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Letter
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Genetic and Microenvironment Features Do Not Distinguish Follicular Lymphoma Patients Requiring Immediate or Deferred Treatment

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Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma.[1] Most patients present with asymptomatic lymphadenopathy, and only 20% present with B symptoms (night sweats, fevers, or unintentional weight loss).[2] Although there is no evidence that overall survival (OS) improves if treatment is started before clinical symptoms or organ disfunction arises,[3] some psychological benefit has been described for upfront treatment with rituximab.[4] This latter benefit is considered insufficient to justify the side effects and cost of treatment, and therefore a Watch-and-Wait (W&W) approach is generally advised for asymptomatic patients with low tumor burden. The reported range of the W&W period before start of treatment is large (3–122 months, mean ± 24 months).[4,5]

Various tools have been developed to predict OS and failure-free survival, such as Follicular Lymphoma International Prognostic Index (FLIPI),[2] and the M7-FLIPI.[6] None of these tools is designed to predict at diagnosis, if the disease allows for a long W&W period before starting treatment.

In this exploratory study, the aim of the Lunenburg Lymphoma Biomarker Consortium was to address whether genetic and microenvironmental features in diagnostic biopsy samples could differentiate which FL patients could be managed with a long W&W period (>5 years) versus those who required treatment immediately following diagnosis (based on clinical features).

Stage III/IV, histologic grade 1–3A nodal FL cases as confirmed by central pathology review with complete clinical information at diagnosis and follow-up with availability of representative formalin-fixed paraffin-embedded diagnostic biopsy samples were included in this study in 2 subcohorts, representing the extremes of the clinical spectrum, with strictly applied inclusion

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criteria applied to patients from all sources, irrespective of sites and countries.

For the W&W cohort, FL patients without any active treatment for ≥5 years after initial biopsy were included from German Low-Grade Lymphoma Study Group (GLSG, now German Lymphoma Alliance) GLSG2000 trial[7] and population/institution-based registries; Haematological Malignancy Research network Registry,[8] Swedish National Lymphoma Registry, St Bartholomew's Hospital, London and Stanford University Medical Center, Stanford, USA.

For the immediate treatment (IT) cohort FL patients from the above sources were supplemented with patients from the Lymphoma Study Association FL2000 study,[9] with first-line treatment <3 months after initial diagnosis. To ensure that only patients were included that required immediate treatment for symptomatic disease, at least 2 of the following criteria were required for inclusion: high lactate dehydrogenase (LDH), tumor mass >7 cm, B symptoms, or hemoglobin (Hb) <10 g/dL (Suppl. Table S1: clinical study inclusion criteria; Suppl. Table S2A: cases per collaborator; Suppl. Table S2B: treatment modalities).

Immunohistochemical (IHC) analysis for microenvironment-related biomarkers, included T-cell subsets (identified by CD8, CD4, CD3, PD1, and FOXP3) and macrophages (CD68, CD163), performed on tissue microarrays with semiautomated quantification by image analysis.

Copy number aberrations (CNA) analysis was performed using the R-script QDNAseq (v1.12.0) and Gistic (v2.0) from 50-bp single read shallow whole genome sequencing data.[10] Targeted next-generation sequencing panel for mutations (369 target genes) used for mutation and translocation analysis was conducted on 150-bp paired-end data of a 3 Mb SeqCapEZ capture panel (Roche NimbleGen, Madison, WI; order ID 43712) both sequenced on a HiSeq 4000 (Illumina, San Diego, CA)[10] (see Suppl. Methods for more details).

Patient's clinical characteristics were summarized with descriptive statistics (median (range) for quantitative and frequency (percent) for qualitative variables) and compared using Chi-Square test and Mann-Whitney test.

The IHC biomarker score used in the analysis was the average from 2 cores. Given the multiple tests performed, Bonferroni FWER correction was applied for the IHC biomarkers so the 2-sided α level was 0.05/7 = 0.007.

Fisher exact test was used for frequencies of mutations and translocations. For comparisons between copy number regions, *P* values and false discovery rates (FDR) were calculated with comparative genomic hybridization test, which implements a Wilcoxon rank sum test. *P* values were not corrected for multiple testing, and FDR was controlled at 10% level for mutations and translocations.

Statistical analysis was performed using various strategies in R (version 3.5.1) and SAS (SAS software version 9.4).

