Journal Club

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Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies

Outline

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Trial

Discussion

Appraisal

Zoster (Shingles) ACIP Vaccine Recommendations

BOX. Recommendations for the use of herpes zoster vaccines

In October 2017, the Advisory Committee on Immunization Practices (ACIP) made the following three recommendations:

1. Recombinant zoster vaccine (RZV) is recommended for the prevention of herpes zoster and related complications for immunocompetent adults aged ≥50 years.
2. RZV is recommended for the prevention of herpes zoster and related complications for immunocompetent adults who previously received zoster vaccine live (ZVL).
3. RZV is preferred over ZVL for the prevention of herpes zoster and related complications.

These recommendations serve as a supplement to the existing recommendations for the use of ZVL in immunocompetent adults aged ≥60 years.

Clinical Guidance

General use. RZV may be used in adults aged ≥50 years, irrespective of prior receipt of varicella vaccine or ZVL, and does not require screening for a history of chickenpox (varicella). ZVL remains a recommended vaccine for prevention of herpes zoster in immunocompetent adults aged ≥60 years (*6*). Care should be taken not to confuse ZVL, which is stored in the freezer and administered subcutaneously, with RZV, which is stored in the refrigerator and administered intramuscularly.

Dosing schedule. Following the first dose of RZV, the second dose should be given 2–6 months later (*1*). The vaccine series need not be restarted if more than 6 months have elapsed since the first dose; however, the efficacy of alternative dosing regimens has not been evaluated, data regarding the safety of alternative regimens are limited (*30*), and individuals might remain at risk for herpes zoster during a longer than recommended interval between doses 1 and 2. If the second dose of RZV is given less than 4 weeks after the first, the second dose should be repeated. Two doses of the vaccine are necessary regardless of prior history of herpes zoster or prior receipt of ZVL.

Zoster (Shingles) ACIP Vaccine Recommendations

Immunocompromised persons. As with ZVL, the ACIP recommends the use of RZV in persons taking low-dose immunosuppressive therapy (e.g., <20 mg/day of prednisone or equivalent or using inhaled or topical steroids) and persons anticipating immunosuppression or who have recovered from an immunocompromising illness (*6*). Whereas RZV is licensed for all persons aged ≥50 years, immunocompromised persons and those on moderate to high doses of immunosuppressive therapy were excluded from the efficacy studies (ZOE-50 and ZOE-70), and thus, ACIP has not made recommendations regarding the use of RZV in these patients; this topic is anticipated to be discussed at upcoming ACIP meetings as additional data become available.

Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines Weekly / January 26, 2018 / 67(3);103–108

The Epidemiology of Herpes Zoster in Patients with Newly Diagnosed Cancer

Cancer Epidemiol Biomarkers Prev. 2013 Jan;22(1):82-90.

Table 1. Patient characteristics and HZ rates

	Cancer type							
	Hematologic malignancy				Solid tumor			
Characteristic	Number of patients	Number HZ cases	Person-years	Rate/1,000 person-yrs	Number of patients	Number HZ cases	Person-years	Rate/1,000 person-years (95% CI)
All subjects	2,715	140	4,465	**31.4**	11,955	284	23,072	12.3 (10.9,13.7)
Sex								
Female	1,248	67	2,040	32.8 (25.0,40.7)	5,784	161	11,298	14.2 (12.0,16.5)
Male	1,467	73	2,425	30.1 (23.2,37.0)	6,171	123	11,774	10.4 (8.6,12.3)
Age group (years)								
18–49	415	21	733	28.6 (16.4,40.9)	1,348	26	3,063	8.5 (5.2,11.7)
50–59	452	27	848	31.8 (19.8,43.8)	2,305	56	5,033	11.1 (8.2,14.0)
60–69	604	34	1,079	31.5 (20.9,42.1)	3,151	80	6,383	12.5 (9.8,15.3)
70–79	729	44	1,143	38.5 (27.1,49.9)	3,293	78	5,994	13.0 (10.1,15.9)
80+	515	14	661	21.2 (10.1,32.3)	1,858	44	2,599	16.9 (11.9,21.9)
Race/ethnicity								
Asian	249	15	371	40.4 (20.0,60.9)	1,096	36	2,145	16.8 (11.3,22.3)
Black	211	12	374	32.1 (13.9,50.3)	1,161	29	2,341	12.4 (7.9,16.9)
Hispanic	267	10	447	22.4 (8.5,36.2)	938	17	1,794	9.5 (5.0,14.0)
Other/unknown	92	5	174	28.7 (3.5,53.8)	408	12	808	14.9 (6.5,23.3)
White	1,896	98	3,099	31.6 (25.4,37.9)	8,352	190	15,984	11.9 (10.2,13.6)
Immunosuppression[a]								
None/low	NA	15	1,131	13.3 (6.6,20.0)	NA	171	17,276	9.9 (8.4,11.4)
Moderate	NA	39	1,535	25.4 (17.4,33.4)	NA	37	1,843	20.1 (13.6,26.5)
High/very high	NA	86	1,799	47.8 (37.7,57.9)	NA	76	3,953	19.2 (14.9,23.5)
Chemotherapy[a]								
Currently on	NA	99	2,066	47.9 (38.5,57.4)	NA	120	5,214	23.0 (18.9,27.1)
Currently off	NA	41	2,399	17.1 (11.9,22.3)	NA	164	17,858	9.2 (7.8,10.6)

[a]Classification treated as time varying, with patients moving in and out of categories during follow-up.

- Northern California
- 2001 to 2005

Median follow-up 22 months

General US population:
6.5 /1000 person-yrs

Disease burden and epidemiology of herpes zoster in pre-vaccine Taiwan

Vaccine. 2010 Feb 3;28(5):1217-20.

Using herpes zoster-related ICD-9-CM codes used on Taiwan's National Health Insurance claims, we analyzed overall and age group differences in incidence, complications, utilization of healthcare facilities, lengths of stay, and cost of their medical care in Taiwan's population from 2000 to 2005.

The overall annual incidence of zoster was 4.97 cases per 1000 people, with women having a significantly higher incidence than men (5.20 per 1000 vs. 4.72 per 1000, $p < 0.001$).

Zostavax vs Shingrix

	Zostavax	Shingrix
學名	Zoster Vaccine Live	Zoster Vaccine Recombinant, Adjuvanted
成分	含活性減毒Oka/Merck株水痘帶狀疱疹病毒	含水痘帶狀疱疹病毒glycoprotein E抗原和佐劑$AS01_B$
注射部位	SC	IM
標準劑量	one dose (0.65 mL) once	2 doses (0.5 mL each) at 0 and 2 to 6 months
施打年齡 (仿單)	≥ 50	≥ 50
施打年齡(ACIP)	≥ 60	≥ 50
FDA核准上市時間	2006*	2017

Zostavax vs Shingrix

	Zostavax	Shingrix
副作用	頭痛、四肢疼痛、注射部位反應	肌肉痠痛、疲倦、頭痛、發燒、注射部位反應
禁忌	曾對Neomycin 產生(類)過敏反應[*1]、免疫力不佳、使用免疫抑制治療、懷孕	對Shingrix之任一成分過敏者
對帶狀疱疹的預防效果(%)[*4]	51	97.2
50-59	69.8	96.6
60-69	64	97.4
70-79	41	91.3
同時接種肺炎鏈球菌疫苗	與Pneumovax 23至少間隔4週施打(仿單)[*2]	✔□(CDC)[*3]

Background

Trial

Discussion

Appraisal

Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis

Lancet Infect Dis. 2019 Sep;19(9):988-1000.

Published August 06, 2019

Funding GlaxoSmithKline Biologicals SA.

Group Zoster-039 study group

Division of Transfusion Medicine, Department of Medicine, Taipei Veterans General Hospital and National Yang-Ming University School of Medicine, Taipei, Taiwan (T-J Chiou MD); Complejo

Study objective

Evaluate the immunogenicity and safety of two doses of the adjuvanted recombinant zoster vaccine (Shingrix) in adults aged 18 years and older with haematological malignancies who were undergoing or had just finished immunosuppressive cancer treatments.

