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**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?