The study and protocols to obtain human archival tissues and patient data were approved by the local ethical committee of the VU University Medical Center, Amsterdam (FWA00017598) and for all collaborating centers and complied with the Code for Proper Secondary Use of Human Tissue in the Netherlands (http://www.fmwv.nl).

A total of 191 patients (W&W n = 66, IT n = 125) fulfilled the primary inclusion criteria. Of these, 159 patients had complete IHC data (W&W n = 60, IT n = 99) of which 90 patients with molecular data (W&W n = 44, IT n = 46) (Suppl. Figure S1). The median W&W period was 83 months (range 60–240 months). As a direct result of the pre-set inclusion criteria in this end-of-spectrum study, adverse parameters including >4 involved nodal sites, elevated LDH and Hb, bulky disease, B symptoms, and high FLIPI were overrepresented in the IT cohort (Table 1). It should be noted, that in the W&W cohort, 24% of the patients also presented with a high FLIPI. As expected, the differences in clinical presentation had an impact on 10 years OS W&W versus IT, 85% versus 63% (*P* = 0.001), underpinning the validity of patient selection (Suppl. Figure S2). W&W patients were primarily population-based patients, while IT patients were trial-derived. It is well known that patients treated in clinical trials have a better survival than age/stage matched real-world patients under similar treatment, but systematic tumor-biological differences between trial and real-world patients have not been described.

IHC studies have shown conflicting results with regard to prognostic value of microenvironment-related biomarkers.[11,12] We studied the composition of the immune microenvironment using T-cell and macrophage markers. No differences were seen for any of these cell population within the cohort with complete IHC data (W&W n = 60, IT n = 99) (Figure 1A, Suppl. Table S3A). While statistically significant on the 90-patient cohort, the absolute difference of CD68 (Suppl. Figure S3 and Suppl. Table S3B) was minor and insufficiently to have clinical relevance. Overall, the study was calibrated for a higher anticipated number of patients of 45 versus 250 for W&W versus IT patients with available samples to reach a 80% power to detect a difference of 0.65 standard deviation with a 2-sided corrected alpha threshold of 0.007 (=0.05/7 targeted biomarkers). Despite the lower sample size and resulting reduced power, the observed difference was significantly below the threshold of clinical applicability which indicate that this study had sufficient power to detect clinically relevant differences.

Immune microenvironment interactions and genome alterations are considered complementary drivers of FL lymphomagenesis with impact on outcome and clinical course.[13] In depth next generation sequencing (NGS) characterization showed a spectrum of genetic alterations consistent with previously published data in FL.[6] The most frequent rearrangements in W&W (n = 44) versus IT (n = 46) were *BCL2* (89% versus 98%) and *BCL6* (21% versus 9%) translocations, *KMT2D* (66% versus 63%), *CREBBP* (61% versus 61%), *TNFRSF14* (25% versus 30%), and *EZH2* (16% versus 30%) mutations and somatic hypermutation (SHM) in *BCL2* (Figure 1B, Suppl. Tables S4, S5, S6 and Suppl. Figure S4). No significant differences in the overall spectrum or in individual markers between the cohorts were observed. Specifically, no significant differences were observed for markers frequently associated with more aggressive clinical behavior in FL such as *TP53* mutations (W&W 4.5% versus IT 4.2%) (Figure 1B, Suppl. Table S3). Similar results were seen in the W&W (n = 47) versus IT (n = 55) with only complete NGS data (data not shown).

Analysis of CNAs showed that the most frequent losses found in chromosomes 1p36, 6q, 10q23 and gains of 1p, 2p, 6p, 7, 8, 12, and 18 (Figure 1C, D). Further investigation with GISTIC yielded candidate driver deletions in IT cohort: 6q16, 6q23.3, 8p23.3, 9p21.3 (containing *CDKN2A*), and 10q23.3 and in W&W cohort: 6q23.3, 8p23.3, and 10q23.3. Gains in IT cohort was 2p16.1, and in W&W cohort 1q24.2, 2p16.1, and 8q24.2 (Suppl. Figure S5). A systematic comparison showed no significant differences of CNA frequencies between both cohorts.