PICO

Problem/Patient	Adults with haematological malignancies
Intervention	Shingrix (adjuvanted recombinant zoster vaccine)
Comparison	Placebo
Outcome	Immunogenicity and safety

Study design and participants

Study design

phase 3, randomized, observer-blind, placebo-controlled study

Participants

Participants,

During

Each dose at least 10 days before and after any cancer therapy

After

First dose of the study vaccine between 10 days and 6 months after therapy

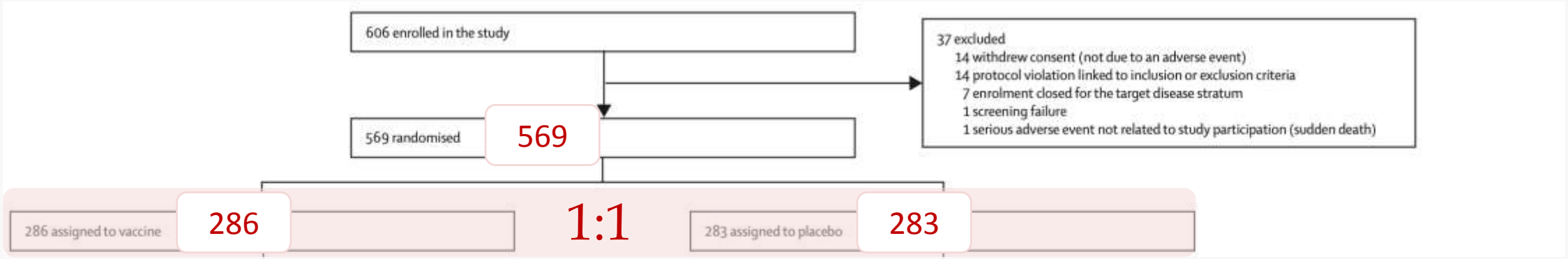
Eligible treatment

- Immunosuppressive cancer therapies (chemotherapy or immunotherapy)
- Radiotherapy was allowed only in combination with either chemotherapy or immunotherapy.
- Antiviral prophylaxis according to local standards was permitted during the study.

Exclusion criteria

1) CLL who is receiving only oral cancer therapy*1
2) Planned HCT
3) HIV infection by clinical history
4) Use of any investigational or non-registered product
5) Previous vaccination against HZ or varicella*5
6) Planned administration of a HZ or varicella vaccine other than the study vaccine*6
7) Occurrence of a varicella or HZ episode by clinical history*7
8) History of any reaction or hypersensitivity
9) (Planned) administration of a live vaccine*9
10) (Planned) administration of a non-replicating vaccine*10

Randomisation and masking



Online centralised randomisation system*

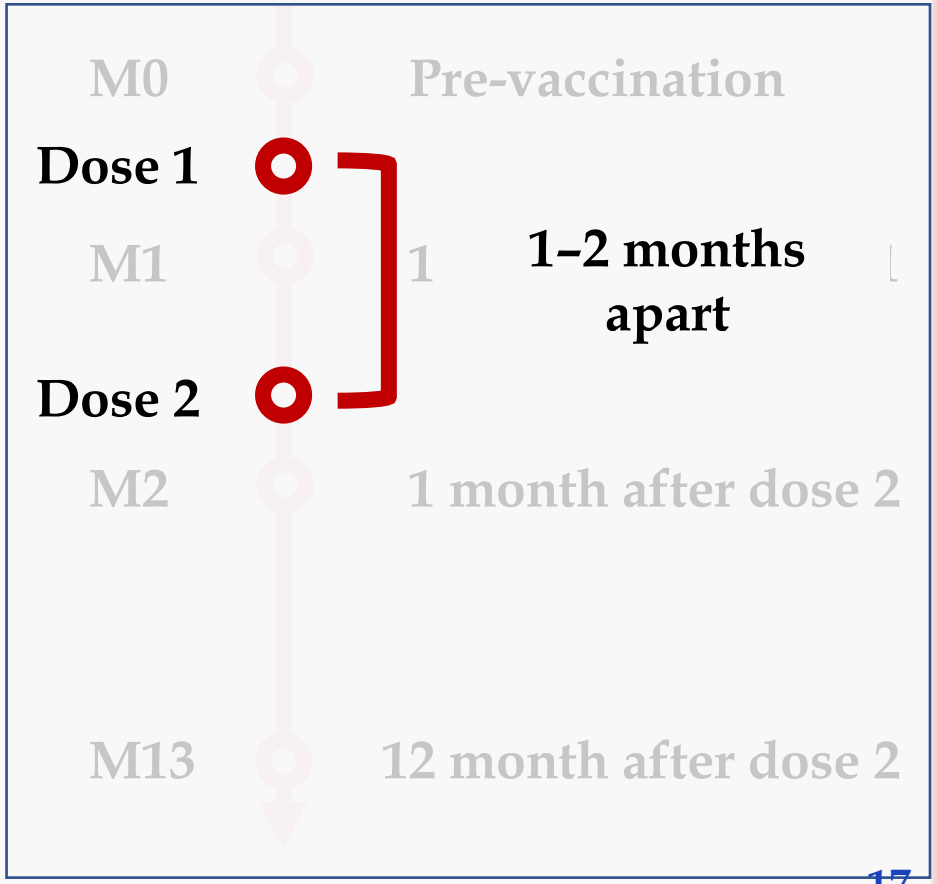
Procedures

Procedures

0.5 mL dose of vaccine
50 µg of the glycoprotein E antigen+
the GSK proprietary AS01B adjuvant system

0.5 mL dose of placebo
20 mg lyophilised sucrose +
150 mM NaCl solution

Follow-up



Measure Vaccine Response Rate

Anti-gE antibody concentrations

Seronegative antibody concentration at M2 ≥ 4x the cut-off (97 mIU/mL) for Anti-gE

Seropositive antibody concentration at M2 ≥ 4x the pre-vaccination antibody concentration

Frequencies of gE-specific CD4[2+] T cells

Below the threshold a 2x increase as compared to the threshold (320 Events/10^6 CD4 T cells)

Above the threshold a 2x increase as compared to pre-vaccination T-cell frequencies

