Changes in immune cell numbers and profile during long-term zanubrutinib treatment in treatment-naïve and relapsed/refractory patients with chronic lymphocytic leukemia

Maria L. Andersson[1,2], Tom A. Mulder[1], Kia Heimersson[1], Sonja Sönnert-Husa[3], Annika Giertz[3], Claes Karlsson[1,2], Jeanette Lundin[1,2], Lotta Hansson[1,2], Anders Österborg[1,2] and Marzia Palma[1,2]

[1]Department of Oncology-Pathology, Karolinska Institutet; [2]Lymphoma Unit, Department of Hematology, Karolinska University Hospital; [3]Center for clinical cancer studies, Karolinska University Hospital, Stockholm, Sweden.

Introduction

Compromised immune function, in part due to expansion of immunosuppressive cells, is one of the hallmarks of chronic lymphocytic leukemia (CLL).

Zanubrutinib (BGB-3111) is a specific and irreversible Bruton's tyrosine kinase (BTK) inhibitor (BTKi) exerting a more selective relative inhibition of BTK versus other kinases than the first-in-class BTKi ibrutinib. One of these kinases is interleukin-2-inducible T cell kinase (ITK).

Changes in T cells have been observed during long-term treatment with ibrutinib in CLL patients (1).

It has been argued that ibrutinib's effects on T cells are completely "off-target", i.e. mainly occur through inhibition of kinases other than BTK, ITK in particular.

However, it is unclear to what extent these changes are induced by ITK inhibition rather than by the reduction of the tumor burden.

Objective

To evaluate the impact of zanubrutinib treatment on T and NK cells in patients with CLL up to 2-years follow-up compared to ibrutinib.

Method

Peripheral blood (PB) samples were collected before treatment start and at week (wk) 4, 8, 12, 16, 24 and at 8, 12 and 24 months (mo) from 8 treatment naïve (TN) pts included in the BGB-3111-304 and 8 relapsed/refractory (R/R) pts in the BGB-3111-305 clinical trials. Nine healthy individuals were included as controls. Baseline characteristics are shown in Table 1.

Peripheral blood mononuclear cells (PBMC) populations were assessed by flow-cytometry including CLL cells, T-cell memory subsets, Th subpopulations, Tregs and NK cells subsets.

Table 1.

Characteristic	BGB-304 (n=8)	BGB-305 (n=8)
Age, years, median (range)	72 (54-81)	75 (52-87)
Gender, male / female (n)	5 / 3	5 / 3
Rai stage, low / intermediate / high-risk (n)	0 / 4 / 4	0 / 0 / 4
ALC (x 10^9/L) at study entry, median (range)	128.7 (14.3-247.5)	154.1 (12.0-571.0)
Number of previous therapies, median number (range)	0	1 (1-2)
Cytogenetic abnormalities (n)		
Del(17p) / TP53 mut	2	3
Del(13q)	5	4
Del(11q)	1	2
Trisomy 12	3	1

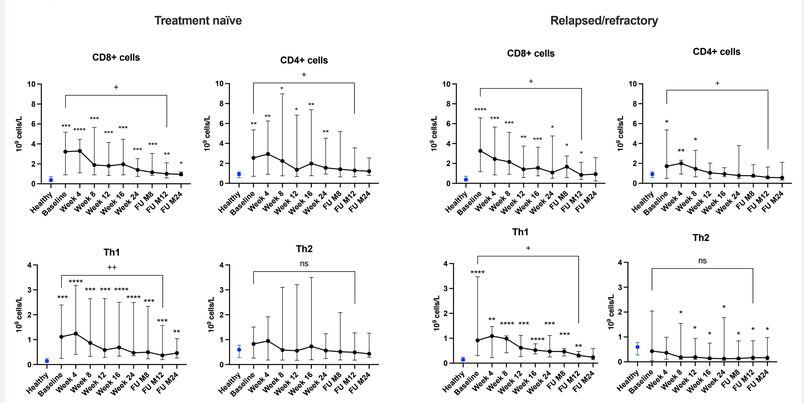
Maria Andersson, MD, PhD student
Department of Oncology-Pathology
Karolinska Institutet, Stockholm, Sweden
E-mail: maria.l.andersson@ki.se

Results

At a 24 mo follow-up, 6/8 pts in the BGB-304 and 6/8 in the BGB-305 trial were still on treatment and had achieved partial response. All the pts stayed on full-dose zanubrutinib during the whole treatment period.

