1222 - KINETICS OF LYMPHOCYTOSIS DURING BTK COVALENT INHIBITORS IN TREATMENT NAÏVE CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS. AN ITALIAN MULTICENTER EXPERIENCE OF REAL LIFE.

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INTRODUCTION: In chronic lymphocytic leukemia (CLL) patients (pts) the first phase of treatment with covalent Bruton's tyrosine kinase inhibitors (cBTKi), Ibrutinib or Acalabrutinib, is characterized by an increased absolute lymphocyte count (ALC), regardless of previous lines of treatment. Ibrutinib, as first-line therapy, induces lymphocytosis in about 57% of pts, and it is more frequent in IGHV mutated CLL patients. This phenomenon, due to the shift of neoplastic lymphocytes from the neoplastic nodal compartment into peripheral blood, is transient in most patients, resolving within 8 months, but can rarely persist over 12 months, without any impact on survival; the term Partial Response with lymphocytosis was coined due to this phenomenon. Despite lymphocytosis in Ibrutinib has been widely investigated, little is known about the effective presence, the kinetics and duration of lymphocytosis in patients treated with Acalabrutinib.

AIMS: The main purpose of this study is to define, in a real-life setting, the kinetics of drug-induced lymphocytosis in CLL patients treated with Acalabrutinib or Ibrutinib, in order to underline possible differences in terms of entity and duration of this phenomenon.

METHODS: In our multicentric retrospective study, we enrolled 204 pts (127 male and 77 female), treated in the first line with cBTKi (136 Ibrutinib and 68 Acalabrutinib) from 16 different Italian centers, between April 2016 and November 2022, with last follow up in April 2023. For each patient we collected data about the burden of disease at baseline (in terms of staging, lymph nodes involvement, presence of splenomegaly), and the biological features of the disease (cytogenetic aberrations and molecular mutations, IGHV status). Then, we evaluated the ALC at the baseline and at well-defined time-points (after two weeks, 1, 2, 3, 6, 9, 12 months) over an observation period of 1 year. Patients' characteristics are reported in **Table 1.**

204 patients (April 2016 - November 2022)					
Follow up: 12 months		All patients n=204	Ibrutinib arm n=136	Acalabrutinib arm N=68	P-value
Age (163/204)	Median years	72	73	71	0.593
Gender (204/204)	M, n (%) F, n (%)	127 (62) 77 (38)	82 (60) 54 (40)	45 (66) 23 (34)	0.413
Rai Stadium (204/204)	A, n (%) B, n (%) C, n (%)	23 (11) 92 (45) 89 (44)	20 (15) 63 (46) 53 (39)	3 (4) 29 (43) 36 (53)	**0.040**
Lymph nodes (203/204)	Absent < 5 cm 5-10 cm > 10 cm	13 118 46 26	11 80 27 18	2 38 19 8	0.34
Splenomegaly (204/204)	n	138	89	49	0.34
FISH, n	del 17p (198/204) del 11q (199/204) del 13q (198/204) trisomy 12 (198/204)	48 19 63 36	42 6 46 23	6 13 17 13	**0.0007** **0.0005** 0.272 0.591
Molecular Biology, n	TP53 (193/204) NOTCH1 (127/204)	66 14	59 6	7 8	**< 0.001** **0.028**
IgVH mutational status, n	mutated unmutated (168/204)	65 93	44 64	21 29	0.464

Table 1. Patients biological characteristics

RESULTS: The main differences between the two groups are observed in FISH and TP53 status, with more prevalent 17p- and mutated TP53 in Ibrutinib-treated patients (p=0.04 and p=0.007). We observed a median ALC increase after the beginning of therapy in both groups. Median lymphocytosis was higher than baseline during the first month of treatment in both cohorts. A progressive decline in median ALC occurred from the second month of treatment in both groups: at this time-point, median lymphocyte count was 62% of baseline in Acalabrutinib cohort versus 84% in Ibrutinib cohort (p=0.025). From the sixth month to the end of the study, we found a statistical difference in the ALC with higher counts in the Ibr group. Indeed, at this time point the median ALC was 6960/microL in Acalabrutinib compared to 11010/microL in Ibrutinib group (13% vs 30% of baseline), at the ninth month it was 4550/microL vs 8230/microL (10% vs 20% of baseline) and at one-year timepoint it was 2740/microL vs 5520/microL (8% vs 13% compared to baseline) in the Acalabrutinib versus Ibrutinib group, respectively. Results are reported in **Figure 1.**

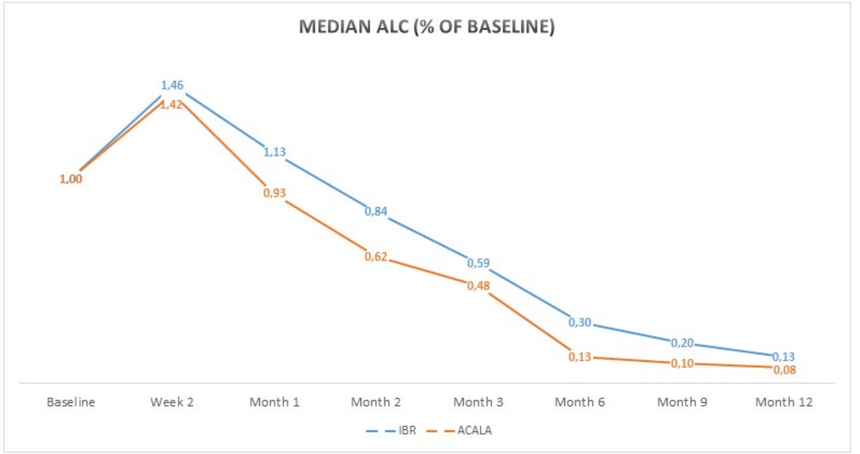

Figure 1. Median ALC trend in terms of percentage of baseline in the two groups of patients

CONCLUSIONS: Acalabrutinib seems to determine, like Ibrutinib, an increase of ALC immediately after the starting of therapy. Therefore, lymphocytosis appears as a cBTKi-class effect. Despite this, the kinetics of lymphocytosis is not overlapping when comparing the two drugs. From the sixth month of treatment, ALC reached almost-normal values in the Acalabrutinib group, with significant statistical differences compared to Ibrutinib. These data suggest that lymphocytosis appears to be less long-lasting in patients treated with Acalabrutinib than in those ones treated with Ibrutinib, and the response criterion of partial response with lymphocytosis may also have a different duration during treatment with different kinds of cBTKi.

REFERENCES: **Woyach et al.** *Blood 2014;* **Barrientos et al**. *Leuk Lymphoma. 2019.*

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