# 1228. A single center real-world study of outcome and resistance of Bruton Tyrosine Kinase inhibitors (BTKi) in Chinese patients with chronic lymphocytic leukemia/small lymphocytic lymphoma

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## Introduction

- Acquired BTK/PLCG2 mutations remain to be the driver of Bruton Tyrosine Kinase inhibitor (BTKi) resistance. But the underlying mechanisms need to be further explored.
- In this study, We retrospectively analyzed clinical and biological characteristics of BTKi-treated CLL patients and report the outcome and resistance in JSPH.

## Research Aim

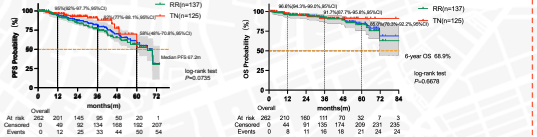
- Search for high-risk factors contribute to disease progression.

## Methods

- Patients enrolled: 262 pts treated with BTKi monotherapy(from January 2014 to March 2023).
- Describe efficacy regarding progression-free survival(PFS) and overall survival(OS) .
- Make comparison between the Responsive cohort and relapsed cohort.

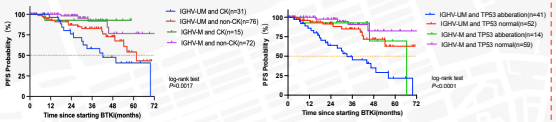
## Results

- BTKi monotherapy demonstrated favorable outcome in CLL/SLL pts. However, 54 pts in our center developed disease progression.

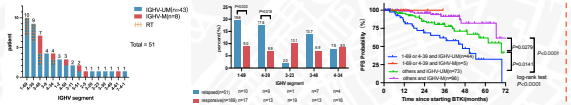



## Results

- With a median follow up of 33.7 months, 208 patients were in durable remission while 54 patients relapsed, the median exposure of BTKi was 26.8m (range, 1-73.8m) and 27.7m (range, 3-69.8m) respectively. The median PFS was 67.2m for the whole cohort. Patients developed RT(n=11) almost 2 years earlier than CLL progression(n=43)(34.7±2.71m vs 10.8±1.65m, $P$<0.0001).
- Clinical and biological characteristics of both cohorts at initiation of BTKi treatment were described and compared. Higher proportion of bulky disease (50.0% vs 23.5%), IGHV unmutated status (84.3% vs 50.5%), del(17p) (44.7% vs 12.9%), TP53 mutation (37.8% vs 15.2%), TP53 aberrations (62.5% vs 24.3%) and complex karyotype (40.5% vs 21.1%) were shown in the BTKi relapsed cohort as compared to responsive cohort.
- Patients with bulky disease, elevated LDH, TP53 mutation and/or del(17p) had inferior PFS as compared to to patients without those. Patients with unmutated IGHV gene had inferior PFS in subgroup analysis irrespective of complex karyotype. And patients with unmutated IGHV gene and TP53 aberration showed the worst PFS.

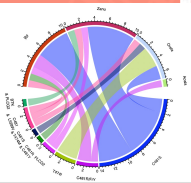



- Further analysis of IGHV usage showed the most frequently used IGHV gene was VH1-69(n=10), followed by VH4-39(n=9) in relapsed pts , which was higher as compared to responsive pts. Pts with 1-69 and 4-39 usage and IGHV UM showed inferior PFS as compared to others and IGHV UM.




## Results

- By integrating NGS and ddPCR results, 54.9% (28/51) relapsed patients acquired BTK/PLCG2 mutation.BTKC481S mutation was the dominant hotspot mutation in all kinds of BTKi relapsed cases. Other mutations at the C481 site included C481R, C481Y, C481F. However, BTKT474 mutation was only detected in Orelabrutinib-resistant cases.6 pts presented with multi-hit mutations.



- Treatment after disease progression on BTKis is still challenging. In our relapsed cohort, 44 patients received salvage treatment and the median PFS was 9.9 months and poorer in RT(n=10) as compared with CLL progression(n=34) (3.0 months vs 12.9 months, P= 0.0263).

## Conclusion

- Pts with IGHV UM, TP53 aberrations, complex karyotype, bulky disease and elevated LDH showed inferior PFS. Higher usage rate of VH1-69 and VH4-39 were founded in relapsed pts with inferior PFS.
- Acquired BTK/PLCG2 mutations remained to be key mechanism of BTKis resistance and BTKC481S mutation was the dominant mutation.
- BTKT474 mutation was only detected in Orelabrutinib-resistant pts in our cohort.
- The prognosis was poor for relapsed pts especially RTs.

## Contact information

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