Markers:
IFN-γ
IL-2
TNF-α
CD40L

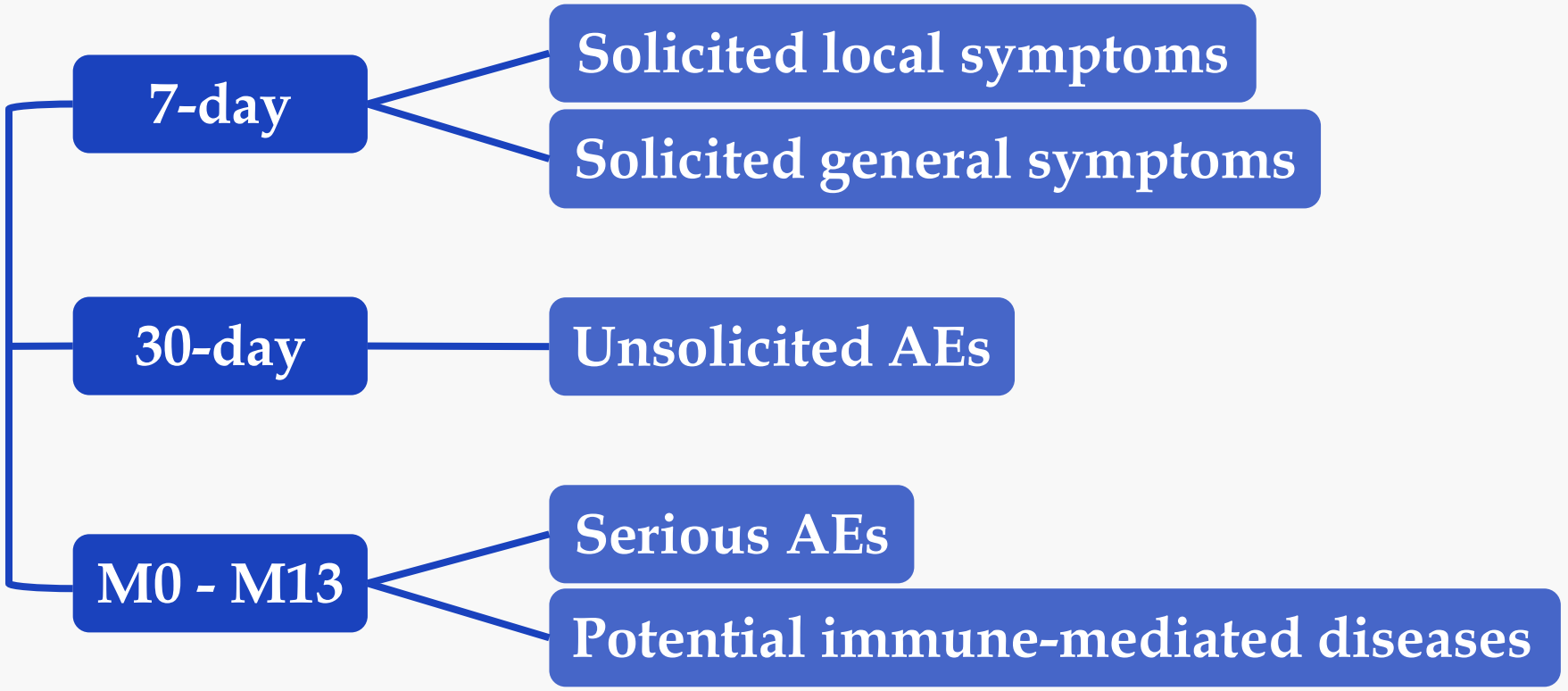
Confirmation of herpes zoster cases

1) PCR on samples collected from lesions*
2) Herpes zoster ascertainment committee (HZAC)

Outcomes

Co-primary objectives

1) Safety and reactogenicity in all participants



2) Vaccine response rates for anti-gE antibody concentrations at M2 in all participants, excluding those with non-Hodgkin B-cell lymphoma and CLL

→Met if the lower limit of the 95% CI> 60%[*1]

3) Adjusted geometric mean concentration of anti-gE antibodies at M2 in all participants, excluding those with non-Hodgkin B-cell lymphoma and CLL

→Met if the lower limit of the 95% CI of the GM ratio (vaccine over placebo)> 3[*2]

Secondary objectives

1) Vaccine response rates for anti-gE antibody concentrations in all participants excluding those with non-Hodgkin B-cell lymphoma	M2
2) Adjusted GMC of Anti-gE antibodies in all participants excluding those with non-Hodgkin B-cell lymphoma	M2
3) Vaccine response rates and anti-gE antibody concentrations	M0, 1, 2 ,13
4) Vaccine response rates for gE-specific CD4 [2+] T-cells	M0, 1, 2 ,13
5) Incidence of confirmed herpes zoster cases	M0 - M13
6) GMCs of anti-gE antibodies in per study group and HZ confirmed/non-confirmed status	M2

Statistical analysis

Sample size

Excluding non-Hodgkin B-cell lymphoma and CLL stratum, between 140 and 158 evaluable participants were needed in each study group to provide 90% power.

In each of the non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia strata, between 20 and 30 evaluable participants were targeted per study group.

Post-hoc analysis*

Results

Table 1: Demographic characteristics of the total vaccinated cohort

	Adjuvanted recombinant zoster vaccine (n=283)	Placebo (n=279)
Age at first vaccination (years)	56·8 (15·5)	57·8 (14·9)
Age group (years)		
18–49	74 (26·1%)	73 (26·2%)
≥50	209 (73·9%)	206 (73·8%)
Sex		
Male	169 (59·7%)	165 (59·1%)
Female	114 (40·3%)	114 (40·9%)
Ethnicity		
American Hispanic or Latino	11 (4·0%)	15 (5·6%)
Not American Hispanic or Latino	261 (96·0%)	253 (94·4%)
Missing	11	11
Geographic ancestry		
African heritage or African American	1 (0·4%)	1 (0·4%)
American Indian or Alaska native	0	1 (0·4%)
Asian—central or south Asian heritage	5 (1·8%)	6 (2·2%)
Asian—east Asian heritage	57 (21·0%)	60 (22·4%)
Asian—southeast Asian heritage	4 (1·5%)	1 (0·4%)
White—Arabic or north African heritage	0	1 (0·4%)
White—Caucasian or European heritage	198 (72·8%)	186 (69·4%)
Other	7 (2·6%)	12 (4·5%)
Missing	11	11

Table 1: Demographic characteristics of the total vaccinated cohort

Timing of study vaccination		
During cancer therapy course—both doses at least 10 days before and after a chemotherapy cycle	102 (36·0%)	106 (38·0%)
10 days to 6 months after the full cancer therapy course	181 (64·0%)	173 (62·0%)
Haematological malignancy		
Chronic lymphocytic leukaemia	42 (14·8%)	41 (14·7%)
2 Hodgkin lymphoma	49 (17·3%)	47 (16·8%)
1 Multiple myeloma	67 (23·7%)	65 (23·3%)
Non-Hodgkin B-cell lymphoma	41 (14·5%)	39 (14·0%)
Non-Hodgkin T-cell lymphoma	13 (4·6%)	16 (5·7%)
Other haematological malignancies	71 (25·1%)	71 (25·4%)
Acute lymphoblastic leukaemia	7 (9·9%)	5 (7·0%)
Acute myeloid leukaemia	44 (62·0%)	37 (52·1%)
Myelodysplastic syndrome	12 (16·9%)	18 (25·4%)
Other	8 (11·3%)	11 (15·5%)

Primary objectives

Safety and reactogenicity in all participants

7-day

Within 7 days after vaccination*
Any solicited injection site symptom
Grade 3 solicited injection site symptom
Any solicited general symptom
Grade 3 solicited general symptom

Fatigue (most common)

Vaccine group 58.3%

Placebo group 37.2%

Median duration

(all-grade general symptoms)

Vaccine group 3.5 days

Placebo group 6 days

Table 2: Safety analysis of the adjuvanted recombinant zoster vaccine

Primary objectives

Safety and reactogenicity in all participants

30-day

Within 30 days after vaccination	
Any unsolicited adverse event	
Considered related by investigator	
Grade 3 unsolicited adverse event	
Considered related by investigator	

The most frequent Unsolicited AEs

1. Nausea

vaccine group 3.9% Placebo group 2.2%

2. Pyrexia

Vaccine group 3.5% Placebo group 1.8%

3. Oropharyngeal pain

Vaccine group 3.5% Placebo group 1.1%

Table 2: Safety analysis of the adjuvanted recombinant zoster vaccine

Primary objectives

Safety and reactogenicity in all participants

M0 - M13

Autoimmune pancytopenia
Gout
Erythema nodosum

Autoimmune haemolytic anaemia
Guillain-Barré syndrome

From first vaccination until study end	
Any serious adverse event	
Considered related by investigator	
Any potential immune-mediated disease	
Any disease-related event†	
Any fatal serious adverse event	
Considered related by investigator	