Although significant differences were not seen at the level of individual mutated genes, structural alterations and CNAs, the overall number of nonsynonymous and splice-site mutations per case (median W&W 9 versus IT 12.5, *P* = 0.003) and the CNA load (median W&W 7.8% versus IT 12.1%, *P* = 0.045) were both significantly higher in the IT cohort. (Figure 1E, F). In a study by Mamessier et al[14] similar lower mutational and CNA loads were observed and associated with so-called "early phase" FL (in situ follicular neoplasia, duodenal-type FL, and partial involvement) as compared with overt FL. The W&W cohort showed a similar lower mutational and CNA load which may suggest a common biology underlying the protracted clinical behavior.

We compared FL patients in whom treatment was deferred for >5 years (W&W) from initial diagnosis to a cohort with an IT indication. Despite major clinical differences, we observed a remarkable similarity of all investigated microenvironmental

Table 1

Demographic and Clinical Characteristics From Time of Diagnose of Watch-and-Wait Versus Immediate Treatment Patients Included for Analysis in the Study

	Watch-and-Wait (N = 60)	Immediate Treatment (N = 99)	*P* Value
Age at diagnosis			0.206[a]
Median years (range)	60.4 (28.4–85.5)	58.0 (25.3–83.3)	
Gender, n (%)			0.785[b]
Female	32 (53.3%)	55 (55.6%)	
Male	28 (46.7%)	44 (44.4%)	
Stage, n (%)			0.043[b]
III	31 (51.7%)	35 (35.4%)	
IV	29 (48.3%)	64 (64.6%)	
ECOG, n (%)			0.043[b]
≤1	58 (98.3%)	88 (88.9%)	
>1	1 (1.7%)	11 (11.1%)	
Missing	1	0	
FLIPI, n (%)			<0.001[b]
High	13 (24.1%)	64 (67.4%)	
Intermediate	32 (59.3%)	25 (26.3%)	
Low	9 (16.7%)	6 (6.3%)	
Missing	6	4	
B symptoms, n (%)			<0.001[b]
Absent	54 (90.0%)	30 (30.3%)	
Present	6 (10.0%)	69 (69.7%)	
Bulky disease, n(%)			<0.001[b]
<7 cm	56 (98.2%)	33 (34.4%)	
≥7 cm	1 (1.8%)	63 (65.6%)	
Missing	3	3	
Bone marrow involvement, n (%)			0.450[b]
No	28 (49.1%)	42 (42.9%)	
Yes	29 (50.9%)	56 (57.1%)	
Missing	3	1	
Hemoglobin, n (%)			0.018[b]
<10 g/dL	0 (0.0%)	11 (11.5%)	
≥10 g/dL	56 (100.0%)	85 (88.5%)	
Missing	4	3	
Elevated LDH at diagnosis, n (%)			<0.001[b]
No (≤ULN)	48 (88.9%)	33 (33.3%)	
Yes (>ULN)	6 (11.1%)	66 (66.7%)	
Missing	6	0	
Number of nodal areas involved (Ann Arbor), n (%)			0.001[b]
1	6 (10.3%)	1 (1.0%)	
2	8 (13.9%)	14 (14.1%)	
3	8 (13.9%)	10 (10.1%)	
4	13 (22.4%)	7 (7.1%)	
>4	23 (39.7%)	67 (67.7%)	
Missing	2	0	

[a]Wilcoxon rank sum *P* value.

[b]Chi-square *P* value.

ECOG = Eastern Cooperative Oncology Group; FLIPI = follicular lymphoma international prognostic index; LDH = lactate dehydrogenase; PS = performance score; ULN = upper limit of normal.

and/or molecular features in the diagnostic biopsy samples. Although overall higher number of CD68+ macrophages, mutational and CNA loads were statistically significantly related to the need to start treatment within 3 months after diagnosis, the observed differences were minor and as such insufficient to provide a basis for decision making between a W&W versus IT approach in individual patients. Whether other tumor-related factors and/or constitutional patient characteristics may contribute to prediction of treatment timing needs further study.[15]

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AUTHOR CONTRIBUTIONS

The Lunenburg Lymphoma Biomarker Consortium, MJK, BY, and DdJ designed the study; WBCS, GTL-dV, EvD, CLJ, AJC, PS performed experiments; WBCS, GTL-dV, EvD, CLJ, BS, AR, DMB, BY, and DdJ analyzed and interpreted the data; WBCS, GTL-dV, EvD, DMB, CLJ, BY, and DdJ wrote the manuscript; and all authors critically revised the manuscript and were

