

# 50<sup>th</sup> General Assembly of ERIC Members

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# Efficacy of the BNT162b2 mRNA COVID-19 Vaccine in Patients with CLL

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# Introduction

- Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a single-stranded RNA virus, which causes Coronavirus Disease 2019 (COVID-19)
- A disease with variable presentations, ranging from mild common cold to severe respiratory failure
- An increased risk for severe disease and death has been noted among elderly patients and persons with preexisting medical conditions

# COVID19 in patients with CLL

- Two large multicenter retrospective studies reported outcomes of COVID-19 infection in patients with CLL
- The case fatality rate was 33% for all patients
- No conclusive results on the impact of anti-CLL therapy on the clinical severity and mortality from COVID-19
- Age and comorbidities were found as risk factors in one study but not in the other.

## Study aim and design

- A prospective study, conducted in the framework of the ERIC
- Investigated the efficacy of BNT162b2 mRNA COVID-19 vaccine in pts with CLL
- Pts with history of SARS-CoV-2 infection were excluded
- Blood serum were collected 2-3 weeks after administration of the second vaccine
- **Primary endpoint:** Proportion of subjects acquiring anti SARS-CoV-2S antibodies

## Study design-cont.

- Serum samples were analyzed by using Elecsys® Anti-SARS-CoV-2S assay on the cobas e 601 (Roche Diagnostics)
- This assay has a measurement range of 0.40-250 U/mL, with a concentration of  $\geq 0.80$  U/mL considered as positive
- Sample results exceeding the upper limit of the measuring range were on-board diluted 1:10 or 1:100 when needed
- To ensure that none of the patients had been recently exposed to SARS-CoV-2, we additionally tested for the presence of antibodies to nucleocapsid

## Results

- From December 2020 through February 2021;

A total of 167 pts with CLL/SLL and

52 age and sex- matched controls were included

- The median time from the second vaccine dose to serology testing was 15 days (IQR, 14-17)

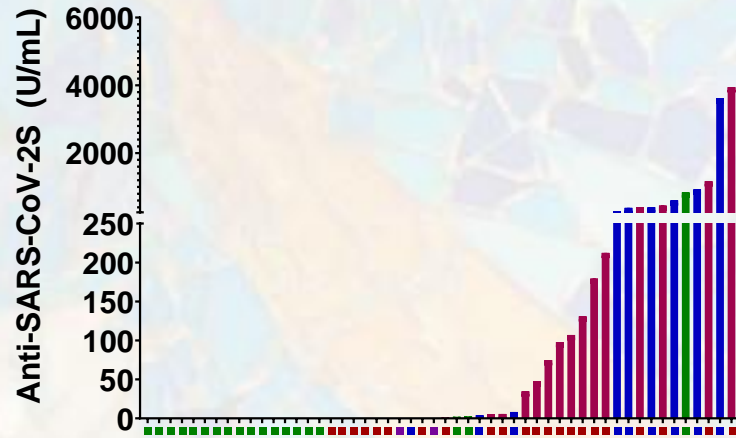
# Patient baseline demographics and disease characteristics

variable	CLL patients (n=167)
<b>Age, median (IQR), (years)</b>	<b>71.0 (63.0-76.0)</b>
≤65years, n (%)	50 (29.9)
<b>Males (n, %)</b>	<b>112 (67.1)</b>
<b>Disease/treatment status, n (%)</b>	
Treatment-naïve	58 (34.7)
On-therapy	75 (44.9)
Off-therapy in remission	24 (14.4)
Off-therapy in relapse	10 (6.0)
<b>IGHV mutational status, n (%)</b>	
Mutated	61 (50.0)
Unmutated	61 (50.0)
<b>FISH, n (%)</b>	
Normal	20 (12.0)
del(13q)	39 (23.4)
Trisomy 12	16 (9.6)
del(11q)	31 (18.6)
del(17p)	19 (11.4)
<b>Protocols of currently treated, n (%)</b>	
Bruton's tyrosine kinase inhibitors	50 (66.7)
Venetoclax ± anti-CD20 antibody	22 (29.3)
Others	3 (4.0)
<b>Time from last anti-CD20 antibody to vaccination, n (%)</b>	
<12 months	22 (28.6)
≥12 months	55 (71.4)