The most frequent Serious AEs

1. Febrile neutropenia

vaccine group 4.9% Placebo group 3.9%

2. Pneumonia

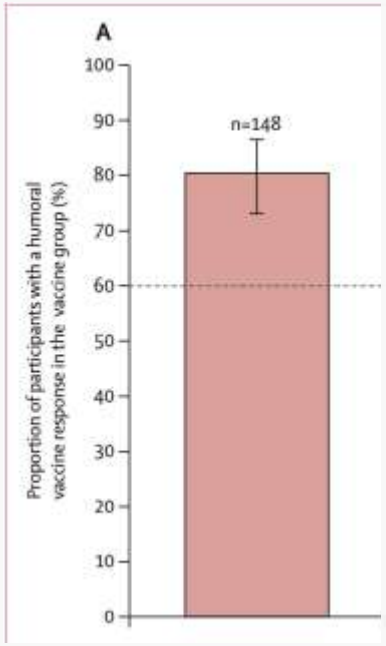
Vaccine group 3.9% Placebo group 3.9%

Table 2: Safety analysis of the adjuvanted recombinant zoster vaccine

Primary objectives

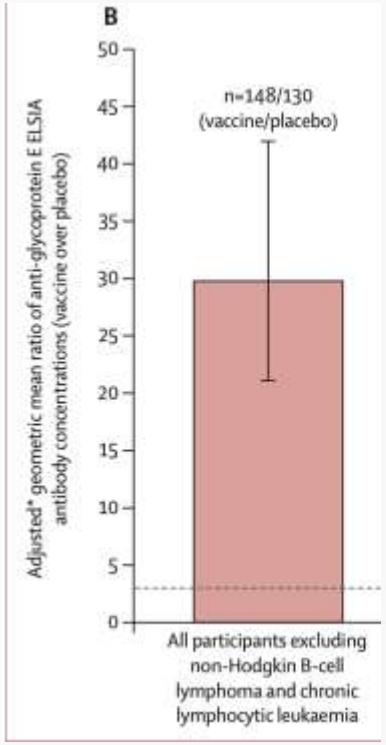
All participants

excluding those with non-Hodgkin B-cell lymphoma and CLL



Vaccine response rates

80.4% > 60%



Adjusted GM ratio

29.75 > 3

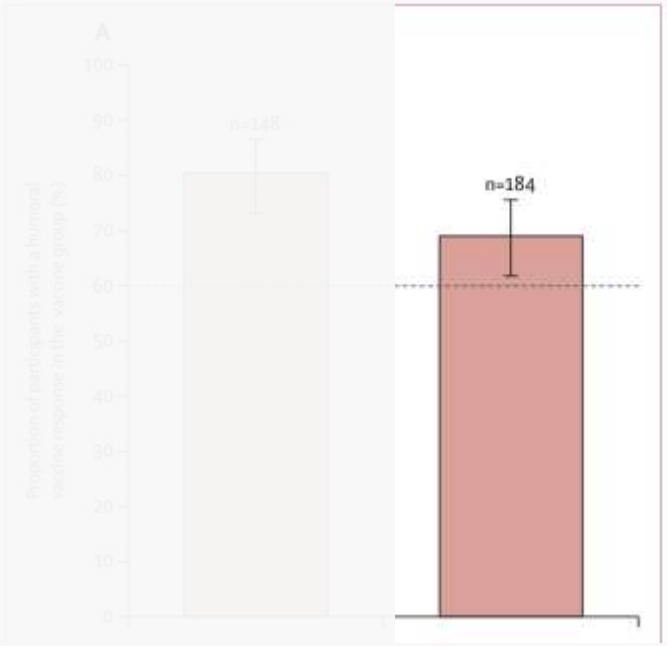
($p<0.0001$)

Figure 2: Evaluation of immunogenicity objectives with predefined success criteria (1 month after dose two, per-protocol cohort for immunogenicity)

Secondary objectives

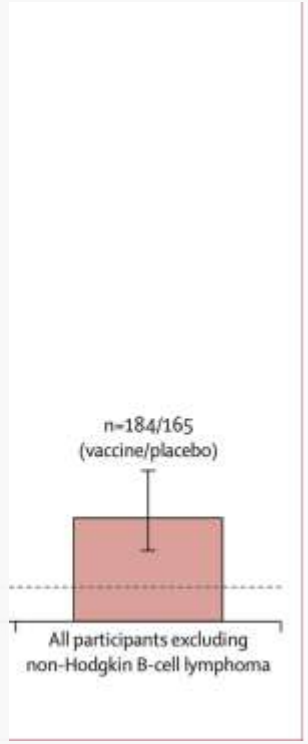
All participants

excluding those with non-Hodgkin B-cell lymphoma



Vaccine response rates

69.0% > 60%



Adjusted GM ratio

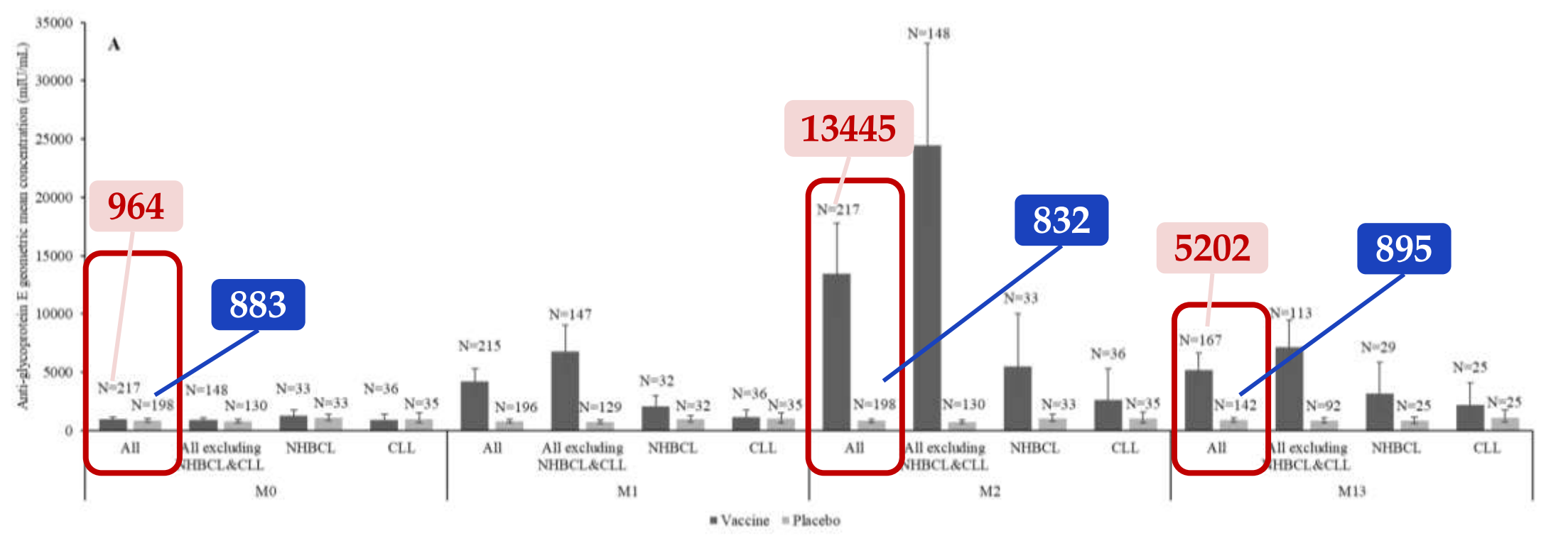
9.02 > 3

(p<0.0001)

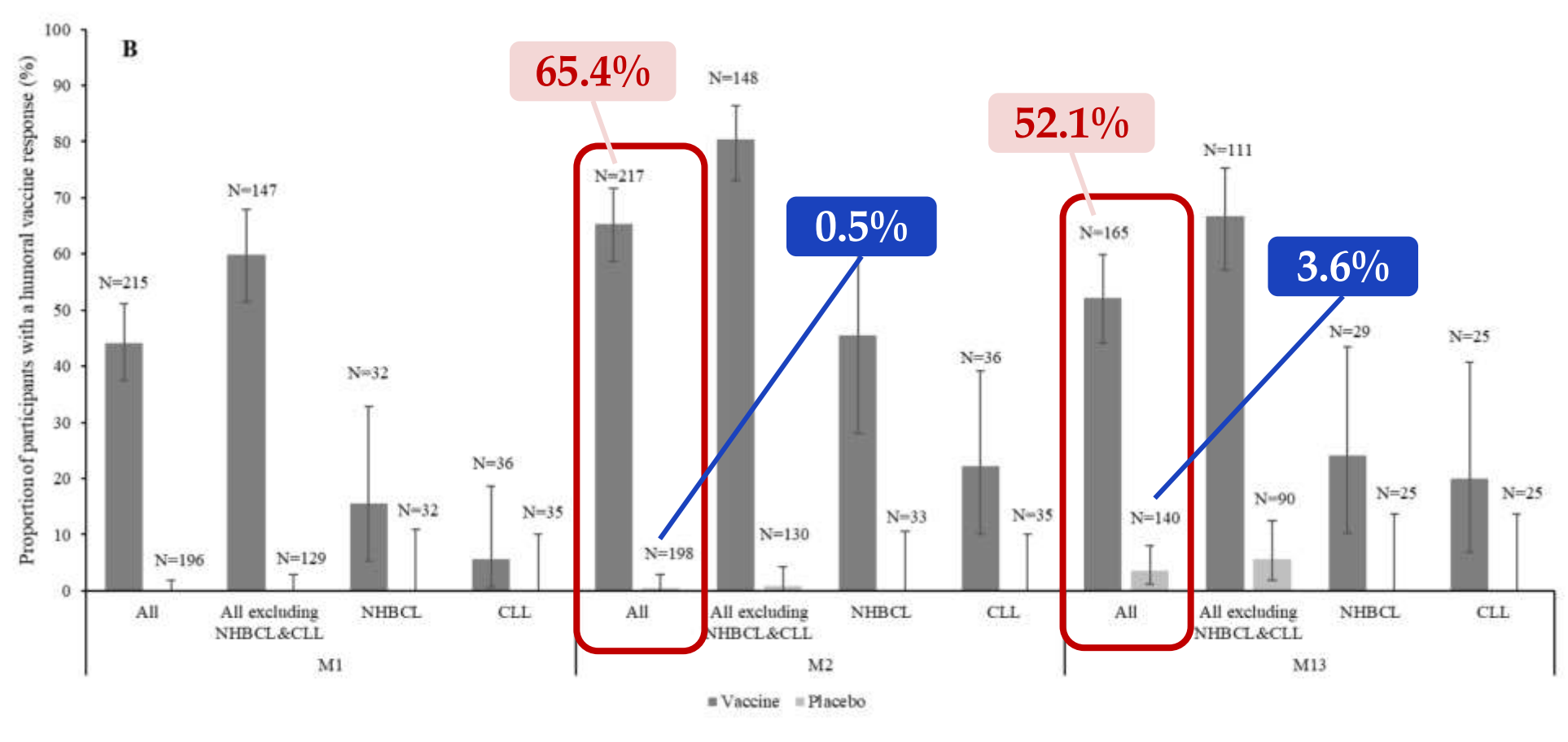
Figure 2: Evaluation of immunogenicity objectives with predefined success criteria (1 month after dose two, per-protocol cohort for immunogenicity)

