

## **Supplementary 1**

### **Details about statistical methods**

1. Pearson's Chi-Square ( $\chi^2$ ) test - analyzing the association between categorical variables.
2. Fisher Exact test - analyzing the association between two dichotomous variables (2x2), when at least one cell has an expected value of  $<5$ .
3. Fisher-Freeman-Halton test - an extension of the Fisher Exact test for comparing between a dichotomous variable and a  $3 \leq$  categorical variable (2xK).
4. Mann-Whitney U test – a non-parametric test for comparing the medians of a quantitative dependent variable between two categories of an independent variable.
5. Kruskal-Wallis H test – a non-parametric test for comparing the medians of a quantitative dependent variable between  $3 \leq$  categories of an independent variable.
6. Binary logistic regression – following the multiple imputation process, examining the best multivariate model for predicting the antibody response, by calculating the odds ratio (OR) and its 95% confidence interval (CI) for each of the model's explanatory variables.
7. McNemar test – considering paired dichotomous samples, this test was applied for comparing the proportions of patients, who reported about having local or systemic adverse events, after the first dose of vaccination and after the second dose of vaccination.
8. Adjusted odds ratio (aOR): in a 2x2 table, when at least one cell contained a value of zero, the Wald's aOR and its 95% CI were calculated, by adding a value of 0.5 to each cell.

**Supplementary Table 1. Means and medians of serologic response**

Variable	Categories	Serologic response (U/mL)				
		Mean	Median	Interquartile range	Range	<i>p</i> -value
Age in time of vaccination (y)	≤65	637.5	1.4	0.4-334.6	0.4-13792	0.009
	>65	173.3	0.4	0.4-4.4	0.4- 3946	
Sex	Females	300.4	1.5	0.4-102.4	0.4- 3946	0.010
	Males	318.1	0.4	0.4-4.5	0.4-13792	
Treatment status (detailed)	Treatment-naïve	261.6	1.7	0.4-136.0	0.4-3946	<0.001
	On-therapy	98.5	0.4	0.4-0.4	0.4-5732	
	Off-therapy in remission (CR or PR)	1214	297.6	1.2-1149.8	0.4-13792	
	Off-therapy in relapse	45.1	0.4	0.4-97.7	0.4-250.0	
Binet stage	A	337.1	47.9	0.4-215.9	0.4- 3946	<0.001
	B or C	47.0	0.4	0.4-1.1	0.4- 964.5	
IGHV	Mutated	231.5	0.4	0.4-159.8	0.4-2949	0.010
	Unmutated	375.6	0.4	0.4-0.5	0.4-13792	
FISH test	Normal	767.4	0.4	0.4-5.3	0.4- 13792	0.084
	Del13q	235.6	0.4	0.4-34.8	0.4- 2949	
	Trisomy 12	423.7	0.4	0.4-530.8	0.4- 3617	
	Del11q	298.8	0.4	0.4-4.8	0.4- 5732	
	Del17p	0.6	0.4	0.4-0.4	0.4- 4.500	
Beta2 microglobulin (mg/L)	≤3.5	288.1	0.5	0.4-158.2	0.4- 3946	0.001
	>3.5	1.0	0.4	0.4-0.4	0.4- 8.210	
Current treatment status	Untreated	486.5	4.2	0.4-241.8	0.4-13792	<0.001
	Treated	98.5	0.4	0.4-0.4	0.4-5732	
Protocol	BTKi	130.6	0.4	0.4-0.4	0.4-5732	0.801
	Venetoclax± anti-CD20 antibody	38.8	0.4	0.4-0.4	0.4-840.4	
	Others	0.7	0.4	0.4-0.4	0.4-1.2	
Anti-CD20 (last treatment)	<12 months prior vaccination	0.4	0.4	0.4-0.4	0.4-0.4	<0.001
	≥12 months prior vaccination	589.2	0.4	0.4-284	0.4- 13792	
Serum IgG level (mg/dL)	<550	74.3	0.4	0.4-0.4	0.4-1152	<0.001
	≥550	291.1	0.7	0.4-101.8	0.4-5732	
Serum IgM level (mg/dL)	<40	65.9	0.4	0.4-0.6	0.4-1964	<0.001
	≥40	441.1	5.0	0.4-233.8	0.4-5732	
Serum IgA level (mg/dL)	<80	234.4	0.4	0.4-1.2	0.4-5732	0.015
	≥80	224.6	0.5	0.4-99.0	0.4-3946	

Abbreviations: FISH - Fluorescence in situ hybridization; IGHV -immunoglobulin heavy chain; P – probability value; y - years

