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Large B-cell lymphoma-IRF4+ in children and young people: time to reduce chemotherapy in a rare malignant mature B-cell neoplasm?

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Abstract:

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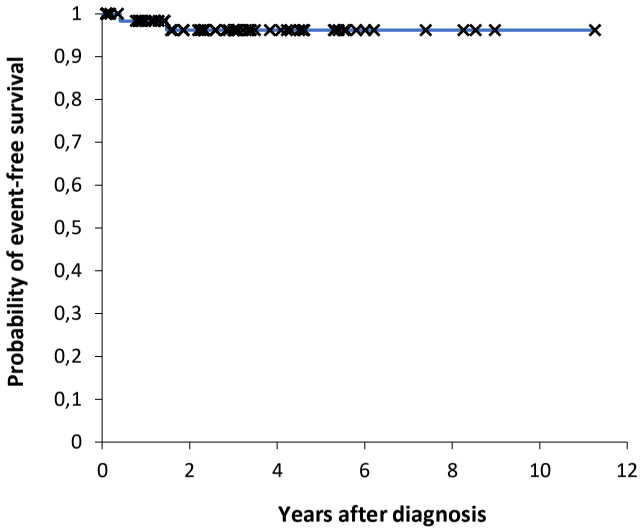
Clinical trial registration information (if any):

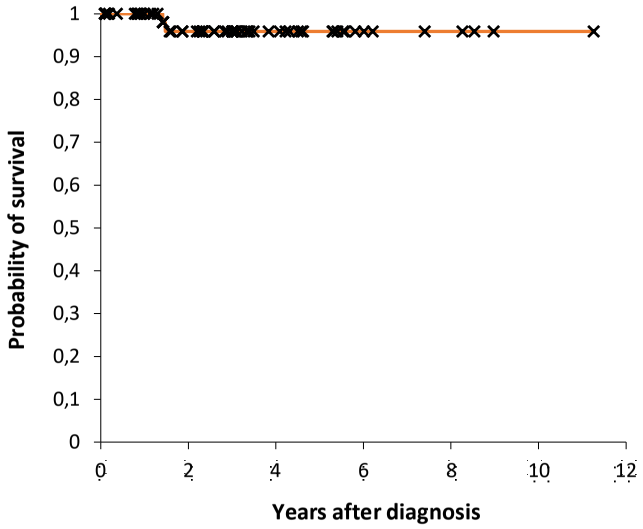
Figure 1

Figure 1A



LBCL-*IRF4*+ (n=65): 2.5-year EFS: 96%±3% (2 events)

Figure 1B



LBCL-*IRF4*+ (n=65): 2.5-year OS: 96%±3% (2 events)

Figure 1

Figure 1C

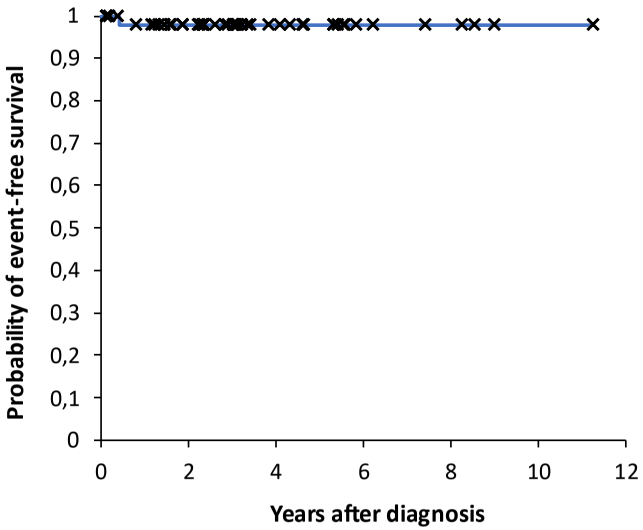
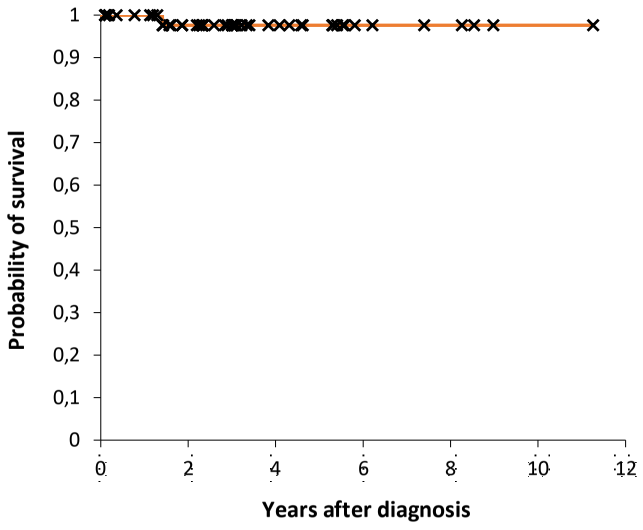