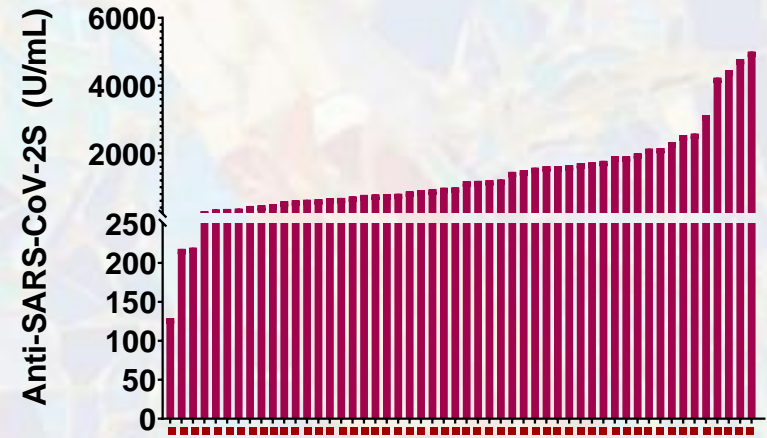


- Antibody-mediated response to the vaccine was evident in only 66 of 167 (39.5%) of all patients with CLL
- Comparing the response rates in 52 patients with CLL and 52 age-sex matched healthy controls, revealed a significantly reduced response rate (52% vs 100%) and lower antibody titers in patients with CLL (median=0.824 U/mL vs 1084 U/mL)
- None of the patients with CLL and the healthy controls had anti-SARS-CoV-2 nucleocapsid antibodies

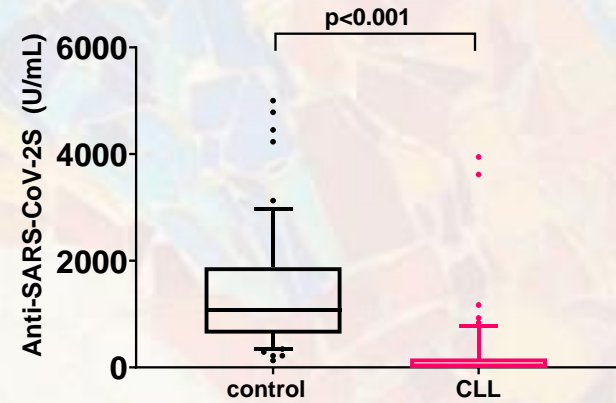
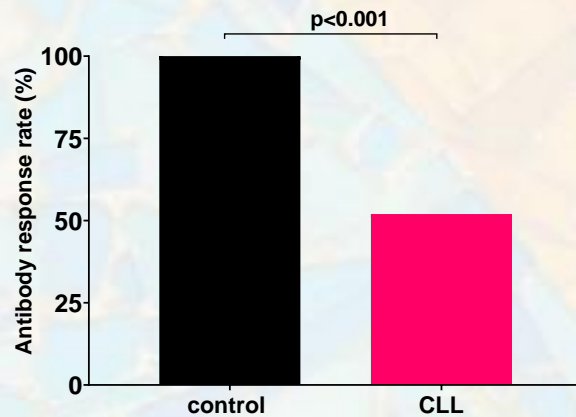
## Anti-SARS-CoV-2 Antibody Response in 52 Patients with CLL and 52 Sex- and Age-Matched Healthy controls



CLL patients



Healthy subjects

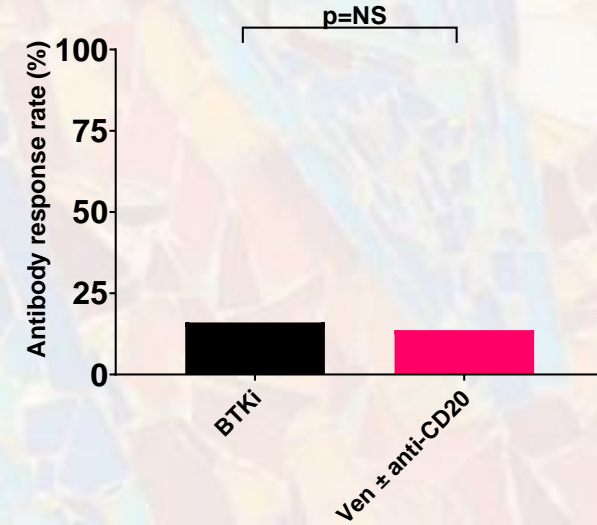
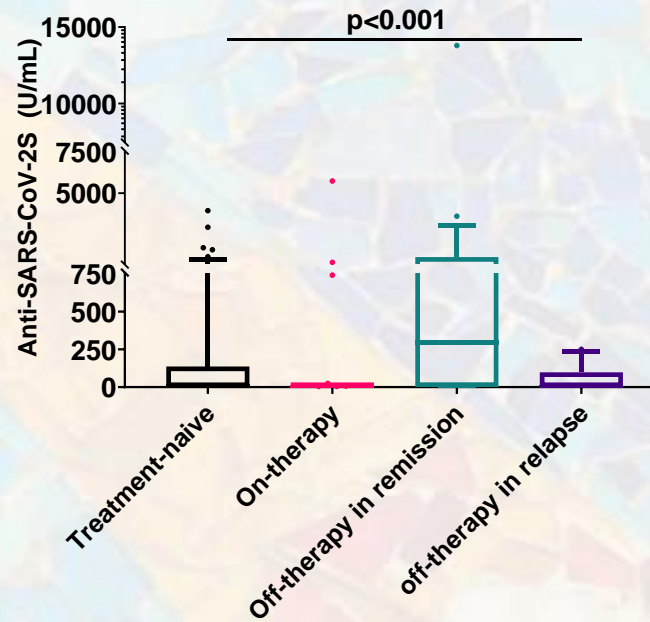
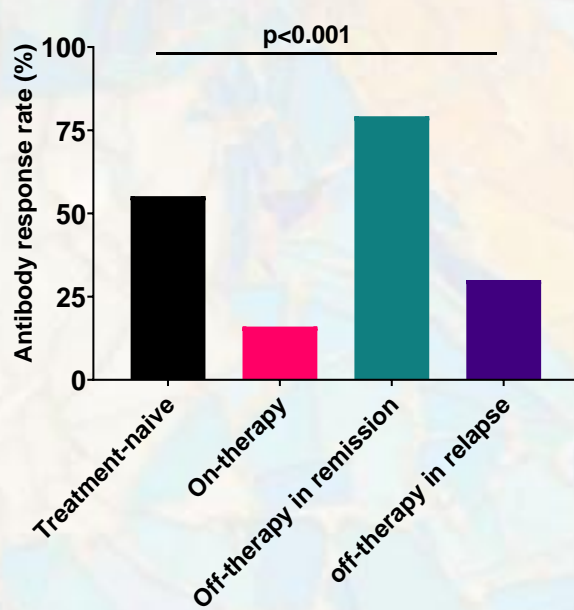


