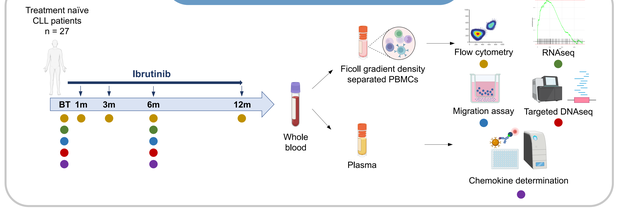
Immune-profiling of ibrutinib-treated CLL patients revealed TMBIM6 as a potential target for CLL and its high expression as an independent variable associated with poor prognosis

D. Medina[1], L. Palomo[1], V. Navarro[1], O. Castells[1], B. Sánchez[1], P.M. Muñoz Torres[1], C. Pagès[1], C. Hernández[1], G. Pujadas[1], C. Ferrà[2], M. Alcoceba[3], M.J. Terol[4], R. Andreu[5], F. Bosch[1], P. Abrisqueta[1] and M. Crespo[1]

Introduction

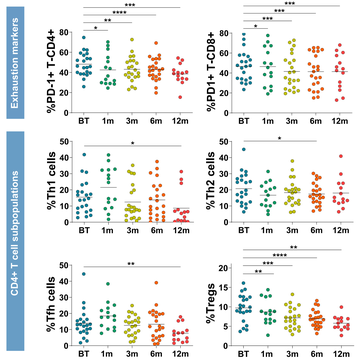
Current limitations of BTK inhibitors, in the context of continuous therapy, are the adverse effects and resistances leading to discontinuations, including *BTK* mutations and Richter transformation[1]. The crosstalk between CLL cells and their microenvironment is crucial for CLL progression and may be also contributing to the development of resistances[2]. Ibrutinib has been shown to improve T cell function and induce an early release of CLL cells from proliferation centers into peripheral blood[3]. We conducted multi-omics analyses to longitudinally assess the immunomodulation of ibrutinib on T cells and CLL cells, aiming to identify potential adaptive mechanisms to BTK inhibition in the first 12 months of continuous treatment in the GELLC7 clinical trial (NCT03280160).

Methods

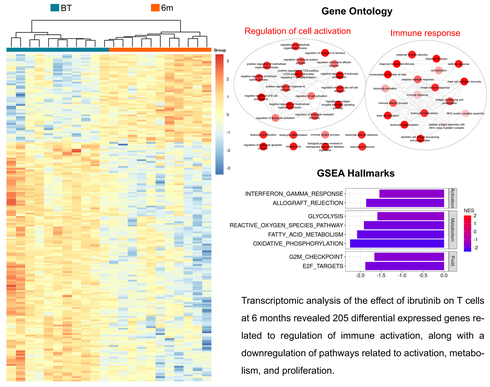


Results

Ibrutinib improves characteristic features associated with T cell dysfunction in CLL

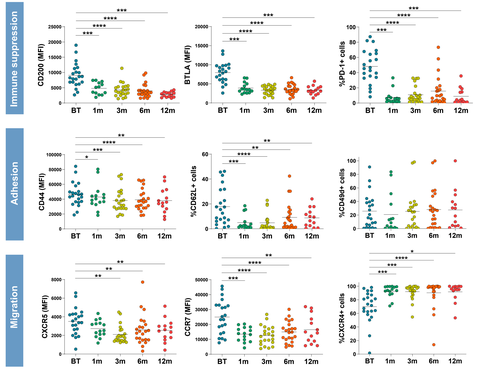


Transcriptomic changes in T cells upon ibrutinib

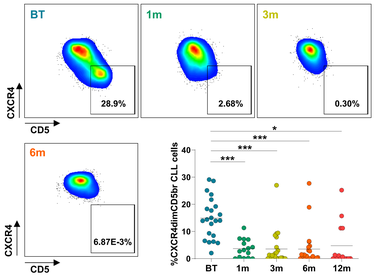


Transcriptomic analysis of the effect of ibrutinib on T cells at 6 months revealed 205 differential expressed genes related to regulation of immune activation, along with a downregulation of pathways related to activation, metabolism, and proliferation.