Figure 1D



LBCL-*IRF4*+ of head-and-neck (n=50): 2.5-year EFS: 98%±2% (1 event)

LBCL-*IRF4*+ of head-and-neck (n=50): 2.5-year OS: 98%±2% (1 event)

Figure 1

Figure 1E

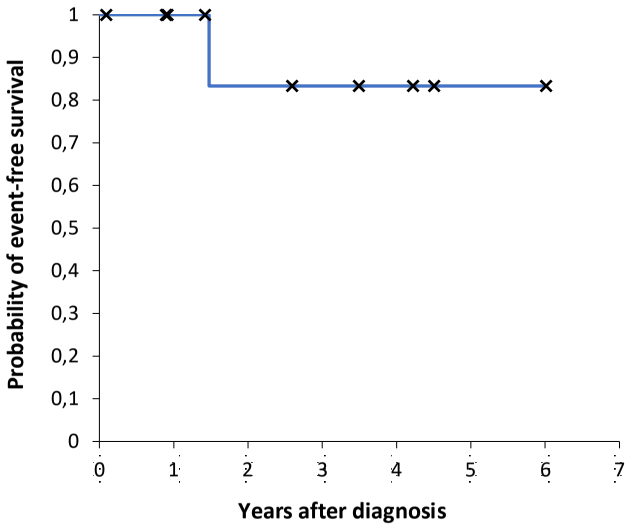
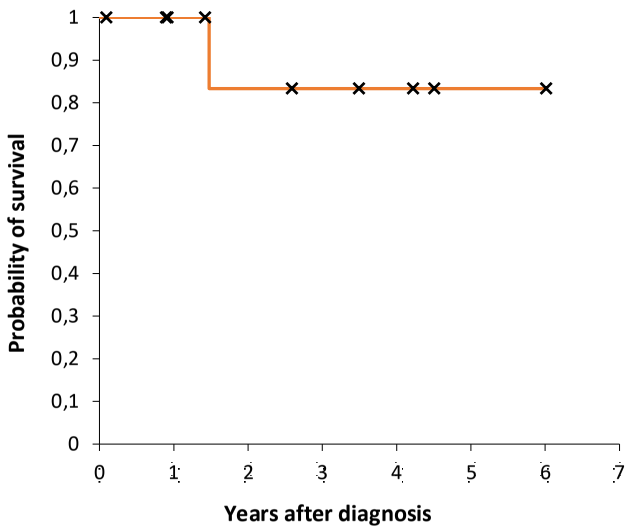


Figure 1F



LBCL-*IRF4*+ of abdomen (n=10): 2.5-year EFS: 83%±15% (1 event)

LBCL-*IRF4*+ of abdomen (n=10): 2.5-year OS: 83%±15% (1 event)

Research Letter

Large B-cell lymphoma-*IRF4*+ in children and young people: time to reduce chemotherapy in a rare malignant mature B-cell neoplasm?