## Univariate analysis for serologic response rate in patients with CLL.

Variable	Serological response		Total	P-value	Odds ratio	95% CI	
	Positive n (%)	Negative n (%)					
Age in time of vaccination (y)	≤65	26 (52.0)	24 (48.0)	50	0.031	2.09	1.01-4.32
	>65	40 (34.2)	77 (65.8)	117			
Sex	Females	30 (54.5)	25 (45.5)	55	0.005	2.53	1.24-5.18
	Males	36 (32.1)	76 (67.9)	112			
Treatment status (detailed)	Treatment-naïve	32 (55.2)	26 (44.8)	58	<0.001	1	
	On-therapy	12 (16.0)	63 (84.0)	75			
	Off-therapy in remission (CR or PR)	19 (79.2)	5 (20.8)	24			
	Off-therapy in relapse	3 (30.0)	7 (70.0)	10			
Binet stage	A	29 (67.4)	14 (32.6)	43	0.001	6.21	1.80-22.96
	B or C	6 (24.0)	18 (75.0)	24			
IGHV	Mutated	29 (47.5)	32 (52.5)	61	0.005	3.04	1.31-7.21
	Unmutated	14 (23.0)	47 (77.0)	61			
FISH test	Normal	9 (45.0)	11 (55.0)	20	0.061	1	
	del(13q)	16 (41.0)	23 (59.0)	39			
	Trisomy 12	6 (37.5)	10 (62.5)	16			
	del(11q)	11 (35.5)	20 (64.5)	31			
	del(17p)	1 (5.30)	18 (94.7)	19			
Beta2 microglobulin (mg/L)	≤3.5	43 (47.8)	47 (52.2)	90	0.004	4.80	1.44-20.54
	>3.5	4 (16.0)	21 (84.0)	25			
Current treatment status	Untreated	54 (58.7)	38 (41.3)	92	<0.001	7.46	3.38-17.14
	Treated	12 (16.0)	63 (84.0)	75			
Treatment Protocol	BTKi	8 (16.0)	42 (84.0)	50	0.601	1	
	Venetoclax ± anti-CD20 antibody	3 (13.6)	19 (86.4)	22			
	Others	1 (33.3)	2 (66.7)	3			
Anti-CD20 (last treatment)	At least 12 months prior vaccination	25 (45.5)	30 (54.6)	55	<0.001	37.6	2.2-651.3
	Within less 12 months	0 (0.0)	22 (100.0)	22			
Serum IgG level (mg/dL)	≥550	53 (49.1)	55 (50.1)	108	<0.001	5.37	2.11-15.34
	<550	7 (14.6)	39 (85.4)	46			
Serum IgM level (mg/dL)	≥40	39 (59.1)	27 (40.9)	66	<0.001	4.84	2.27-10.37
	<40	20 (23.0)	67 (77.0)	87			
Serum IgA level (mg/dL)	≥80	42 (34.5)	47 (54.5)	89	0.012	2.42	1.15-5.19
	<80	17 (24.5)	46 (38.5)	63			