Secondary objectives

Vaccine response rates and anti-gE antibody concentrations



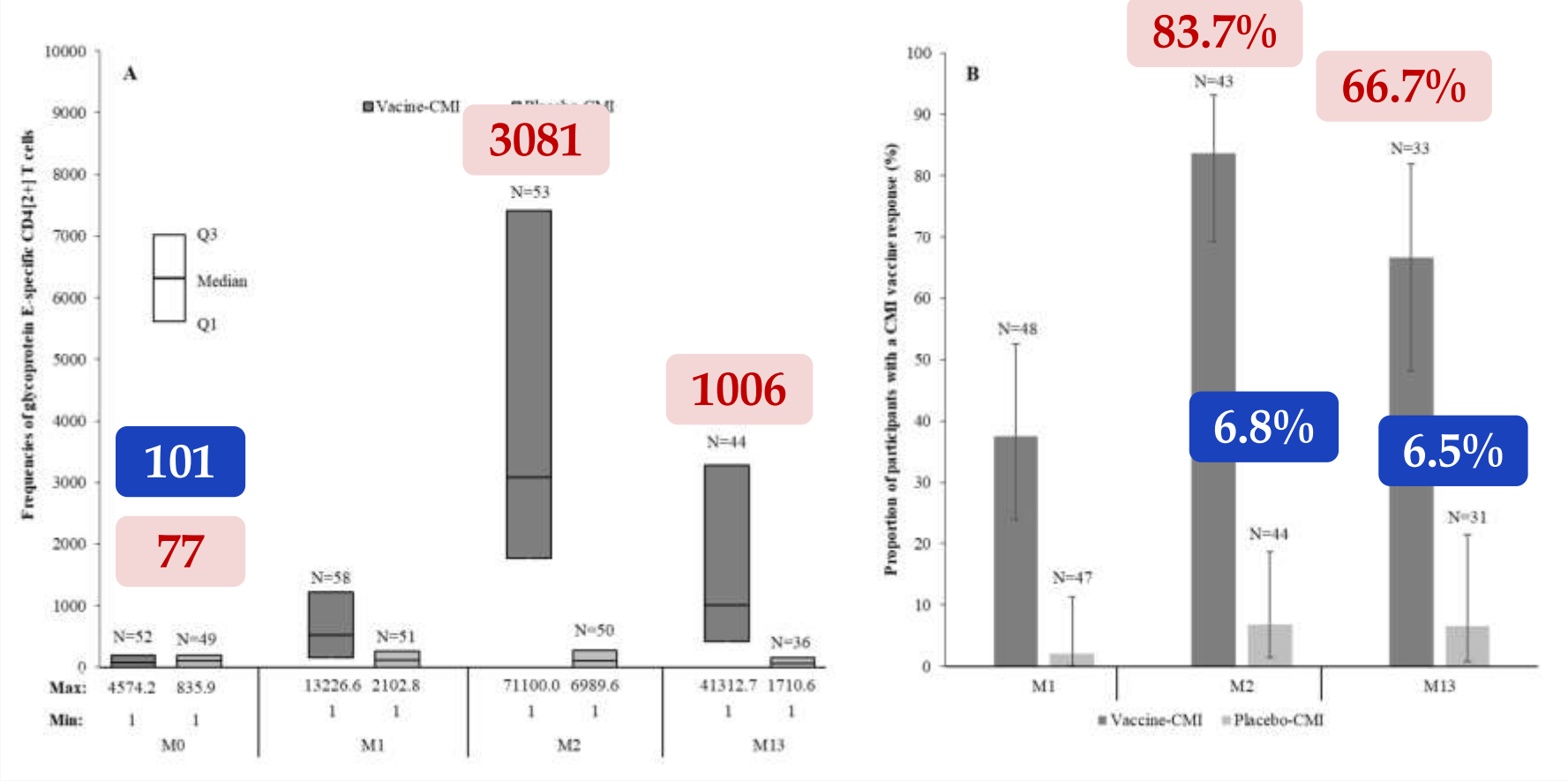
Supplementary figure 1. Humoral immune responses (per-protocol cohort for immunogenicity)
(A) Anti-glycoprotein E antibody geometric mean concentrations.



Supplementary figure 1. Humoral immune responses (per-protocol cohort for immunogenicity) (B) Proportion of participants with a vaccine response in terms of anti-glycoprotein E humoral immune response.

Secondary objectives

Vaccine response rates for gE-specific CD4 [2+] T-cells



Supplementary figure 2. Cell-mediated immune responses (per-protocol cohort for cell-mediated immunity)
(A) Descriptive statistics of glycoprotein E-specific CD4[2+] T-cell frequencies overall.
(B) Proportion of participants with a vaccine response in terms of glycoprotein E-specific CD4[2+] T-cell frequency.

Secondary objectives

Incidence of confirmed herpes zoster cases

Incidence

(per 1000 person-years)

Vaccine group

8.5

Placebo group

66.2

Vaccine efficacy

87.2 %

p=0.0021

Secondary objectives

GMCs of anti-gE antibodies in per study group and HZ confirmed/non-confirmed status

		Herpes zoster cases				Herpes zoster non-cases			
		N	Vaccine	N	Placebo	N	Vaccine	N	Placebo
Seropositivity rate* (95% confidence interval)	**M0**	2	50·0% (1·3–98·7)	12	100·0% (73·5–100·0)	257	96·5% (93·5–98·4)	240	95·8 (92·5–98·0)
	M2	2	50·0% (1·3–98·7)	12	100·0% (73·5–100·0)	253	98·4% (96·0–99·6)	234	94·9 (91·2–97·3)
Anti-glycoprotein E geometric mean concentration (95% confidence interval)	**M0**	2	115·9 (0·0–7406196·0)	12	984·5 (500·7–1935·7)	257	973·6 (835·6–1134·4)	240	866·3 (745·5–1006·6)
	M2	2	184·0 (0·0–4187800000·0)	12	960·5 (454·2–2031·1)	253	12517·4 (9662·0–16216·6)	234	802·9 (686·7–938·9)
		N'		**N'**		**N'**		**N'**	
Mean geometric increase	**M2 over M0**	2	1·6 (0·0–565·5)	12	1·0 (0·8–1·2)	253	13·1 (9·9–17·2)	233	0·9 (0·9–1·0)

Supplementary table 2. gE-specific humoral immune responses in participants with or without herpes zoster cases (cohort for the assessment of the Correlation of vaccine-induced humoral immune responses with Protection against herpes zoster)