**Supplementary Table 2. Baseline characteristics and serologic response of patients "off-therapy in remission".**

	All patients (n=24)*	Time intervals from last treatment to vaccination (months)	
		<12 (n=6)	≥12 (n=17)*
Age, median (IQR), (years)	70.5 (60.0-76.5)	63.5 (54.0-73.0)	70.0 (63.0-77.0)
Males, n (%)	15 (62.5)	4 (66.7)	10 (58.8)
Serologic response, n (%) **	19 (79.2)	3 (50.0)	16 (94.1)
Serologic response (U/mL), median (IQR)	297.6 (1.2-1149.8)	0.8 (0.4-934.7)	384.4 (6.3-1558)
IgG (mg/dL), median (IQR)	688 (486-995)	642 (318.5-965.0)	900.0 (537.0-997.0)
IgM (mg/dL), median (IQR) ***	30 (0-58.5)	20.0 (0.0-20.0)	49.0 (7.0-61.0)
IgA (mg/dL), median (IQR)	83.5 (20.0-118.0)	35 (7.0-90.0)	97.0 (26.0-120.0)

\*\* P=0.040; \*\*\* P=0.027

Abbreviations: IgG – Immunoglobulin G; IgM – Immunoglobulin M; IgA – Immunoglobulin A; IQR – Interquartile range

**Supplementary Table 3. Serologic response of patients "off-therapy in remission" by last treatment protocol**

Treatment protocols	n (%)	Time from last treatment to vaccination, median, months (IQR)	Serologic response, n (%)	Serologic response (U/mL), median (IQR)
<b>Chemoimmunotherapy</b>	<b>13 (54.1)</b>	<b>44.7 (24.5-101.5)</b>	<b>11 (84.6)</b>	<b>196.3 (2.0-1149.8)</b>
FCR	6 (46.2)	88.6 (33.1-137.2)	5 (83.3)	1035 (3.1-1768.3)
ChIO	5 (38.5)	42.3 (24.5-50.6)	4 (80.0)	4.4 (0.8-1184)
BR	1 (33.3)	54.1	1 (100)	311.1
RCHOP	1 (33.3)	24.1	1 (100)	8.2
<b>Novel agents</b>	<b>7 (29.2)</b>	<b>5.3 (2.2-15.9)</b>	<b>6 (85.7)</b>	<b>604.0 (1.1-2524.0)</b>
Venetoclax+BTKi	4 (57.1)	9.3 (1.6-22.7)	4 (100)	2244 (794.7-10975)
Venetoclax monotherapy	2 (28.6)	22.2 (5.3-39.1)	2 (100)	302.6 (1.1-302.6)
Venetoclax+Obinutuzumab	1 (14.3)	2.2	0 (0)	0.4
<b>Obinutuzumab monotherapy</b>	<b>3 (12.5)</b>	<b>16.7 (10.8-16.7)</b>	<b>1 (33.3)</b>	<b>0.4 (0.4-0.4)</b>
<b>Other (radiotherapy)</b>	<b>1 (4.2)</b>	<b>72.7</b>	<b>1 (100)</b>	<b>22.3</b>
<b>Total</b>	<b>24</b>	<b>25.0 (10.8-55.8)</b>	<b>19 (79.2)</b>	<b>297.6 (1.2-1149.8)</b>
Abbreviations: BR – Bendamustine and rituximab; ChIO – Chlorambucil plus Obinutuzumab; FCR – Fludarabine, cyclophosphamide, rituximab; IQR – Interquartile range; RCHOP – Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.				

## Adverse events

### Supplementary Table 4. Cases of adverse events, post first and post second vaccinations

Cases of adverse events, number of cases (% out of 167 patients)

Post vaccination	Local												Enlarged axil lyn	Allergy	Nausea	Others	Total
	Local pain	redness/edema	Weakness	Dizziness	Headaches	Myalgia	Arthralgia	Fever	Chills								
First	50 (29.9)	5 (3.0)	11 (6.6)	2 (1.2)	9 (5.4)	3 (1.8)	0 (0.0)	4 (2.4)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	87			
Second	54 (32.3)	7 (4.2)	14 (8.4)	3 (1.8)	10 (6.0)	8 (4.8)	0 (0.0)	11 (6.6)	10 (6.0)	2 (1.2)	0 (0.0)	3 (1.8)	1 (0.6)	123			

### Supplementary Table 5. Matching of patients who reported about adverse events, post first and post second vaccination

		Post vaccination		P*
		First, n (%)	Second, n (%)	
Any adverse events	Yes	64 (38.3)	79 (47.3)	0.024
	No	103 (61.7)	88 (52.7)	
Only local	Yes	43 (25.8)	40 (24.0)	0.629
	No	124 (74.2)	127 (76.0)	
Systemic	Yes	21 (12.6)	39 (23.4)	0.005
	No	146 (87.4)	128 (76.6)	
<b>Total</b>		<b>167</b>	<b>167</b>	

\*McNemar test