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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Patients with Chronic Lymphocytic Leukemia Carrying t(14;19) Display a Distinctive Transcriptomic Profile and Adverse Outcome, Which Might be Overcome Continuous Therapy with BTK Inhibitors. an Italian Campus CLL and Eric Study

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Introduction Rearrangements of the *BCL3* gene due to the translocation t(14;19)(q32;q13) can be identified in up to 1% of chronic lymphocytic leukemias (CLL) with stimulated karyotype and is associated with an adverse outcome. In this study, we aimed at unraveling the clinico-molecular features of CLL harboring t(14;19), including the response to novel therapies.
Methods CLL with t(14;19) were collected within databases from the Italian Campus CLL , European Research Initiative on CLL, German CLL study group and Ohio State University. Treatment-free survival (TFS), time to next treatment (TTNT), overall survival (OS) curves were compared with the Log-rank tests.
For RNA sequencing (RNA-seq), RNA was extracted from 10^6 purified B-cells, processed by TruSeq Stranded Total RNA Ribo-Zero Gold, sequenced by Illumina at an average read depth of $120x10^6$ per sample. Linear and circular RNAs (circRNA) were identified and quantified with CirComPara2 software. Differential expression analysis was conducted imposing a 0.01 Benjamini-Hochberg adjusted p value threshold by using the DESeq2 and limma-voom R/Bioconductor packages for gene and circRNA expression, respectively. Pathway enrichment was conducted using the gene set enrichment analysis (GSEA) method from the clusterProfiler R.
Results We gathered data from 88 patients with t(14;19) CLL from 16 centers, 52% were males, the median age at diagnosis was 58±13years, 93% (68/73) had an unmutated IGHV status [U-IGHV, including 25% stereotyped subset #8], 60% carried trisomy 12 (+12), 52% a complex karyotype (CK, 52% ≥3 aberration, 19% ≥5), 39% atypical phenotype (22/57, Matutes score <3) and 15% *TP53* abnormality (abn, deletion and/or mutation).
To dissect the role of t(14;19) in CLL pathobiology, we analyzed the transcriptomes of 25 t(14;19) samples (comparable in terms of TFS and OS to the whole cohort), 22 control CLL without t(14;19) (11 with +12 and 11 with both normal FISH and karyotype, 10 being U-IGHV) and B cells from 9 healthy donors. Among the differentially expressed genes between t(14;19) cases and control CLL, 708 were upregulated and 1230 downregulated. In particular, among the top upregulated genes we found *BCL3, CD79b* (confirming their atypical phenotype), *CDKN2A, U2, TP63* and *LAG3* whereas among the downregulated CD274 and TIGIT. Of note, the t(14;19) cases displayed a significant enrichment (p-adjusted<0.01) of distinct Gene Ontology pathways, primarily downregulation of leukocyte chemotaxis, immune effector process and cytokine-mediated signaling. Further, we detected over 23000 circRNAs expressed from 7024 genes. Most circRNAs were backspliced from known exons (97%), whereas 1.8% and 1.2% involved intronic and intergenic regions, respectively. We found 60 circRNA upregulated and 197 downregulated circRNAs in t(14;19) cases compared to control CLL, including 28 also differentially expressed against normal B cells, such as circCDK14, not annotated and generated by antisense gene.
After a median follow-up of 7.6 years, the median TFS and OS were 2 and 12.6 years, respectively. In univariate analysis, no clinic-biological variables correlated with TFS and OS. The poor outcome of t(14;19) patients was similar to CLL cases without t(14;19) but harboring *TP53* abn or CK5, and even shorter than CK3 or +12 patients (historic data from the Italian Campus CLL). By analyzing the first-line therapy, 28 patients received FCR/BR, 6 venetoclax-based (VEN) therapy (5 within the CLL13 trial), 12 BTK inhibitor (BTKi, 10 ibrutinib and 2 acalabrutinib), 34 other therapies. TTNT was longer with BTKi (p<0.001, Figure 1). At 3-year 59%, 67%, 100% and 35% for patients treated with FCR/BR, VEN, BTKi and others did not need a further line of therapy. In the relapse setting, 11 patients received VEN and 29 BTKi; a trend for a longer TTNT was observed with BTKi (3-year, 16% vs 64%, p=0.09)
Discussion In this international retrospective study we report that t(14;19) i) is recurrent in young CLL with sterotyped #8; ii) portends a negative prognostic impact superimposable to CK5 or *TP*53 cases; iii) display by a distinct gene expression profile characterized by the deregulation of immune checkpoints, offering a hint for innovative therapeutic approaches, and of circRNAs, whose pathogenetic role in CLL is still unknown and deserves further investigation. Finally, for this aggressive subset of CLL, a continuous therapy with a BTKi resulted in improved treatment outcomes

