutinib, so **BTK C481S mutations typically confer cross-resistance** to these agents as well. **Pirtobrutinib** is particularly relevant for C481S-resistant cases because it binds reversibly and doesn't depend on C481.

Alternative Strategies for PLCG2 Mutations

Since **PLCG2** mutations bypass BTK entirely, alternative approaches may include:

- **Venetoclax** (BCL-2 inhibitor) - targets a different pathway
- **PI3K inhibitors** - target upstream signaling

Would you like more detail on any of these therapeutic options or mechanisms?

(i) Turn on web search in Search and tools menu. Otherwise, links provided may not be accurate or up to date.

Start your own conversation