Ibrutinib downregulates markers of immune supression, adhesion, and migration in CLL cells but not CXCR4

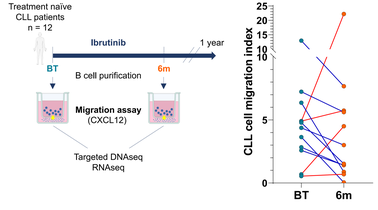


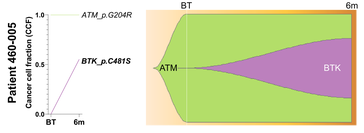
The proliferative CXCR4$_{dim}$CD5$_{br}$ CLL cells are depleted by ibrutinib



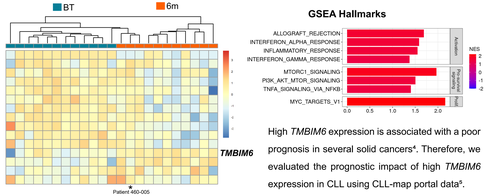
CXCR4 expression is upregulated upon ibrutinib treatment. CXCR4 homing is crucial for CLL cells to re-enter to proliferation centers. This process is known to be inhibited by ibrutinib in the short term; however, patients require continuous therapy, and discontinuations due to resistances or Richter transformation still occur. Thus, we aimed to study the role of CXCR4 homing capacity at 6 months upon ibrutinib treatment as an adaptative mechanism.

CLL cells with retained CXCR4 migration include a *BTK C481S* subclone

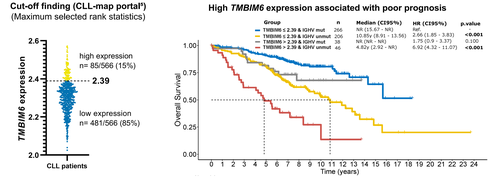




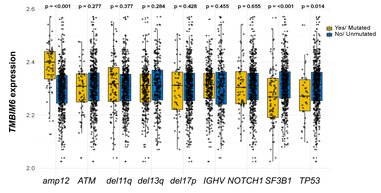
TMBIM6 is upregulated in CLL cells with retained CXCR4 migration and is a poor prognosis factor

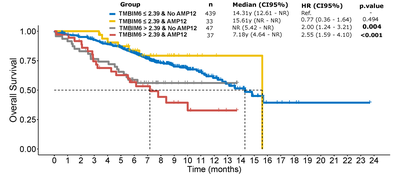


High *TMBIM6* expression is associated with a poor prognosis in several solid cancers[4]. Therefore, we evaluated the prognostic impact of high *TMBIM6* expression in CLL using CLL-map portal data[5].

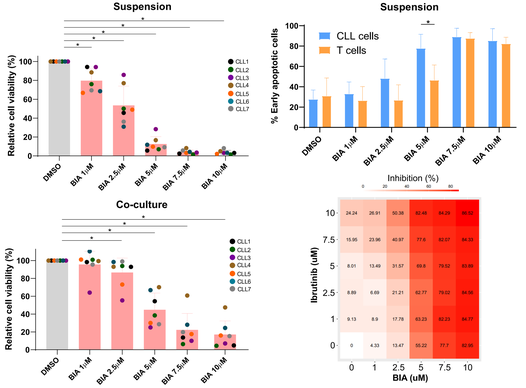


High *TMBIM6* expression stratifies patients with *amp12* into two risk groups





BIA[4], a TMBIM6 antagonist, induces apoptosis in CLL cells and synergizes with ibrutinib



Conclusions

Ibrutinib reduces the expression of exhaustion markers and supportive CD4+ T cell subpopulations. CLL cells with retained CXCR4 migration upregulate *TMBIM6* expression. High *TMBIM6* expression is a novel independent poor prognosis factor in CLL which distinguishes a higher-risk group of patients carrying amplification in chromosome 12. BIA, a TMBIM6 antagonist, demonstrated the induction of CLL cell apoptosis and a synergystic effect when combined with ibrutinib. Collectively, these results indicate that TMBIM6 may be a potential novel target for CLL, and that combining it with ibrutinib could be a valid approach for time-limited therapy.

References

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Affiliations

1. *Vall d'Hebron Institute of Oncology (VHIO), Barcelona.*
2. *Institut Català d'Oncologia-Hospital Germans Trias i Pujol, Badalona.*
3. *Centro de Investigación del Cáncer de Salamanca-IBMCC, Salamanca.*
4. *Hospital Clínico Universitario de Valencia, Valencia.*
5. *Hospital Universitario Politécnico "La Fe", Valencia.*

Email
Presenter: dmedina@vhio.net
Corresponding author: macrespo@vhio.net