Disclosures Visentin: *CSL behring:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *AstraZeneca:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *BeiGene:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Takeda:* Speakers Bureau; *Janssen:* Membership on an entity's Board of Directors or advisory committees. **Furstenau:** *Abbvie:* Honoraria, Research Funding; *Roche:* Research Funding; *Janssen:* Research Funding; *AstraZeneca:* Research Funding; *BeiGene:* Research Funding. **Woyach:** *Newave:* Consultancy; *Loxo:* Consultancy; *Beigene:* Consultancy; *AstraZeneca:* Consultancy; *Abbvie:* Consultancy; *Schrodinger:* Research Funding; *Morphosys:* Research Funding; *Karyopharm:* Research Funding; *Janssen:* Consultancy, Research Funding; *Pharmacyclics:* Consultancy, Research Funding. **Baliakas:** *Gilead:* Honoraria. **Rogers:** *Novartis:* Research Funding; *Loxo@Lilly:* Consultancy; *Janssen:* Consultancy; *AstraZeneca:* Consultancy; *Beigene:* Consultancy; *Genentech:* Consultancy, Research Funding; *Pharmacyclics:* Consultancy; *AbbVie:* Consultancy, Research Funding. **Miller:** *AbbVie:* Research Funding. **Haferlach:** *MLL Munich Leukemia Laboratory:* Cur-

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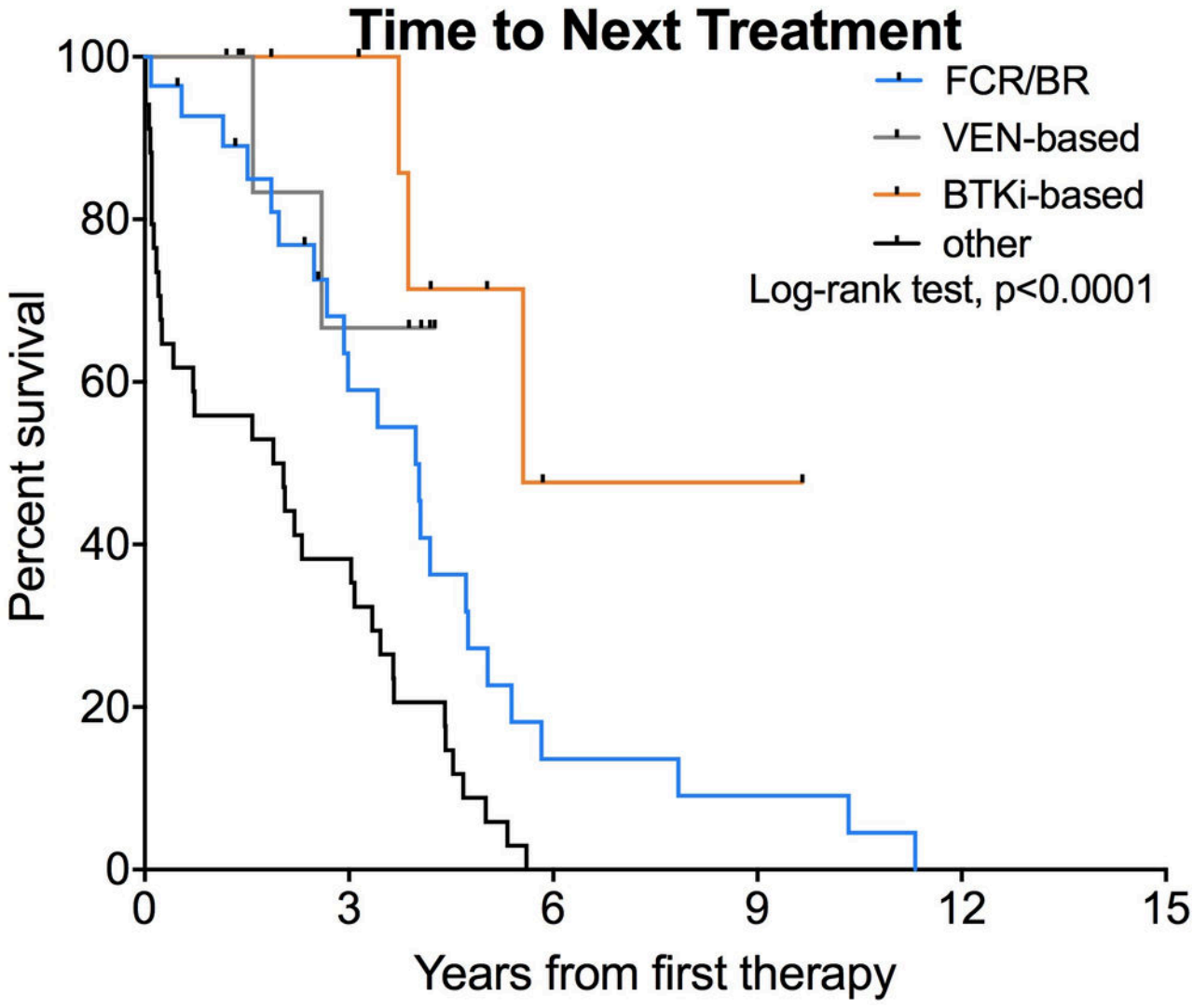

Figure 1

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