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Data sharing statement: For original data, please contact the last author at andishe.attarbaschi@stanna.at.;

Running title: LBCL *IRF4+* in children and young people;

Body text: 1308 words; **No. of references:** 27; **Tables:** 1; **Figures:** 1; **Supplemental figures:** 1

Since 2022 large B-cell lymphoma with *IRF4*-rearrangment (LBCL-*IRF4*+) has been recognized as a definite entity by the World Health Organization (WHO) classification

of hematolymphoid tumors.[1;2] It is characterized by a follicular and/or diffuse growth pattern as well as a strong expression of IRF4, which is due to translocation of *IRF4* with an immunoglobulin gene.[1;3-6] Essential and desirable diagnostic criteria are set by the WHO including clinical, morphological, immunophenotypical and molecular-genetic parameters.[1;2]

Given that most LBCL-*IRF4*+ patients are children and young people, the rarity of this lymphoma and lack of any prospective trials, most data on LBCL-*IRF4*+ come from small reports.[7-12] Thus, two of the largest childhood non-Hodgkin lymphoma (NHL) consortia, the European Intergroup for Childhood NHL (eicnhl) and the international Berlin-Frankfurt-Münster (i-BFM) Group, designed a retrospective multinational study of LBCL-*IRF4*+ in children and young people. Here we present data from this series, the largest reported to date.

Between December 2022 and November 2023, we performed an international survey of LBCL-*IRF4*+ cases diagnosed between 2010 and 2022 from 15 eicnhl and/or i-BFM Study Group members, but only included patients with centrally reviewed histopathology. Questionnaires were sent out to obtain data on demographics, histopathology, treatment, and outcome.[3;11] A total of 75 patients up to 21-years of age were identified including 10 cases for whom only initial characteristics and basic therapy components were collected as they were still included in an ongoing trial (NCT03206671). Diagnosis of LBCL-*IRF4*+ was based on the WHO criteria which emphasize that a cytogenetically cryptic translocation of *IRF4* can be detected by molecular-genetic methods in most cases.[1;2] Staging procedures and protocols are described elsewhere.[13-20] Patients were included in national studies and/or registries and treated with informed consent from their legal guardians. Studies were conducted in accordance with the Declaration of Helsinki and approval was delivered by the ethics committees and/or IRBs. Event-free survival (EFS) was

calculated from the date of diagnosis to the date of the first event. Events considered included relapse, progression, or death. Overall survival (OS) was defined as the time from diagnosis to death from any cause or date of last follow-up. EFS and OS were estimated by the Kaplan-Meier-method.

The study cohort is shown in Table 1A+B. The male-to-female ratio was 1:1 and median age 10.0 years. Four patients (5%) had a pre-existing immunodeficiency. Three histological growth patterns were described: i) follicular (n=14; 19%), ii) diffuse (n=47; 62%), iii) follicular and diffuse (n=12; 16%) and not available in 2 (3%) cases. An *IRF4*-rearrangement was detected by molecular-genetic methods in 73 (97%), while for the remaining 2 patients (3%) the diagnosis was established by strong IRF4-positivity through immunohistochemistry and typical histopathology as allowed by the WHO criteria.[1;2] For 12 cases an *IRF4::IGH* fusion gene was reported while not available for the remainder. *BCL2*- and *MYC*-rearrangements were absent in all patients analyzed, while for 3/38 patients (8%) analysed, *BCL6 was* rearranged. After a median follow-up of 2.84 years, the 2.5-year EFS and OS of the 65 LBCL-*IRF4*+ patients, for whom outcome data was available, was 96%±3% for both outcomes (Figure 1-A/B).

The site of involvement was the head-and-neck region in 57 patients (76%) with 43 (75%) including a pharyngeal location. Histopathology showed a follicular, diffuse, and follicular and diffuse pattern in 13, 34, and 9 of the 56 patients (not available for 1), respectively. No patient had LDH levels ≥2x upper limit of normal (ULN). Twenty-six had stage I (46%) and 31 stage II (54%) disease. Sixteen/57 patients (28%) had a complete resection, with 2 cases undergoing watchful waiting and 14 receiving chemotherapy (3 with rituximab). All other 41 patients (72%) without a complete resection received chemotherapy (4 with rituximab). Only 1 patient relapsed after 5 months of watchful waiting and died while in complete lymphoma

remission from a viral infection after allogeneic stem cell transplantation, which was performed due to the underlying immunodeficiency. Both 2.5-year EFS and OS were 98%±2% for the 51 patients with head-and-neck LBCL-*IRF4*+ (6 without outcome data; Figure 1-C/D).