As expected, a gradual reduction of the number of CD19⁺ cells occurred, significant from mo 8 in both R/R and TN pts. In both groups, CD8⁺ cell numbers were higher compared to controls at baseline and significantly decreased during treatment, at 12 mo in TN patients and at wk 16 in R/R patients, respectively. At 24 mo, normalization of CD8⁺ cell numbers had occurred in R/R patients but not in TN patients (Fig. 1).

Figure 1.

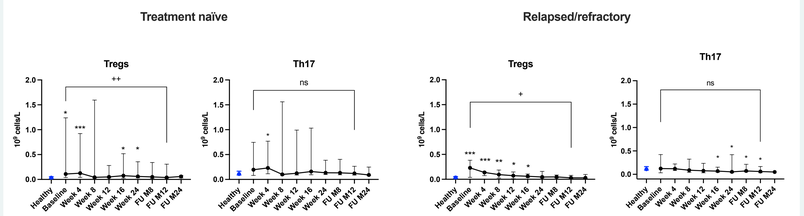


Plus signs indicate a statistically significant difference between baseline and 12 months as analyzed by Wilcoxon signed-rank tests. Stars indicate a statistically significant difference between healthy donors and the respective time point as analyzed by Mann-Whitney U tests. */+ p< 0.05, **/++ p< 0.005,*** p< 0.0005, ns= not significant

In both TN and R/R patients, T helper (Th) 1 cell numbers were higher at baseline compared to controls while Th2 did not significantly differ in TN and were lower compared to controls in R/R patients. In the TN group, Th1 cells decreased but never reached normal levels, while this occurred in R/R patients. In neither group significant changes were observed for Th2 cells.

Regulatory T cells (Treg) numbers decreased in both groups, in the R/R patients from wk 12 and in TN patients at 12 mo and normalized to the levels of the controls, at wk 24 and 8 mo, respectively. Th 17 numbers remained stable in both groups (Fig 2.)

Figure 2.



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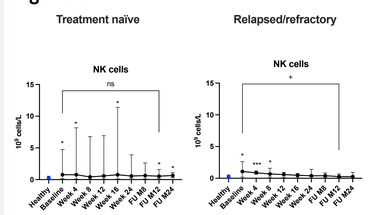
In both R/R and TN patients, naïve CD4+ and CD8+ T-cells remained unchanged during treatment. Central memory (CM) CD4+ and CD8+ normalized in R/R patients but remained unchanged and were significantly higher compared to controls in TN patients. In both groups, effector memory (EM) CD4+ and CD8+ cells were higher compared to controls and significantly decreased and normalized during treatment. EM CD8+ T effector memory re-expressing CD45RA (TEMRA) were also higher at baseline and decreased and normalized while CD4+ TEMRA remained unchanged in normal levels.

The number of cells expressing the immune checkpoints PD-1 and CTLA-4, which was high on CD4⁺ and CD8⁺ cells at baseline, gradually decreased significantly during the treatment.

NK cells decreased from wk 16 and normalized at wk 12 in R/R patients while remaining stable in TN patients (Fig 3).

Figure 3.



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Conclusion

During long-term zanubrutinib therapy, changes in the T and NK cells profiles occur in both TN and R/R patients, similarly to what previously observed in ibrutinib-treated patients. This suggests that the observed changes are related to the reduction of the tumor burden rather than to ITK inhibition.

Acknowledgements

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References

1. Tom.A.Mulder et al. Ibrutinib Has Time-dependent On- and Off-target Effects on Plasma Biomarkers and Immune Cells in Chronic Lymphocytic Leukemia. Hemasphere.2021

KAROLINSKA University Hospital
Karolinska Institutet