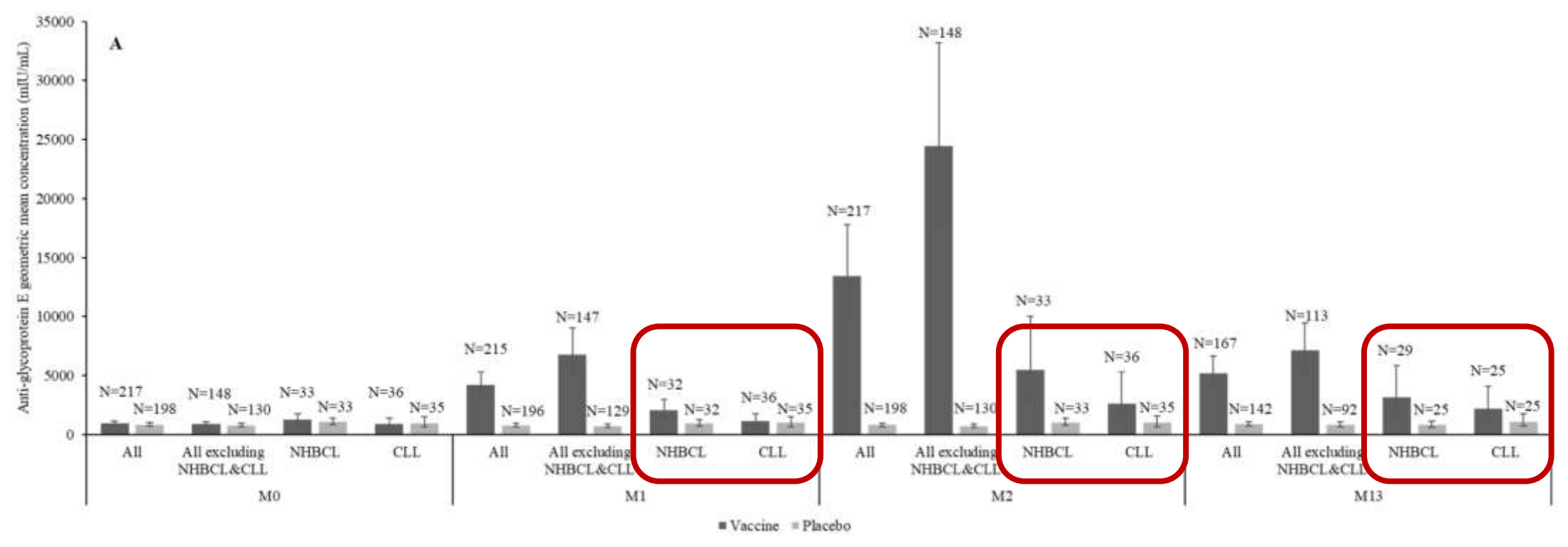
Background

Trial

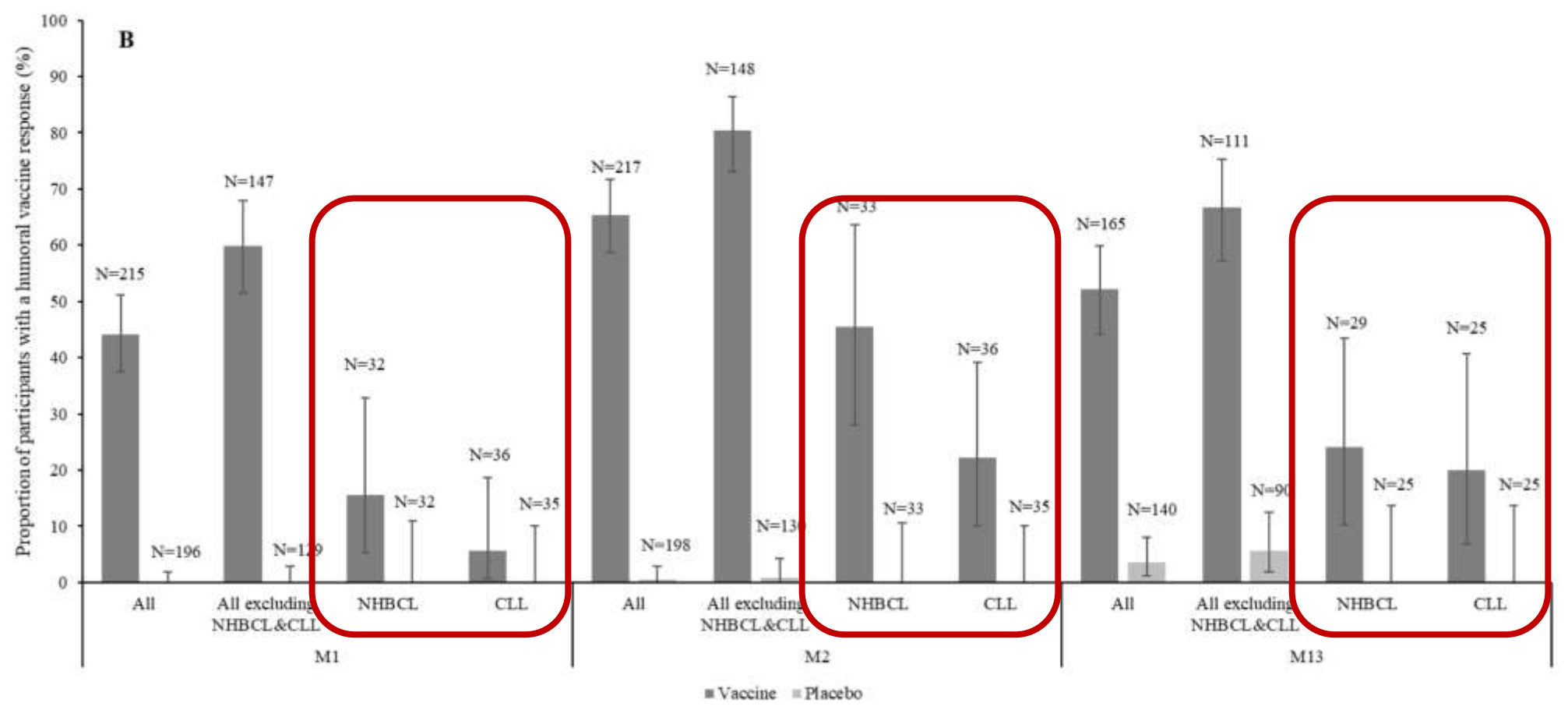
Discussion

Appraisal

Exclusion of NHBCL and CLL?



