Analysis of resistance-related mutations in patients with Chronic Lymphocytic Leukemia treated with BTK or BCL2 inhibitors suggests different underlying resistance mechanisms and subclonal dynamics

Miguel Bastos Boente[1,2], María García Álvarez[1], Cristina Jiménez Sánchez[1], Alicia Antón Gómez[1], Ana Balanzategui Echevarría[1], María Eugenia Alonso Sarasquete[1], Alejandro Herrera Medina[1], Rebeca Maldonado Sánchez[1], María Jesús Vidal Manceñido[2], Abelardo Bárez García[2], Ana Smucler Simonovich[2], María Jesús Peñarrubia Ponce[2], Emilia Pardal de la Mano[2], José Antonio Queizán Hernández[2], Francisco Javier Díaz Gálvez[2], Alberto Albarrán Severo[2], Carlos Aguilar Franco[2], Luis García Martín[2], Ramón García Sanz[2], Cristina de Ramón Sánchez[1,2], Norma Carmen Gutiérrez Gutiérrez[1,2], Almudena Navarro Bailón[1,2], Miguel Alcoceba Sánchez[1,2]

1. Servicio de Hematología, Hospital Universitario de Salamanca (HUS – IBSAL), CIBERONC e Instituto de Investigación del Cáncer de Salamanca – IBMCC (CSIC – Universidad de Salamanca), Salamanca, España.

2. Grupo de trabajo cooperativo de linfomas y procesos linfoproliferativos de la Sociedad Castellano-Leonesa de Hematología y Hemoterapia (SCLHH)

Miguel Bastos Boente *mbastos.ibsal@saludcastillayleon.es*

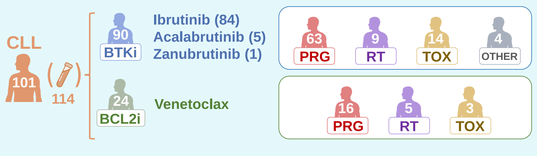
INTRODUCTION

Bruton tyrosine kinase (BTK) and B-cell lymphoma 2 (BCL2) inhibitors have revolutionized the treatment of chronic lymphocytic leukemia (CLL). However, acquired resistance remains a major clinical challenge. *BTK* and *PLCG2* mutations are the primary drivers of resistance to BTK inhibitors (BTKi), while *BCL2* mutations are associated with resistance to BCL2 inhibitors (BCL2i). Understanding the clonal evolution driven by these mutations is essential for optimizing subsequent therapeutic choices.

OBJECTIVES

1. **To describe the mutations found in patients resistant to ibrutinib and/or venetoclax**
2. **To study the mechanism of resistance in ibrutinib-treated patients and the time required for resistance to develop**
3. **To analyze the importance of the compartment in resistance evaluation**
4. **To analyze the clonal evolution of *BTK* mutation after ibrutinib and venetoclax treatment**

METHODS



We included 114 samples from 101 CLL patients treated with BTKi (84 ibrutinib, 5 acalabrutinib, 1 zanubrutinib) and/or BCL2i (24 venetoclax). N=90 patients discontinued BTKi (63 for progression, 9 due to Ritcher's transformation [RT], and 18 for toxicity or other causes). N=24 discontinued Venetoclax (16 for progression, 5 for RT and 3 for toxicity).

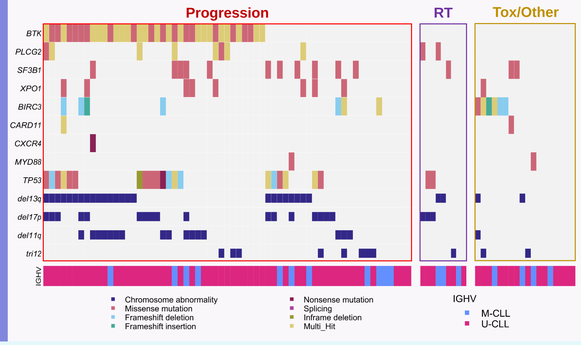
Eleven patients who progressed on ibrutinib and subsequently on venetoclax had both samples sequenced.

All cases were analysed using a custom next-generation sequencing panel with a limit of detection of 0.5% in an Illumina MiniSeq System.