The site of involvement was the abdomen for 14 patients (19%) with 13 (93%) involving the gastrointestinal tract. Histopathology showed a follicular, diffuse, and follicular and diffuse pattern in 1, 9, and 3 of the 14 patients (not available for 1), respectively. Only 1 patient had LDH levels ≥2xULN. Stage II (50%) and III (50%) disease was present in 7 patients each, respectively. While 3/14 (21%) had a complete resection, all patients received chemotherapy (4 with rituximab). No patient relapsed. The only patient, who died, had ataxia telangiectasia and succumbed due to interstitial lung disease. Both 2.5-year EFS and OS were 83%±15% for all 10 patients with abdominal LBCL-*IRF4*+ (4 without outcome data; Figure 1-E/F).

Among the remaining 4 patients (5%), sites of involvement included head-and-neck and abdomen (n=1), liver only (n=1), and lymph nodes only outside the head-and-neck region (n=2). Histopathology showed a diffuse pattern in all 4 cases. Three patients had stage III and 1 patient stage II disease. Although the latter patient had no complete resection of the involved lymph nodes, watchful waiting was pursued. The other 3 patients received chemotherapy and rituximab and all 4 patients have survived event-free.

To our knowledge, this report, including 75 LBCL-*IRF4*+ patients represents by far the largest series of LBCL-*IRF4*+ in children and young people reported to date.[3;7-10;12;21-23] Our results show that LBCL-*IRF4*+ affects both sexes equally and is associated with a median age of 10.0 years, normal LDH levels, an absence of stage IV disease, and, possibly, with an underlying immunodeficiency.[9;10] Due to the latter

observation, we believe that prospectively systematic screening for an underlying predisposition shall be performed for all LBCL-*IRF4+* patients in future clinical trials.

We, for the first time, show the relative distribution of cases between the head-and-neck and the gastrointestinal location, with 76% occurring in the former location, and that almost all purely follicular cases are confined to the head-and-neck region. Event-free survival rates of 96%±3% for the whole cohort, 98%±2% for the head-and-neck and 83%±15% for the abdominal tumors are comparable to what has been reported in the literature.[3;7-10;12;21-23] If the 4 patients with an immunodeficiency are excluded, outcome for LBCL-*IRF4+* was excellent with no events in our cohort.

While 25% of cases had a primary complete resection of their tumor (n=19; 16 head-and-neck and 3 abdominal tumors), only 2 of them underwent watchful waiting, reflecting the obvious cautionary approach of treating physicians and lack of separate treatment recommendations for LBCL-*IRF4+*. In addition, only 6/19 (32%) patients with complete resection had a purely follicular LBCL-*IRF4+*, which, due to its clinical and biological closeness to pediatric-type follicular lymphoma, could have indicated a watchful waiting approach, but this was only done in 1 patient.[11;12;24-26]

Taking our results into account, we could neither confirm that watchful waiting is already performed in completely resected disease (n=2) nor that LBCL-*IRF4+* patients can be cured with approaches other than standard-of-care B-NHL chemotherapy (Table 1, Suppl. Table 1). Nevertheless, due to the extraordinarily good prognosis, we believe that LBCL-*IRF4+* could work as prototype of an ultra-rare malignant mature B-cell neoplasm for which treatment is not stratified by stage, but histopathology alone, allowing stage I-III patients to be included in the lowest-risk arms where treatment could be de-escalated in a non-randomized (due to its rarity) manner in prospectively controlled trials. Such trials might also test watchful waiting

for (in)completely resected, purely follicular LBCL-*IRF4+* of the head-and-neck region.[12;24-27]

Our study has limitations including its retrospective nature, with potential for reporting bias, and the small patient numbers. However, given the rarity of this entity, these data are likely to be the best available to determine the prognosis of LBCL-*IRF4+* in children and young people and to develop future therapy studies. They will also allow us assessing the true overall incidence of this rare LBCL entity among childhood NHL and, in particular, comparing its biology and clinical behavior to pediatric-type follicular lymphoma and other diffuse LBCL.

