LymphomaHub

CLL/SLL

ASH 2017 | Identifying mechanisms of venetoclax resistance in CLL

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On Saturday 9 December 92017 during an oral abstract session at the 59th Annual meeting American Society of Hematology (ASH), Lukas P. Frenzel of the Center of Integrated Oncology Cologne-Bonn at the University of Cologne in Cologne, Germany, on behalf of his colleagues, presented results from their clinical study, which was designed to better understand the genetic causes of treatment resistance towards venetoclax in chronic lymphocytic leukemia (CLL).

This abstract (#263), "Mechanisms of Venetoclax Resistance in Chronic Lymphocytic Leukemia," was presented during Oral Session: 641. "Biology and Pathophysiology, excluding Therapy: Therapeutic Resistance in CLL". The summary here provides data from the presentation at the session and may supersede date in the pre-published ASH abstract.

Highlights

- Whole exome sequencing and methylation array profiling was performed in a pilot set of 8 patients (7 men, 1 woman) with pre-treated (1-8 pretreatments) and TP53-deficient CLL, who had progressive disease or relapsed under oral venetoclax therapy
- Serial CLL specimen from peripheral blood before treatment initiation and from peripheral blood, lymph node or bone marrow and at 1-2 follow-up time points during disease progression/relapse were investigated
- Total of 25.5 exonic mutations (including silent, insertions, and deletions), prior to venetoclax therapy, were discovered
- Recurrent non-synonymous mutations developing under venetoclax treatment were seen in TP53, NOTCH1, and BTG1
    - BRAF, SF3B1, RB1, BIRC3, and MLL3 were non-synonymously affected in single patients only
- Recurrent genomic changes that evolved during venetoclax treatment were homozygous deletions affecting CDKN2A/B in 3 patients and BTG1 missense mutations in 2 cases

While this was a small exploratory study, it's notable that the mutations in BTG1 and homozygous deletions in CDKN2A/B occurred in a relatively large percentage of patients. Whole exome sequencing from 8 of these patients before the initiation of venetoclax therapy and at the time of venetoclax resistance revealed diverse patterns of clonal evolution.

The authors of this study agreed that in order to further pinpoint genetic mechanisms of venetoclax resistance, larger studies with repeated longitudinal sampling of CLL cell material under therapy and at disease progression/relapse are necessary.

References

1. Frenzel L P *et al.* Mechanisms of Venetoclax Resistance in Chronic Lymphocytic Leukemia. Oral Abstract #263: ASH 59th Annual Meeting and Exposition, December 2017. Atlanta, GA.