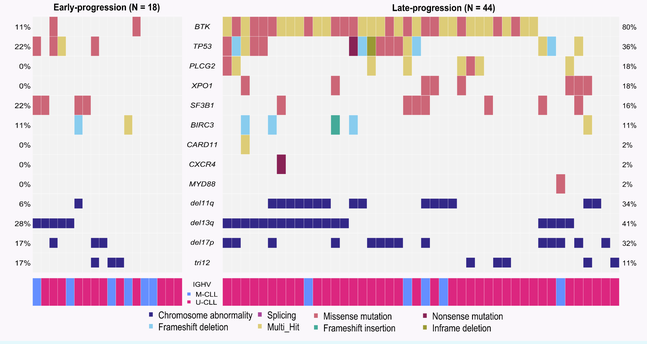
RESULTS

BTKi resistance

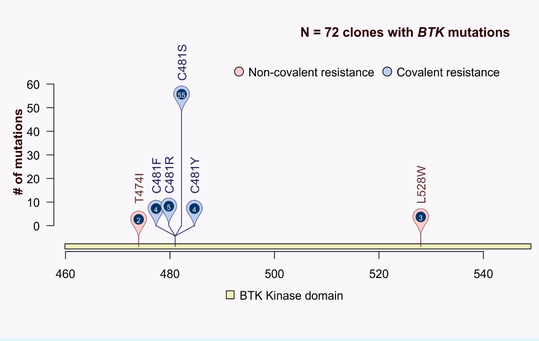
MORE THAN A THIRD OF THE PATIENTS WHO PROGRESSED DID NOT SHOW *BTK/PLCG2* MUTATIONS



DIFFERENCES WERE OBSERVED BETWEEN PATIENTS WITH EARLY AND LATE PROGRESSION

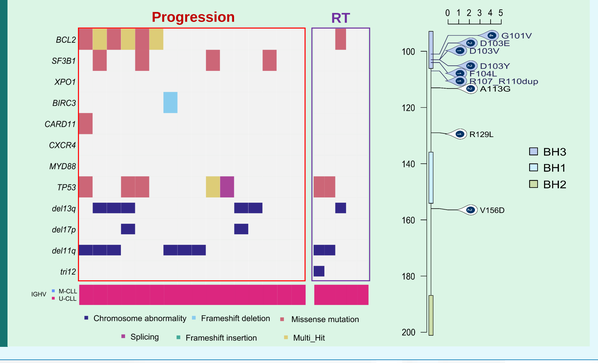


UNDER IBRUTINIB, MUTATIONS THAT CONFER RESISTANCE TO NON-COVALENT INHIBITORS COULD APPEAR



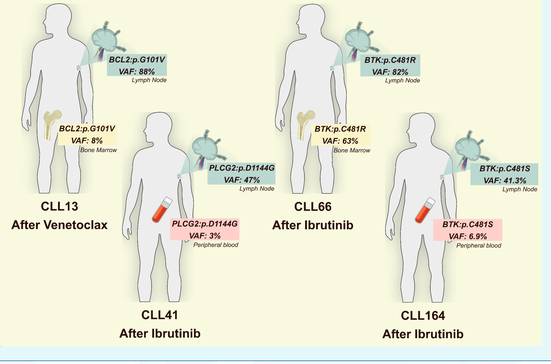
Venetoclax resistance

VENETOCLAX RESISTANCE SEEMED NOT TO BE ONLY DEPENDENT OF THE *BCL2* MUTATION



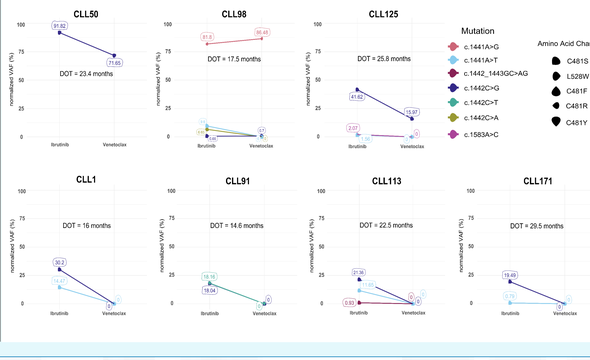
Compartment analysis

THE COMPARTMENT ANALYZED IS IMPORTANT WHEN FINDING VARIANTS IN *BTK* AND *BCL2*



Clonal persistance

VARIANT ALLELE FREQUENCY (VAF) MAY CONDITION TREATMENT WITH A NEW BTKI AFTER VENETOCLAX



CONCLUSIONS

- Although most of the mutations conferring resistance to ibrutinib involve known genes, **in more than a third of cases the biological explanation is unknown** and the **acquisition of *BTK* mutations** requires **minimal time of exposure to the drug.** This is evidence for the possible existence of primary resistance mechanism that explain the early progression in some patient groups.
- **Under ibrutinib**, mutations conferring resistance to the **new non-covalent inhibitors** may occur, so the **entire kinase region needs to be studied** prior to administration of the latter in patients treated with an BTKi.
- The analysed compartment **is crucial** to elucidate whether resistance mutations are present.
- The **variant allelic frequency of *BTK*** during **progression to ibrutinib** could condition the **persistence of this clone after venetoclax** administration. This could be taken into account when **considering treatment with a new BTKi after venetoclax**.

ACKNOWLEDGEMENTS

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MORE INFORMATION

More data