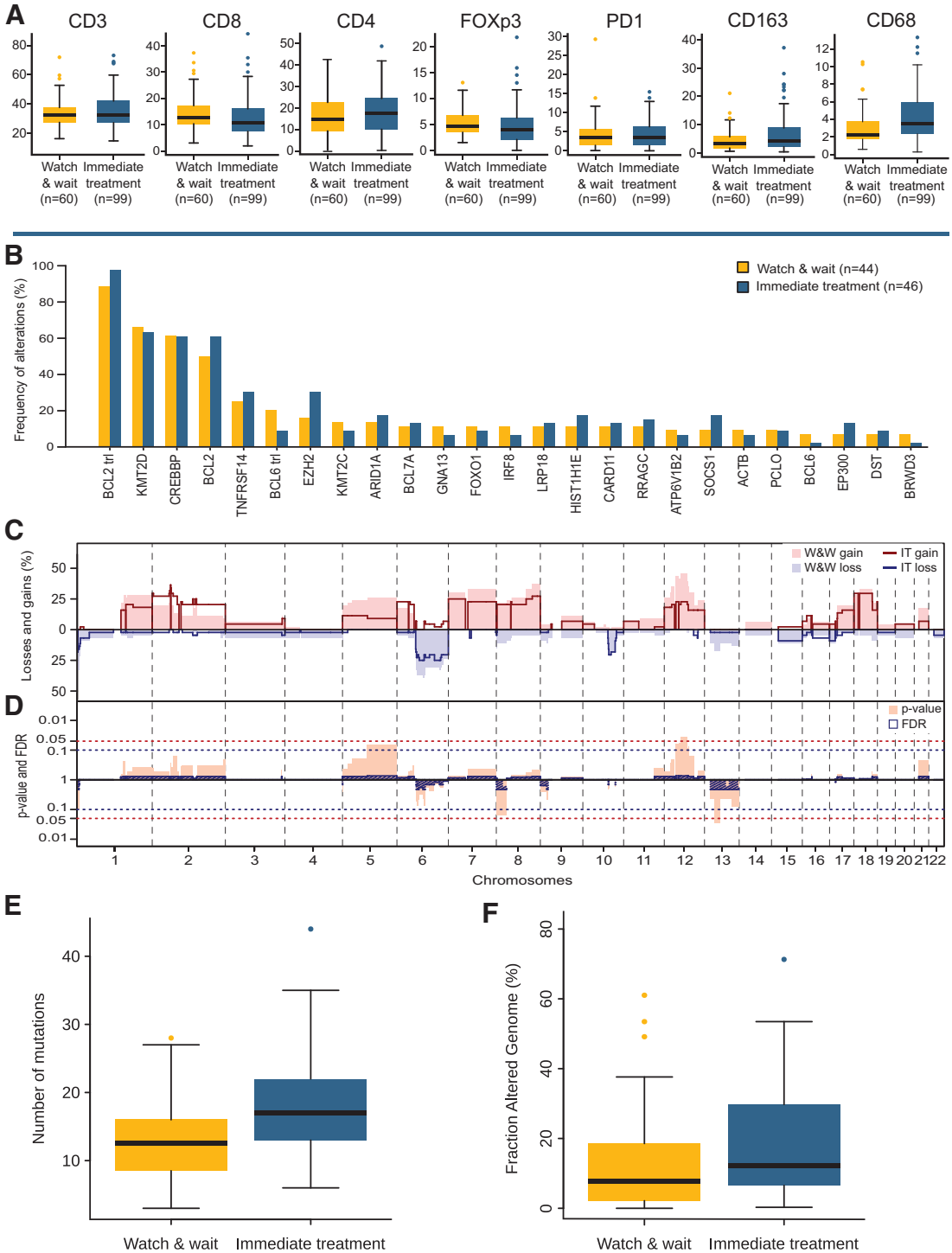

Figure 1. Microenvironment, mutations, translocations, and copy number landscape of Watch-and-Wait vs Immediate Treatment patients with follicular lymphoma. (A) For W&W (n = 60) and IT (n = 99) CD4, CD8, CD3, FOXP3, and PD1 are computer assisted scored and the percentage of positive nucleated cells of all nucleated cells are depicted as boxplots. CD163 and CD68 are computer assisted scored and the percentage of positive area of the total cell area scored are plotted in the boxplots. None of the markers show a significant difference. (B) Frequency of top 25 alterations including *BLC2* and *BLC6* translocations and mutated genes, W&W (n = 44) is depicted in yellow and IT (n = 46) in blue, no significant differences were found ($P < 0.05$, Fisher exact test and FDR using Benjamini&Hochberg method). (C) Comparison plots for CNAs between W&W (filled n = 44) and IT (line n = 46) depicted are percentages of the number of cases with gains (positive value red) and losses (negative value blue), sorted for chromosome position (x-axis). (D) *P* values (orange) calculated with a 2-sided rank sum test with 10,000 permutations and FDR (striped blue segments) of the difference in CNAs, the horizontal red dotted lines show the significance thresholds *P* value <0.05, and the FDR in blue <0.1. No significant differences were found. (E) Total number of nonsynonymous and splice-site mutations per patient are depicted in boxplots. With a median of 9 nonsynonymous and splice-site mutations (mean 9.52, range 2–22) in the W&W cohort (yellow) vs a median of 12.5 nonsynonymous and splice-site mutations (mean 13.07, range 4–32) in the IT cohort (blue), this is a significant difference, Wilcoxon test *P* value = 0.003. (F) Copy number load is depicted in boxplots. For the W&W cohort (yellow), a median of 7.79% (mean 13.22%) vs a median of 12.11% (mean 19.18%) for the IT cohort (blue), this is a significant difference, Wilcoxon test *P* value = 0.045. CNAs = copy number aberrations; FDR = false discover rates; IT = immediate treatment; W&W = Watch-and-Wait.

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DATA AVAILABILITY

All sequence data has been uploaded to the European Genome-phenome Archive (EGA; accession number EGAS00001005755).

DISCLOSURES

The authors have no conflicts of interest to disclose.