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Contribution:

MH, AA, MP, BB, and WW designed and planned the study; AA and MH wrote the manuscript; MH, AA, and HvM were in charge of data pooling, data checking and

statistical analysis; all other authors (OA, MA, OB, AB, EC, AC, MC, BAD, MdV, GG, DH, WK, RK, EK, NM, VMC, AN, CR, IS, IT, JV, HvM) as well as MH, AA, MP, BB, and WW were principal or co-investigators in their study groups and institutions, coordinated the national trials and/or registries in their countries, provided study materials and recruited patients. All authors read and approved the final version of the manuscript.

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References

1. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia.* 2022;36(7):1720-1748.
2. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127(20):2375-2390.
3. Au-Yeung RKH, Arias Padilla L, Zimmermann M, et al. Experience with provisional WHO-entities large B-cell lymphoma with IRF4-rearrangement and Burkitt-like lymphoma with 11q aberration in paediatric patients of the NHL-BFM group. *Br J Haematol.* 2020;190(5):753-763.
4. Quintanilla-Martinez L, Laurent C, Soma L, et al. Emerging entities: high-grade/large B-cell lymphoma with 11q aberration, large B-cell lymphoma with IRF4 rearrangement, and new molecular subgroups in large B-cell lymphomas. A report of the 2022 EA4HP/SH lymphoma workshop. *Virchows Arch.* 2023;483(3):281-298.
5. Quintanilla-Martinez L, Sander B, Chan JK, et al. Indolent lymphomas in the pediatric population: follicular lymphoma, IRF4/MUM1+ lymphoma, nodal marginal zone lymphoma and chronic lymphocytic leukemia. *Virchows Arch.* 2016;468(2):141-157.

6. Salaverria I, Martin-Guerrero I, Burkhardt B, et al. High resolution copy number analysis of IRF4 translocation-positive diffuse large B-cell and follicular lymphomas. *Genes Chromosomes Cancer.* 2013;52(2):150-155.

7. Chen L, Al-Kzayer LF, Liu T, et al. IFR4/MUM1-positive lymphoma in Waldeyer ring with co-expression of CD5 and CD10. *Pediatr Blood Cancer.* 2017;64(2):311-314.

8. Chisholm KM, Mohlman J, Liew M, et al. IRF4 translocation status in pediatric follicular and diffuse large B-cell lymphoma patients enrolled in Children's Oncology Group trials. *Pediatr Blood Cancer.* 2019;66(8):e27770.

9. Czarny J, Andrzejewska M, Zajac-Spychala O, et al. Successful Treatment of Large B-Cell Lymphoma in a Child with Compound Heterozygous Mutation in the ATM Gene. *Int J Mol Sci.* 2023;24(2).

10. Elhodaky M, Gunderman LM, Bachula M, et al. Relapse of large B-cell lymphoma with IRF4 rearrangement associated with SLAM-associated protein deficiency. *Pediatr Blood Cancer.* 2023:e30478.

11. Ramis-Zaldivar JE, Gonzalez-Farre B, Balague O, et al. Distinct molecular profile of IRF4-rearranged large B-cell lymphoma. *Blood.* 2020;135(4):274-286.

12. Woessmann W, Quintanilla-Martinez L. Rare mature B-cell lymphomas in children and adolescents. *Hematol Oncol.* 2019;37 Suppl 1(53-61.

13. Minard-Colin V, Auperin A, Pillon M, et al. Rituximab for High-Risk, Mature B-Cell Non-Hodgkin's Lymphoma in Children. *N Engl J Med.* 2020;382(23):2207-2219.

14. Pillon M, Mussolin L, Carraro E, et al. Detection of prognostic factors in children and adolescents with Burkitt and Diffuse Large B-Cell Lymphoma treated with the AIEOP LNH-97 protocol. *Br J Haematol.* 2016;175(3):467-475.

