The II ERIC international meeting (1st-3d October 2020) - highlights:

This was the first virtual ERIC meeting that despite the lack of direct contacts, was superbly organised and genuinely interactive.

The meeting started with a brilliant keynote lecture from Prof Freda Stevenson on exploring the roads to CLL. Prof Stevenson set the scene to the meeting by discussing CLL pathogenesis in the context of normal B cell development and immune response to external antigens as well as autoantigens. She discussed the significance of the microenvironment for support of CLL survival and proliferation and emphasized the difference between *IGHV* unmutated CLL that is less anergic and less dependent on T cell help and *IGHV* mutated CLL that is more anergic and more dependent on T cell help. This was followed by the talks (Rawstron, Scarfo) on mononuclear B cell lymphocytosis (MBL) emphasizing the biological difference between low count MBL that is lacking dysfunction in the BCR pathway, and the high count MBL with BCR dysfunction where the difference from CLL is only arbitrary.

In the genetic section, Stankovic discussed an interplay between reduced CLL genomic complexity, reduced trafficking and proliferation, and improved T cell immunity which renders spontaneous CLL regression. Kathy Wu addressed different genetic evolutionary patterns dring AlloSCT, an absence of clonal evolution associated with early relapses and the presence of clonal evolution associated with late relapses. Her laboratory established a new method with synthetic functionalized barcodes that integrates genomic, epigenomic, and transcriptomic single-cell analysis to increase the resolution study of clonal heterogeneity. This approach has the potential to enhance even further our understanding of the mechanisms behind disease progression. Stilgenbauer tackled CLL intrinsic drivers, suggesting that *IGHV* unmutated status drives early progression, whereas *TP53* alterations drive treatment resistance and early CLL relapses, and BTK, BCL-2, and PLCg2 mutations drive resistance to specific targeted treatments. In light of those observations, he suggested a need for management algorithms to override specific intrinsic drivers.

In the apoptosis section, Efremov discussed two mechanisms of CLL resistance to Venetoclax: BCR-induced mechanism that operates through MCL-1 upregulation and BCL-2 phosphorylation and CD40-induced mechanism that operates via BCL-xL upregulation. He discussed how kinase inhibitors against BTK, PI3K, SYK, and IRAK1/4 can interfere with these intrinsic resistance mechanisms.

Davide Rossi presented a promising strategy of targeting immune checkpoints in Richer transformation. Baliakas addressed the risk of developing second primary malignancy in CLL, particularly in patients treated with fludarabine as well as those with clonal hematopoiesis of indeterminate potential (CHIP).

Apart from regular talks, the meeting included several highly productive workshops. The conclusions from the workshop on immunogenetics were that patients with unmutated *IGVH* genes clearly benefit from new targeted treatments, that *IGVH* mutated CLL is not always indolent, that *IGHV* borderline cases have uncertain prognoses and that patients with the *IGHV* stereotyped subset 2 do not benefit from chemoimmunotherapy.

In the genetic workshop, the take-home messages were that *TP53* status is still the most important prognostic feature across different treatments and as such should be addressed both by FISH and by sequencing using *TP53* specific databases to interpret identified variants. It has been suggested that the vast majority of variants with an allelic frequency above 5-10% are pathogenic whereas the clinical significance of low-frequency *TP53* mutations is still questionable.

In the workshop on optimizing clinical outcomes, the best strategies for the front line and second-line treatment were discussed. The consensus was that while both immunochemotherapy and BTK inhibitors have their place in the front line, venetoclax based treatments appear to be a choice of therapy for the progressive CLL. The current Covid-19 crisis was also discussed revealing that Covid-19 infection is not necessarily an indication for the interruption of treatment with BTK inhibitors.