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REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375–2390.
2. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood*. 2004;104:1258–1265.
3. Nastoupil LJ, Sinha R, Byrtek M, et al. Outcomes following watchful waiting for stage II-IV follicular lymphoma patients in the modern era. *Br J Haematol*. 2016;172:724–734.
4. Ardeshna KM, Qian W, Smith P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. *Lancet Oncol*. 2014;15:424–435.
5. Yuda S, Maruyama D, Maeshima AM, et al. Influence of the watch and wait strategy on clinical outcomes of patients with follicular lymphoma in the rituximab era. *Ann Hematol*. 2016;95:2017–2022.
6. Pastore A, Jurinovic V, Kridel R, et al. Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. *Lancet Oncol*. 2015;16:1111–1122.
7. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*. 2005;106:3725–3732.
8. Smith A, Howell D, Crouch S, et al. Cohort profile: the Haematological Malignancy Research Network (HMRN): a UK population-based patient cohort. *Int J Epidemiol*. 2018;47:700–700g.
9. Bachy E, Houot R, Morschhauser F, et al. Long-term follow up of the FL2000 study comparing CHVP-interferon to CHVP-interferon plus rituximab in follicular lymphoma. *Haematologica*. 2013;98:1107–1114.
10. Los-de Vries GT, Stevens WBC, van Dijk E, et al. Genomic and microenvironmental landscape of stage I follicular lymphoma, compared with stage III/IV. *Blood Adv*. 2022;6:5482–5493.
11. Stevens WBC, Mendeville M, Redd R, et al. Prognostic relevance of CD163 and CD8 combined with EZH2 and gain of chromosome 18 in follicular lymphoma: a study by the Lunenburg Lymphoma Biomarker Consortium. *Haematologica*. 2017;102:1413–1423.
12. Wahlin BE, Aggarwal M, Montes-Moreno S, et al. A unifying microenvironment model in follicular lymphoma: outcome is predicted by programmed death-1--positive, regulatory, cytotoxic, and helper T cells and macrophages. *Clin Cancer Res*. 2010;16:637–650.
13. Scott DW, Gascoyne RD. The tumour microenvironment in B cell lymphomas. *Nat Rev Cancer*. 2014;14:517–534.
14. Mamessier E, Song JY, Eberle FC, et al. Early lesions of follicular lymphoma: a genetic perspective. *Haematologica*. 2014;99:481–488.
15. Cerhan JR. Epidemiology of follicular lymphoma. *Hematol Oncol Clin North Am*. 2020;34:631–646.