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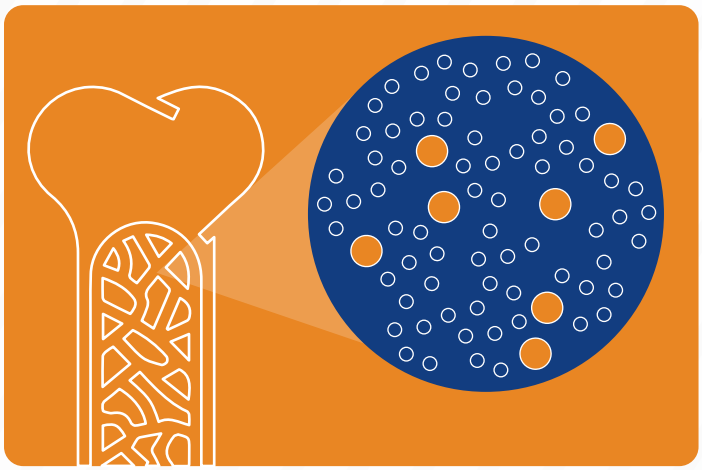
Exploring the Latest Advancements in B-Cell Neoplasm Treatment

An overview of the latest developments in Bruton's tyrosine kinase inhibitors

Chronic lymphocytic leukaemia: an overview

Chronic lymphocytic leukaemia (CLL) is a B-cell malignancy characterised by:[1]



- Night sweats
- Significant fatigue
- Autoimmune complications
- Progressive lymphocytosis
- Development of/worsening anaemia
- Development of/worsening thrombocytopenia
- Progressive/symptomatic splenomegaly
- Progressive/symptomatic lymphadenopathy
- Fever ≥38 °C without evidence of infection
- Unintentional weight loss ≥10% in the past 6 months

A recent cohort study has demonstrated that patients with CLL can be categorised based on the mutational status of the variable region of the immunoglobulin heavy chain (IGHV) gene[2–6]

Survival[4] — Mutated *IGHV* — Risk of genetic lesion[5,6]

Outline for CLL treatment[7]

Bruton's tyrosine kinase inhibitors (BTKis) have evolved to be an effective treatment option for CLL in first-line (1L), second-line (2L), and third-line (3L) therapy stages

Diagnosis of CLL based on the International Workshop on CLL (iwCLL) criteria

Screening and categorisation of patients based on mutations in tumour protein 53 (TP53) and *IGHV*

- Frontline therapy
- 2L therapy
- 3L therapy

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CLL management with BTKis

The last decade has witnessed the development and approval of many second- and third-generation BTKis

Regulatory status of BTKis for CLL/small lymphocytic lymphoma (SLL)[8–10]

Agent	Method of action	EU (CLL/SLL)	US (CLL/SLL)
Ibrutinib	Covalent	Approved	Approved
Acalabrutinib	Covalent	Approved	Approved
Zanubrutinib	Covalent	Approved	Not yet approved
Pirtobrutinib	Noncovalent	Not approved; phase III BRUIN CLL-313 (NCT05023980), BRUIN CLL-314 (NCT05254743), BRUIN CLL-321 (NCT04666038), BRUIN CLL-322 (NCT04965493), trials ongoing	
Nemtabrutinib	Noncovalent	Not approved; phase II (NCT04728893), ongoing	

The efficacy of the BTKis is supported by strong phase III trial evidence

BTKis	Trial	Comparator	Finding
Ibrutinib[11–15]	RESONAT 2	Chlorambucil	Superior PFS and OS
	iLLUMINATE	Obinutuzumab + chlorambucil	Superior PFS
	ECOG 1912	FCR	Superior PFS and OS
	ALLIANCE	Bendamustine and rituximab	Superior PFS
	RESONATE	Ofatumumab	Superior PFS
Acalabrutinib[16]	ELEVATE TN	Obinutuzumab + chlorambucil	Superior PFS; better OS
	ASCEND	NA	Superior PFS
Zanubrutinib[17]	SEQUOIA	Bendamustine and rituximab (BR)	Superior PFS vs BR

PFS: progression-free survival; OS: overall survival

Comparison of the approved BTKis amongst each other showed:

Acalabrutinib	Comparable efficiency	Ibrutinib
Zanubrutinib	Superior to	Ibrutinib
Acalabrutinib	Could not be directly compared	Zanubrutinib
Ibrutinib	Superior to	Chemoimmunotherapy

How do tumour cells become resistant to BTKis?

Novel mutations in the BTK receptor's catalytic domain confer resistance to BTKis

- Covalent — C481
- Noncovalent — BTK L528W, V416L, M437R T474I, A428D

BTK resistance

- Diminishes efficacy of BTKis
- Promotes disease progression

BTKis and toxicities

BTKis are associated with adverse effects (AEs) that need to be managed in a timely fashion

Haemorrhage

Cardiotoxicity

Infections

Ibrutinib dosage can be tailored for patients experiencing:

- Grade >3 non-haematological toxicity
- Grade >3 neutropenia with infection or fever
- Grade 4 haematological toxicities

Optimising CLL therapy

Patient selection

- Past medical history, comorbid conditions
- Adherence assessment
- Goals of care
- Financial implications of indefinite therapy

Drug interactions

- Thorough medicine reconciliation
- Evaluation of herbal medications
- Alert pharmacist about new medications

AE management

- Counsel patients on common and serious AEs
- Empower patients to manage AEs on their own
- Provide patient-friendly guidance information
- Optimise blood pressure (ibrutinib), manage tumour lysis syndrome (venetoclax)
- Manage headaches (acalabrutinib), infusion-related reactions (CD20 mAb)

Key takeaways

- BTKis are highly effective as 1L and relapse treatment strategies for CLL
- Cardiovascular toxicities are a major limitation of covalent BTKis
- Continuous BTKis monotherapy is superior to chemoimmunotherapy
- Second generation BTKis are safer and as effective as ibrutinib
- Updated knowledge of BTKis can be used to select eligible patients and personalise treatments

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