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High-risk IPS-E identifies CLL at risk of progression to treatment in the OxPLoreD study, a prospective observational study for early lymphoproliferative disease

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LAY SUMMARY

The earliest stage of CLL occurs when small numbers of lymphocytes occur in the blood. A small number of people with early CLL go on to need cancer treatment. At present, there are no good tools to identify at diagnosis who will remain well for many years and require CLL treatment. The OxPLoreD study aims to find out more about factors which could help to predict which people with early blood abnormalities might go on to need cancer treatment. For people with CLL needing treatment, gene changes affecting the Immunoglobulin heavy chain gene (IGHV) help predict outcomes after treatment. We applied the IPS-E (International Prognostic Score for early asymptomatic CLL) to learn whether it could reliably identify OxPLoreD participants who will need cancer treatment. The score combines the number of lymphocytes in the blood, whether the person has enlarged lymph glands or not with the IGHV status (mutated or unmutated) to divide people into low, intermediate and high-risk groups. No participants with low-risk IPS-E score needed CLL treatment to date but 9.3% participants with high-risk score have progressed to treatment.

MATERIALS AND METHODS

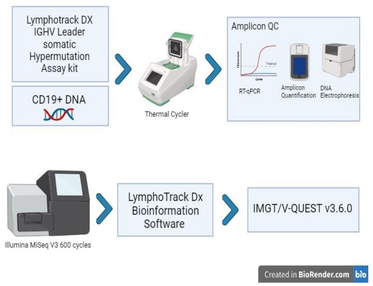


Figure 1: Laboratory workflow for determination of SHM using Lymphotrack Dx IGHV Leader somatic hypermutation assay (Invivoscribe Inc, San Diego, CA).

The IGHV status was obtained using LymphoTrack assay on DNA extracted from CD19+ B-Cells (n = 121) **(Figure 1)**. Results were determined by using a cut-off of 98% germline homology.

For 45 additional patients, IGHV status was determined from WGS data using IgCaller (Nadeu 2020). To assign CLL stereotypes, the IgCaller output was used as input for AssignSubsets online tool (Bystry et al. 2015). Where more than one rearrangement was detected, the highest scoring rearrangement was considered as the principal rearrangement.

The IPS-E score is calculated based on palpable lymphadenopathy, lymphocytosis > 15 x10^9/L and Unmutated-IGHV, which all score 1 point. The V3-21 subset #2 was considered equivalent to Unmutated (UM) (Condoluci, 2020). The sum is translated into: Low-risk, Intermediate-risk and high-risk with Score 0, Score 1 and score 2-3, respectively.

OxPLoreD STUDY and PARTICIPANT POPULATION

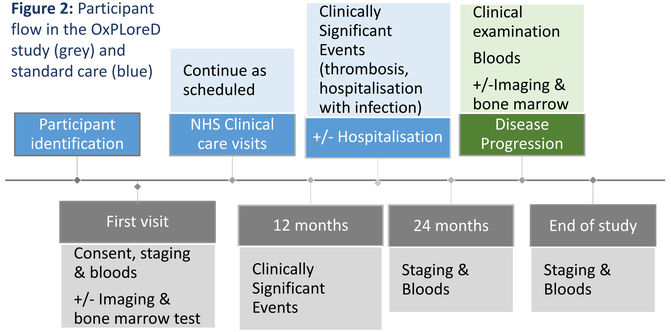


Figure 2: Participant flow in the OxPLoreD study (grey) and standard care (blue)

Oxford Pre-Cancerous Lymphoproliferative Disorders (OxPLoreD) is an observational cohort study which targets newly diagnosed early lymphoproliferative disorders

Inclusion criteria for MBL/CLL Cohort:

1. High count Monoclonal B-cell Lymphocytosis (clonal B-cells 0.5-4.9x10^9/L)
2. Rai Stage 0/2 or Binet Stage A/B **and** no IWCLL indication for treatment
3. ECOG performance status 0, 1 or 2
4. >16 years and able to provide informed consent

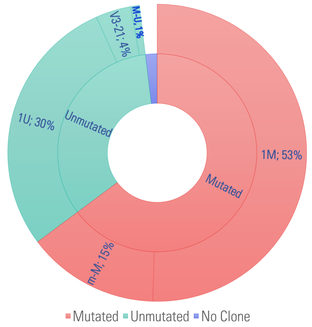
Objectives:

- Identify the clinical, genomic and immunological predictive markers of progression to CLL requiring treatment
- Assess the quality of life, study other clinical complications (infection, thrombosis, second cancers), and establish evidence-based guidance for monitoring and follow up of patients with pre-cancerous conditions,

383 participants with MBL and early asymptomatic CLL have been recruited (31-Aug-2023). 241 participants enrolled to trial prior to the interim data lock **(Table 1).** Participants provided blood, saliva +/- bone marrow aspirate samples. For this preliminary analysis, IGHV status was determined from 121 participants by NGS (Invivoscribe). For an additional 45 patients, IGHV status was identified from WGS of paired CD19+ B-Cells and salivary germline DNA.

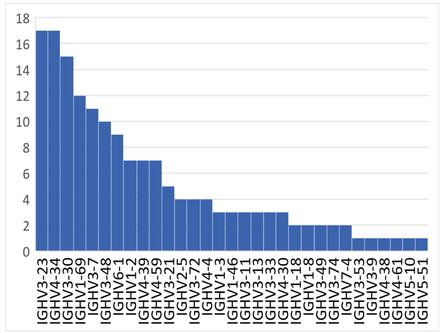
RESULTS

Figure 3. IGHV mutational status (N=121)



Legend: 68% of participants are Mutated (red, <98%), 30% Unmutated (green, >98 or V3-21 #subset2. No clone was identified in 2%.

Figure 4. Frequency barplot of IGHV genes.



Legend: Productive IGHV rearrangements by frequency

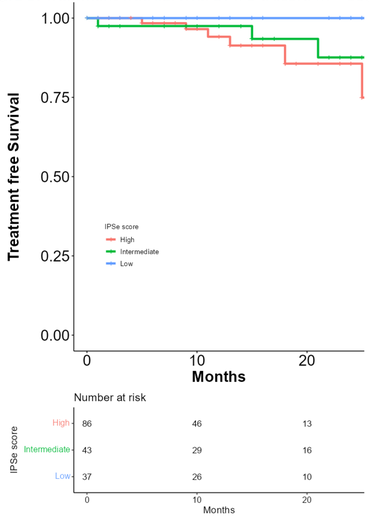
Table 1: OxPLoreD Participants (n=241)

Age	67 years (IQR 60-73 years)
Gender	137 male; 104 female
Clinical stage	MBL 46 participants Rai 0-I 143 participants Rai II-III 36 participants Data missing 16
Median follow-up	11.4 months

Table 2: IPS-E group and progression to treatment (up to 27-Aug-2023)

Low-risk IPS-E	0/37
Intermediate-risk IPS-E*	4/43 (9.3%)
High-risk IPS-E	8/86 (9.3%)
Missing data	3/74 (4%)
*includes three V3-21 #subset2 participants	

Figure 5: Treatment free survival by IPS-e score (n = 166)



Legend: IPS-E score for 166/241 participants

CONCLUSIONS

IPS-E prospectively applied to newly diagnosed OxPLoreD participants identifies low-risk CLL participants who do not progress and participants at higher risk of needing treatment. Our finding requires testing in the larger OxPLoreD cohort (n=500).

ACKNOWLEDGEMENTS and CONTACT DETAILS

OxPLoreD website

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Transforming patient healthcare, pioneering tomorrow's technology

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