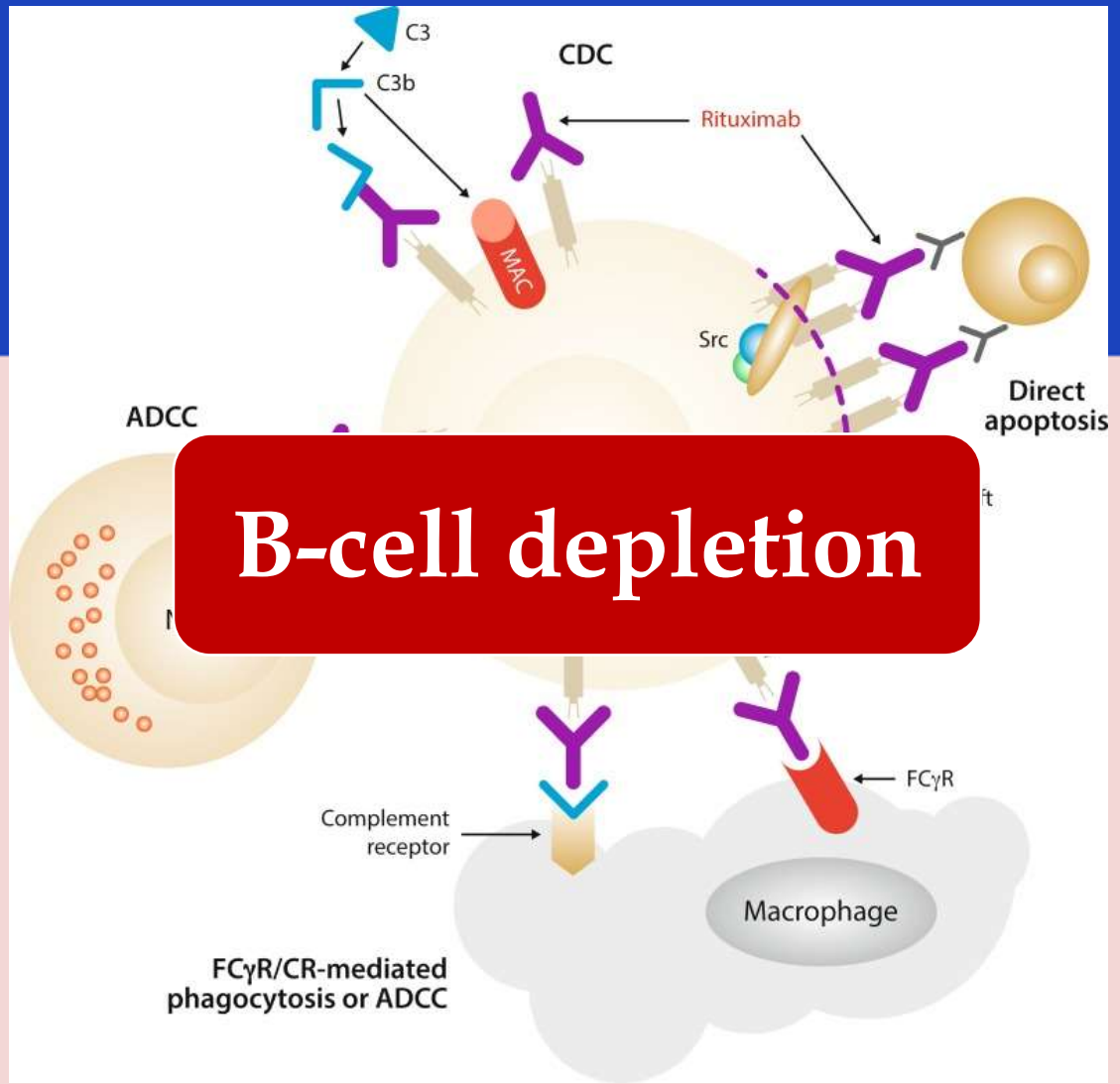
Supplementary figure 1. Humoral immune responses (per-protocol cohort for immunogenicity)
(A) Anti-glycoprotein E antibody geometric mean concentrations.



Supplementary figure 1. Humoral immune responses (per-protocol cohort for immunogenicity) (B) Proportion of participants with a vaccine response in terms of anti-glycoprotein E humoral immune response.

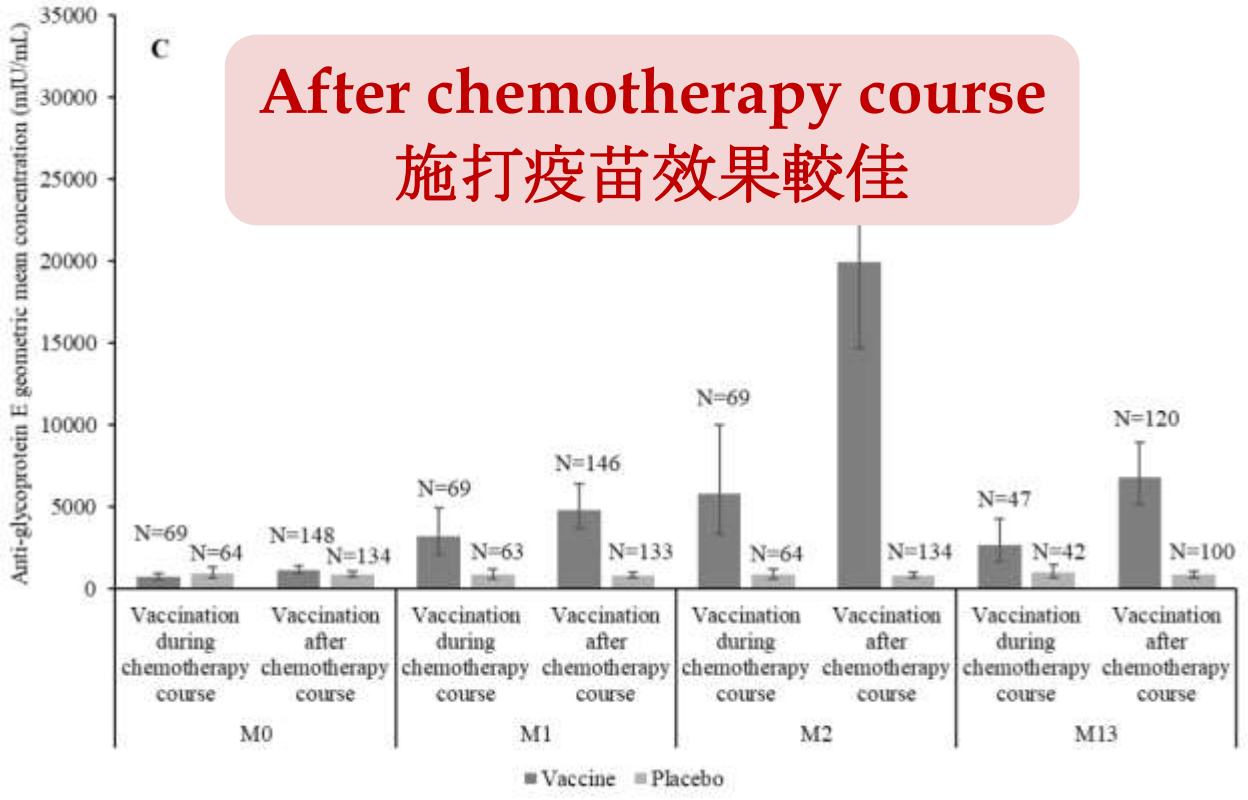
Rituximab

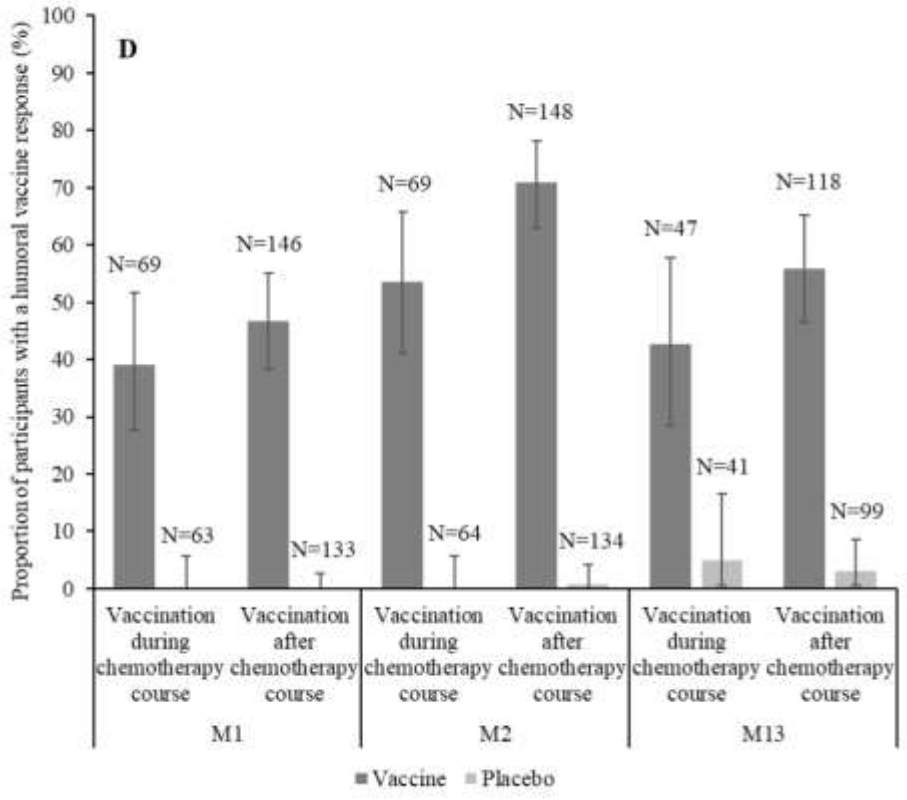
	Vaccine group	Placebo group
Non-Hodgkin B-cell lymphoma	97%	97%
Chronic lymphocytic leukaemia	81%	94%
Excluding NHBCL and CLL	2%	0.8%



During or After chemotherapy course?

