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# IGLV3-21$^{R110}$ as a prognostic marker for early stage CLL patients – clinical implications in patients treated with BTK inhibitors and diagnostic challenges


Deyan Y. Yosifov[1,2], Sandra Robrecht[3,4], Adam Giza[3,4], Armin Riecke[1,5], Christof Schneider[1], Palash Chandra Maity[6], Billy Jebaraj[1], Hassan Jumaa[7], Marc Young[7], Manish Kumar[6], Anna-Maria Fink[3,4], Kirsten Fischer[3,4], Barbara Eichhorst[3,4], Michael Hallek[3,4], Petra Langerbeins[3,4], Stephan Stilgenbauer[1,8], Eugen Tausch[1,8]

*[1]Division of CLL, Department of Internal Medicine III, Ulm University Hospital, Ulm, Germany; [2]German Cancer Research Center (DKFZ), Heidelberg, Germany; [3]Faculty of Medicine and University Hospital Cologne, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf; [4]German CLL Study Group, University of Cologne, Cologne, Germany; [5]Internal Medicine, Division of Hematology, German Military Hospital Ulm, Ulm, Germany; [6]Institute of Experimental Cancer Research, Ulm University Medical Center, Ulm, Germany; [7]Institute of Immunology, Ulm University Hospital, Ulm, Germany; [8]Comprehensive Cancer Center Ulm (CCCU), Ulm University Hospital, Ulm, Germany*

E-mail: deyan.yosifov@uniklinik-ulm.de, eugen.tausch@uniklinik-ulm.de


## OBJECTIVES

- To compare different methods for detection of IGLV3-21$^{R110}$.
- To evaluate the outcomes of early-stage CLL patients with IGLV3-21$^{R110}$ in the context of treatment with ibrutinib.
- To find molecular evidence for differential response of IGLV3-21$^{R110}$-positive CLL to ibrutinib.

## CONCLUSIONS

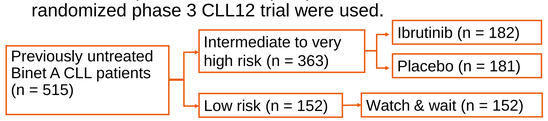
- IGLV3-21$^{R110}$ is an independent prognostic factor for shorter EFS in early stage CLL.
- IGLV3-21$^{R110}$ inhibits antigen-triggered signaling through the BCR/BTK pathway *in vitro* and is associated with suboptimal effectiveness of ibrutinib *in vivo*.
- IGLV3-21$^{R110}$ occurred exclusively in cases with IGLJ1 or IGLJ3 usage.
- tNGS, Sanger sequencing and msPCR show very good concordance in detection of IGLV3-21$^{R110}$ although a single false negative result occurred with each of them.

## INTRODUCTION

IGLV3-21$^{R110}$ is a point mutation that can confer the ability for autonomous signaling to B cell receptors (BCR) using light chains encoded by the allele *IGLV3-21*01* or *IGLV3-21*04*.[1] Chronic lymphocytic leukemia (CLL) patients with IGLV3-21$^{R110}$ have a shorter time to first treatment and shorter overall survival, independent of their IGHV mutational status.[2] This data derives mainly from cohorts without treatment or treated with chemoimmunotherapy.

## METHODS

- Patient samples from the prospective, double-blind, randomized phase 3 CLL12 trial were used.




- Primary endpoint: event-free survival (EFS) (event defined as death, symptomatic progression or initiation of CLL treatment)
- Amplicon-based targeted next generation sequencing (tNGS) of 515 samples
- Analysis pipeline based on ScanIndel and IgCaller to detect rearrangements in the IGLV3-21 locus and the G110R mutation
- Cross-validation of the IGLV3-21$^{R110}$ status of selected samples via additional methods:
  - flow cytometry;
  - Sanger sequencing;
  - multiplex IGLV3-21$^{R110}$-specific PCR (msPCR).[3]
- Expression of CLL derived BCRs in murine B cells:
  - Calcium flux measurement;
  - Cell viability.

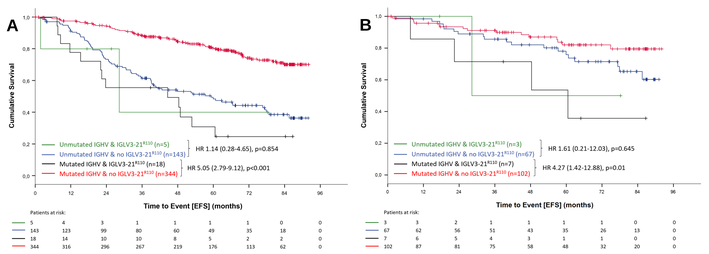
### Table 1. Multivariable analysis of the effects of various prognostic variables* on EFS

| Prognostic factor | Hazard ratio (95%CI) | P value |
|---|---|---|
| **Treatment with ibrutinib** | 0.251 (0.170-0.371) | <0.001 |
| **Unmutated IGHV** | 3.525 (2.449-5.076) | <0.001 |
| **del(17p)** | 3.357 (1.683-6.696) | <0.001 |
| **IGLV3-21$^{R110}$** | 3.178 (1.731-5.832) | < 0.001 |

* Other variables considered in the analysis: serum β2-microglobulin, del(11q), trisomy 12, IGLV3-21 rearrangement.