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

## Anti-SARS-CoV-2 Antibody Responses in Pts with CLL according to the Disease Status and Treatment



# Venetoclax and anti-CD20 therapy

- **Venetoclax monotherapy:**

2/5 (40%) pts that received venetoclax monotherapy achieved a positive serologic response, with relatively low antibody titers (range, 2.19-4.5 U/mL)

- **Previous exposure to anti-CD20 therapy:**

22 pts, <12 months prior to vaccination (median 5.3 months), 81% in combination with venetoclax

55 pts, ≥12 months before vaccination (median 53.1 months), 78.1% in combination with chemotherapy

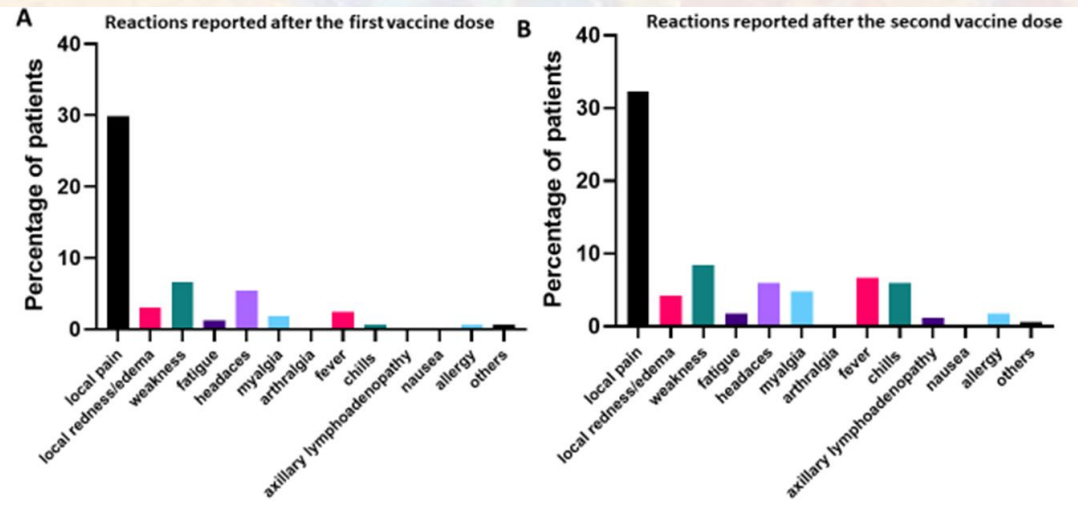
None of the pts, treated with anti-CD20 antibodies within the last 12 months responded vs. 45.5% of those that were exposed ≥12 months prior to vaccination

## Multivariate analysis for serologic response in CLL patients

Variable	Odds ratio	95% CI	P-value
Age ≤65y	3.17	1.16-8.67	0.025
Females	3.66	1.46-9.18	0.006
Mutated IGHV	1.39	0.47-4.10	0.543
Beta-2-micglobulin ≤3.5mg/dL	1.36	0.36-5.19	0.645
Lack of active therapy	6.59	2.30-18.86	<0.001
Serum IgG level ≥550mg/dL	3.70	1.08-12.66	0.037
Serum IgM level ≥40mg/dL	2.92	1.21-7.02	0.017
Serum IgA level ≥80mg/dL	1.09	0.41-2.94	0.862

# Local and Systemic Reactions

- 31.1% of pts reported mild local reactions after the first dose of the vaccine and 33.5% after the second dose
- 12.5% of pts reported systemic adverse events after the first dose and 23.4% after the second vaccine dose, being more frequent after the second dose (P=0.005)
- All AEs were mild
- No statistically significant correlation was found between local or systemic reactions and a positive serological response to the vaccine.



## Summary

- Antibody response to COVID19 vaccine in pts with CLL is markedly impaired (40%) and affected by disease activity and treatment
- Response rate was highest in pts who obtained clinical remission after treatment (79.2%), followed by in treatment-naïve (55.2%) and only 16% in pts on-treatment at the time of vaccination
- In pts treated with either BTK inhibitors or venetoclax ± anti-CD20 antibody, response rates were considerably low (16.0% and 13.6%, respectively)
- None of the pts exposed to anti-CD20 antibodies <12 months prior to vaccination responded
- In MVA, the independent predictors of response were younger age, females, lack of currently active treatment, IgG levels  $\geq 550$  mg/dL and IgM levels  $\geq 40$ mg/dL.



## In the future...

- The effect of SARS-CoV-2 vaccines on the cellular immunity protection should be also studied in CLL, especially in pts who failed to achieve an antibody-mediated response
- A longer follow-up is required to assess the clinical outcome (e.g. infection rate and disease severity)
- Furthermore, it remains to be established for how long the immune response to the vaccine is maintained and the usefulness of another booster dose



THANK YOU  
FOR  
YOUR  
ATTENTION  
ANY QUESTIONS?