15. Rigaud C, Auperin A, Jourdain A, et al. Outcome of relapse in children and adolescents with B-cell non-Hodgkin lymphoma and mature acute leukemia: A report from the French LMB study. *Pediatr Blood Cancer.* 2019;66(9):e27873.

16. Tsurusawa M, Mori T, Kikuchi A, et al. Improved treatment results of children with B-cell non-Hodgkin lymphoma: a report from the Japanese Pediatric Leukemia/Lymphoma Study Group B-NHL03 study. *Pediatr Blood Cancer.* 2014;61(7):1215-1221.

17. Woessmann W, Seidemann K, Mann G, et al. The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the BFM Group Study NHL-BFM95. *Blood.* 2005;105(3):948-958.

18. Jourdain A, Auperin A, Minard-Colin V, et al. Outcome of and prognostic factors for relapse in children and adolescents with mature B-cell lymphoma and leukemia treated in three consecutive prospective "Lymphomes Malins B" protocols. A Societe Francaise des Cancers de l'Enfant study. *Haematologica.* 2015;100(6):810-817.

19. Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. *Semin Oncol.* 1980;7(3):332-339.

20. Rosolen A, Perkins SL, Pinkerton CR, et al. Revised International Pediatric Non-Hodgkin Lymphoma Staging System. *J Clin Oncol.* 2015;33(18):2112-2118.

21. Frauenfeld L, Castrejon-de-Anta N, Ramis-Zaldivar JE, et al. Diffuse large B-cell lymphomas in adults with aberrant coexpression of CD10, BCL6, and MUM1 are enriched in IRF4 rearrangements. *Blood Adv.* 2022;6(7):2361-2372.

22. Jiang XN, Yu F, Xue T, et al. IRF4 rearrangement may predict favorable prognosis in children and young adults with primary head and neck large B-cell lymphoma. *Cancer Med.* 2023;12(9):10684-10693.

23. Streich S, Frauenfeld L, Otto F, et al. Prevalence of IRF4 rearrangement in large B-cell lymphomas of the Waldeyer's ring in adults. *Virchows Arch.* 2023;482(3):551-560.

24. Attarbaschi A, Abla O, Arias Padilla L, et al. Rare non-Hodgkin lymphoma of childhood and adolescence: A consensus diagnostic and therapeutic approach to pediatric-type follicular lymphoma, marginal zone lymphoma, and nonanaplastic peripheral T-cell lymphoma. *Pediatr Blood Cancer.* 2020;67(8):e28416.

25. Attarbaschi A, Beishuizen A, Mann G, et al. Children and adolescents with follicular lymphoma have an excellent prognosis with either limited chemotherapy or with a "Watch and wait" strategy after complete resection. *Ann Hematol.* 2013;92(11):1537-1541.

26. Xavier AC, Suzuki R, Attarbaschi A. Diagnosis and management of rare paediatric Non-Hodgkin lymphoma. *Best Pract Res Clin Haematol.* 2023;36(1):101440.

27. Ronceray L, Abla O, Barzilai-Birenboim S, et al. Children and adolescents with marginal zone lymphoma have an excellent prognosis with limited chemotherapy or a watch-and-wait strategy after complete resection. *Pediatr Blood Cancer.* 2018;65(4).

Table 1A: Initial characteristics, treatment approach and outcome of 75 patients with LBCL-*IRF4+*

Variable	No. of pts.	%	Variable	No. of pts.	%
Sex			Resection status		
Male	37	49.3	Complete	19	25.3
Female	38	50.7	Incomplete/biopsy	55	73.3
			Not available	1	1.3
Age					
Median (years)	10.0	-	Treatment #1		
Range (years)	3.0–21.7	-	Risk groups[d]		
<10 years	37	49.3	Low- & intermediate	53	70.7
≥10 years	38	50.7	High	3	4.0
			Miscellaneous	6	8.0
Pre-existing disorder			Watchful waiting	3	4.0
Yes[a]	4	5.3	Not available[e]	10	13.3
No	70	93.3			
			Treatment #2		
Serum LDH level			Chemotherapy	62	82.7
<2x ULN	65	86.7	+ radiotherapy	2	3.2
≥2x ULN	1	1.3	+ rituximab	14	22.6
Not available	9	12.0	Watchful waiting	3	4.0
			Not available[e]	10	13.3
Stage of disease[Ref. 19,20]					
I	26	34.7	Complete resection		
II	39	52.0	Watchful waiting	2	10.5
III	10	13.3	Chemotherapy	13	68.4
IV	0	-	+ radiotherapy	0	-
			Not available	4	21.1
Site of disease					
Head-and-neck	57	76.0	Outcome of 65 pts.		
Pharynx[b]	43	-	Relapse	1	1.3
Lymph nodes only	13	-	Second malignancy	0	-
Epiglottis	1	-	Death	2	2.7