### Figure 3. EFS in CLL12 according to IGLV3-21$^{R110}$ and IGHV status

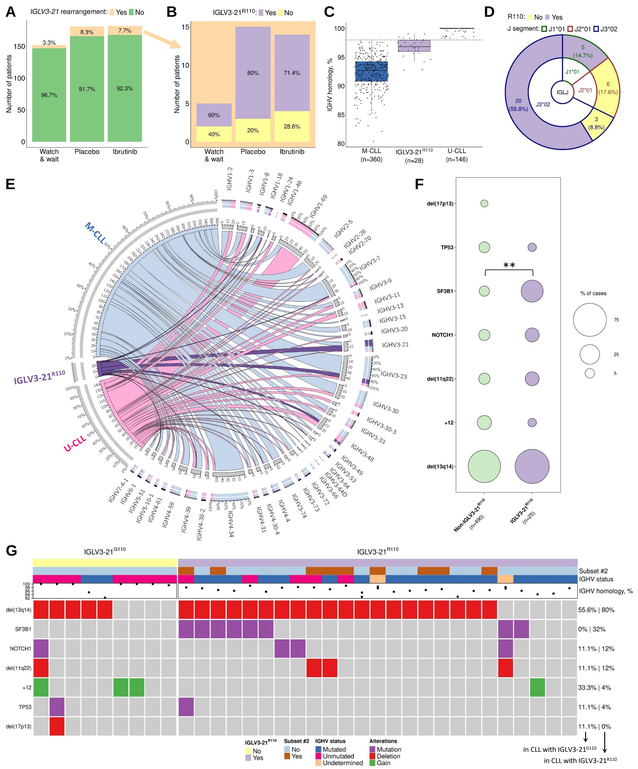
**A,** All trial arms combined; **B,** Only patients from the ibrutinib arm.




## RESULTS

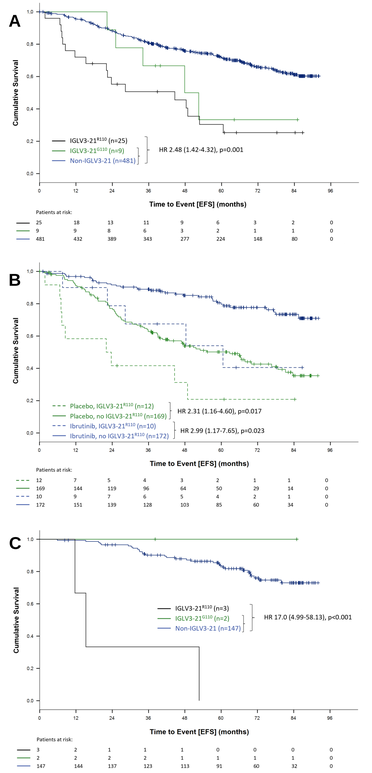
### Figure 1. Prevalence of IGLV3-21$^{R110}$ in the CLL12 cohort and correlation with other genetic markers

**A,** IGLV3-21 rearrangement in all arms of the trial; **B,** G110R in patients with IGLV3-21 rearrangement; **C,** IGHV mutational load; **D,** IGLJ segment usage among cases with IGLV3-21 rearrangement; **E,** IGHV genes usage among M-CLL, U-CLL and IGLV3-21$^{R110}$ cases; **F,** Association of IGLV3-21$^{R110}$ with mutations in *SF3B1*; **G,** Most common drivers in CLL cases with IGLV3-21 rearrangement.



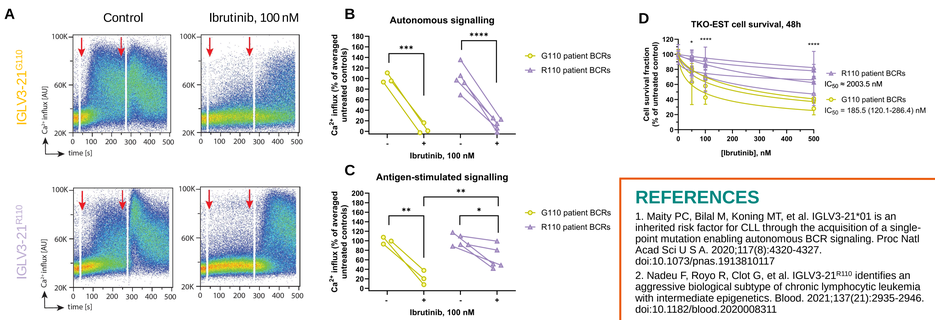

### Figure 2. EFS in CLL12 according to IGLV3-21$^{R110}$ status

**A,** All trial arms combined; **B,** Patients from the placebo and ibrutinib arms separately; **C,** Patients from the observational arm.




### Figure 4. IGLV3-21$^{R110}$ reduces the effectiveness of ibrutinib

**A-C,** $Ca^{2+}$ influx (autonomous and antigen-stimulated) in TKO-EST cells expressing patient BCRs; **D,** Survival of TKO-EST cells expressing patient BCRs after treatment with ibrutinib.

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