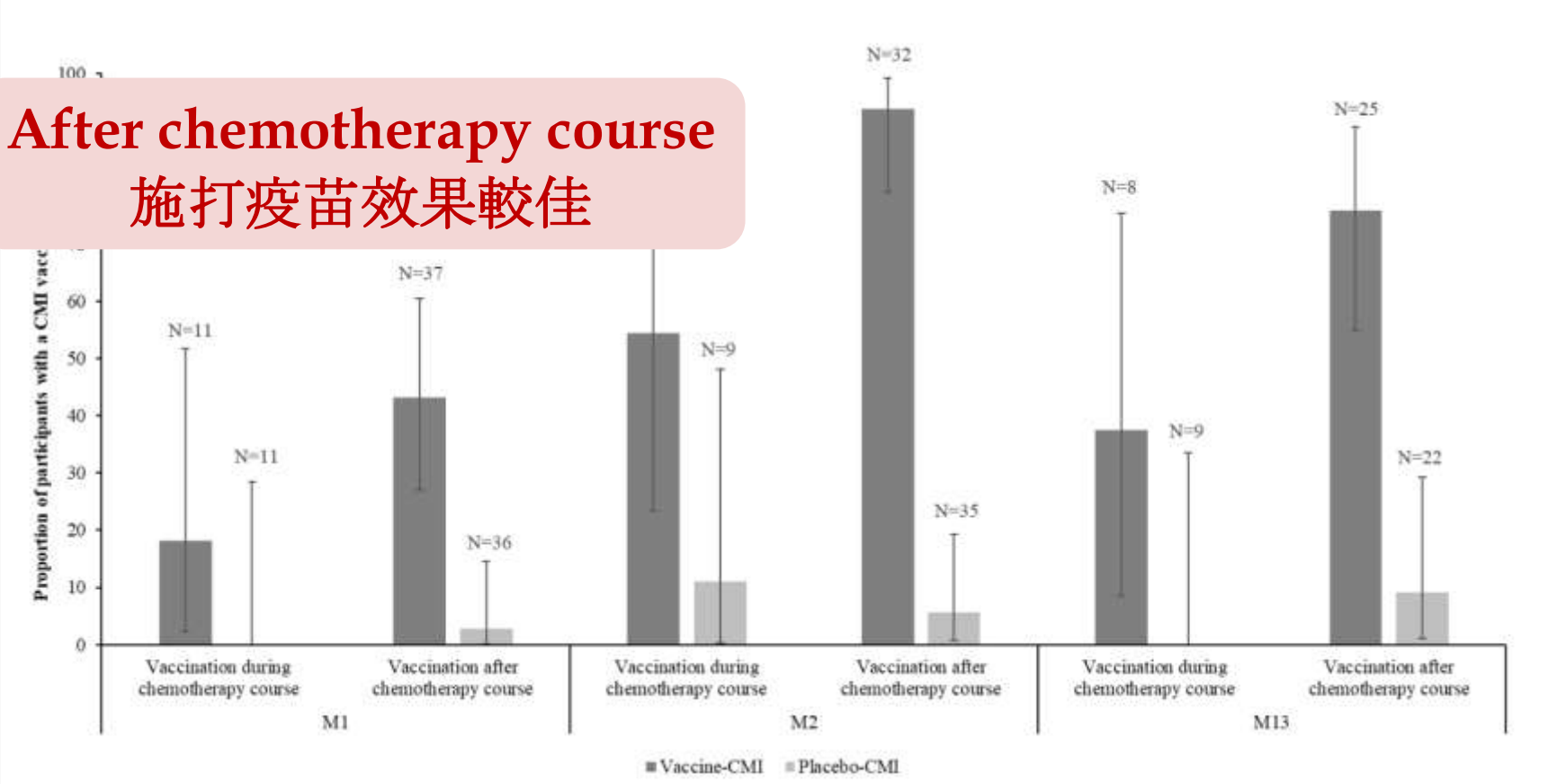
After chemotherapy course
施打疫苗效果較佳





Supplementary figure 1. Humoral immune responses (per-protocol cohort for immunogenicity)

After chemotherapy course
施打疫苗效果較佳



Supplementary figure 2. Cell-mediated immune responses (per-protocol cohort for cell-mediated immunity)

Comparison of the efficacy of Shingrix in other immunocompromised patients

	Vaccine group incidence	Placebo group incidence	Vaccine efficacy (%)	Median follow-up (months)
Hematopoietic stem cell transplantation	30	94	68.2	21
Solid tumor malignancies	6.7	18.5	63.6	29.4
Hematological malignancies	8.5	66.2	87.2*	11.1

Safety and efficacy of inactivated varicella zoster virus vaccine in immunocompromised patients with malignancies: a two-arm, randomised, double-blind, phase 3 trial

19 Jul 9;322(2):123-133.

Lancet Infect Dis. 2019 Sep;19(9):1001-1012.

Strengths and limitation

Strengths

1) Multicenter RCT

2) Geographical diversity and broad age range of the study population

3) Inclusion of patients with a range of haematological malignancies

4) High percentage of initially enrolled participants completed the study

Limitation

1) Small sample size*1

2) Short follow-up period*2

3) No stratification was done according to disease stage or number of treatment lines received

4) Lack of data to evaluate the incidence of herpes zoster–related complications*3

Background

Trial

Discussion

Appraisal

Appraisal

Section A: Is the basic study design valid for a randomised controlled trial?	
1) Did the trial address a clearly focused question?	YES
2) Was the assignment of participants to interventions randomized?	YES
3) Were all participants who entered the study accounted for at its conclusion?	YES
4) Were the participants, health workers and study personnel 'blind' to treatment ?	YES
5) Were the study groups similar at the start of the trial?	YES
6) Aside from the experimental intervention, were the groups treated equally?	YES

Appraisal

Section B: What are the results?	
7) How large was the treatment effect? - What outcomes were measured? - Is the primary outcome clearly specified? - What results were found for each outcome?	1) Safety and reactogenicity in all participants 2) VRR for anti-gE antibody concentrations at M2 in all participants, excluding those with NHBCL and CLL: **80.4% in vaccine group; 0.8% in the placebo group** 3) Adjusted GMC of anti-gE antibodies at M2 in all participants, excluding those with NHBCL and CLL: **23132.9 mIU/mL in vaccine group; 777.6 mIU/mL in the placebo group**
8) How precise was the estimate of the treatment effect? - What are the confidence limits?	2) Vaccine group 95% CI 73.1–86.5 Placebo group 95% CI 0.0–4.2 3) Vaccine group 95% CI 16642.8–32153.9 Placebo group 95% CI 702.8–860.3 Adjusted geometric mean ratio 29.75, 21.09–41.96; p<0.0001

Appraisal

Section C: Will the results help locally?	
9) Can the results be applied in your context? (or to the local population?)Patients?	Yes
10) Were all clinically important outcomes considered?	YES
11) Are the benefits worth the harms and costs?	Can’t tell

Appraisal

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9) Can the results be applied	
10) Were all clinically import	
11) Are the benefits worth th	

9

Geographic ancestry		
African heritage or African American	1 (0·4%)	1 (0·4%)
American Indian or Alaska native	0	1 (0·4%)
Asian—central or south Asian heritage	5 (1·8%)	6 (2·2%)
Asian—east Asian heritage	57 (21·0%)	60 (22·4%)
Asian—southeast Asian heritage	4 (1·5%)	1 (0·4%)
White—Arabic or north African heritage	0	1 (0·4%)
White—Caucasian or European heritage	198 (72·8%)	186 (69·4%)
Other	7 (2·6%)	12 (4·5%)
Missing	11	11

Appraisal

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9) Can the results be applied	
10) Were all clinically import	
11) Are the benefits worth th	

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Vaccine efficacy 87.2%

Harms

No significant differences in the incidence of adverse events during all time periods evaluated

Costs

Unknown 台灣未核准使用

Question

是否同意讓血液腫瘤的病患預先接種Shingrix (adjuvanted recombinant zoster vaccine)疫苗來預防帶狀皰疹？

同意

需要更多文獻支持

不同意

謝謝大家☺

Q&A