Abdomen	14	18.7
GIT	13	-
Other	1	-
Other sites[c]	4	5.3

2.5-year EFS	96±3%	-
2.5-year OS	96±3%	-
Follow-up		
Median (years)	2.84	-
Range (years)	0.09–11.26	-

Table 1B: Histopathological features and genetics of 75 patients with LBCL-*IRF4+*

Variable	No. of pts.	%
Growth pattern		
Purely follicular	14	18.7
Diffuse	47	62.7
Follicular and diffuse	12	16.0
Not available	2	2.7
CD10 expression		
Positive	43	57.3
Negative	31	41.3
Not available	1	1.3
CD20 expression		
Positive	73	97.3
Negative	1	1.3
Not available	1	1.3
BCL6 expression		
Positive	60	80.0
Negative	2	2.7
Not available	13	17.3
BCL2 expression		
Positive	52	69.3
Negative	19	25.3
Not available	4	5.3
CD5 expression		
Positive	14	18.7
Negative	22	29.3
Not available	39	52.0

Variable	No. of pts.	%
IRF4 rearrangement		
Positive[f]	73	97.3
Negative	2	2.7
IRF4 fusion gene partner		
IGH	12	16.4
IGK	0	-
IGL	0	-
Not available	61	83.6
MYC rearrangement		
Positive	0	-
Negative	57	76.0
Not available	18	24.0
BCL6 rearrangement		
Positive	3	4.0
Negative	35	46.7
Not available	37	49.3
BCL2 rearrangement		
Positive	0	-
Negative	42	56.0
Not available	33	44.0

Abbreviations: No., number; pts., patients; LDH, lactate dehydrogenase; ULN, upper limit of normal; GIT, gastrointestinal tract; EFS, event-free survival; OS, overall survival

[a] ataxia telangiectasia; Griscelli syndrome type-2; severe combined immunodeficiency: ZAP70 + FFAP24 mutations; selective IgA deficiency; notably, 1 patient with hypothyroidism was also reported, but not accounted for a predisposing disorder.

[b] including 13 patients with additional involvement of the cervical lymph nodes

[c] head-and-neck + abdomen, n=1 (stage III); liver only, n=1 (stage III); peripheral lymph nodes outside the head-and-neck region, n=2: inguinal and pelvic lymph nodes (stage II), inguinal and mediastinal lymph nodes (stage III)

[d] NHL-BFM therapy, n=28, including 10[e] with no risk group available due to inclusion in an ongoing trial; FAB/LMB therapy, n=20; AIEOP LNH therapy, n=6; SHOP LNH therapy, n=5; JPSLG B-NHL therapy, n=7; watchful waiting, n=3; miscellaneous therapy, n=6 (watchful waiting after only a prephase with COP, n=1; R-CHOP, n=2; R-EPOCH, n=1; R-CHOEP, n=1; details of chemotherapy not available, n=1); please refer to references #13 – #18.

[f] proven in 72/73 cases by fluorescence *in-situ* hybridization analysis and in 1 case by next-generation sequencing.

Legends

Figure 1: **A and B**, Event-free survival (EFS) and overall survival (OS) of the 65 LBCL-*IRF4+* patients; **C and D**, EFS and OS of the 50 head-and-neck LBCL-*IRF4+* patients;

E and F, EFS and OS of the 10 abdominal LBCL-*IRF4+* patients.