Brown Bag Lunch:
COVID19 & Cancer

Elad Sharon, MD, MPH
Senior Investigator
Cancer Therapy Evaluation Program
Division of Cancer Treatment & Diagnosis
National Cancer Institute

Outline

- Basic Immunology
- Case Fatality Rate in Patients with Cancer
- Defects in Immune Response to Vaccine (Heme vs Solid Tumor)
- COVID19 Vaccines (and Boosters)
- Evusheld
- Paxlovid

Basic Immunology Definitions

- Immune system = cells, tissues, and molecules that mediate resistance to infections
- Immunology = study of structure and function of the immune system
- Immunity = resistance of a host to pathogens and their toxic effects
- Immune response = collective and coordinated response to the introduction of foreign substances in an individual mediated by the cells and molecules of the immune system

Role of the immune system

- Defense against microbes
  - Kill cells infected with viruses
- Defense against the growth of tumor cells
  - Kill cancer cells
- Homeostasis
- Destruction of abnormal or dead cells
  (e.g. dead red or white blood cells, antigen-antibody complex)

Immune system: Cells

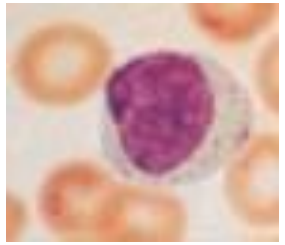
- Lymphocytes
  - T-lymphocytes (mediators of cellular immunity)
  - B-Lymphocytes, plasma cells (producers of antibodies)
  - Natural Killer Cells
- Monocytes, Macrophage
- Granulocytes
  - Neutrophils
  - Eosinophils
  - Basophils

Innate immunity

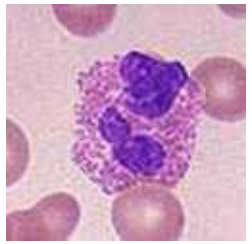
- Based on genetic make-up
- Relies on already formed components
- Rapid response: within minutes of infection
- Not specific
  - same molecules / cells respond to a range of pathogens
- Has no memory
  - same response after repeated exposure
- Does not lead to clonal expansion

Innate immunity: mechanisms

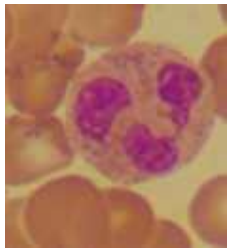
- Mechanical barriers / surface secretion
  - skin, acidic pH in stomach, cilia
- Humoral mechanisms
  - lysozymes, basic proteins, complement, interferons
- Cellular defense mechanisms



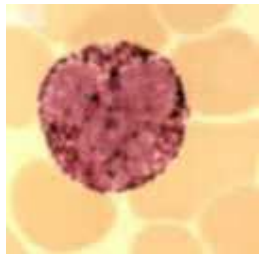
NK Cell



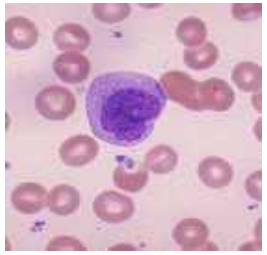
Eosinophils



Neutrophil



Basophils & Mast cells



Monocyte Macrophage

Adaptive Immunity: Second Line of Response

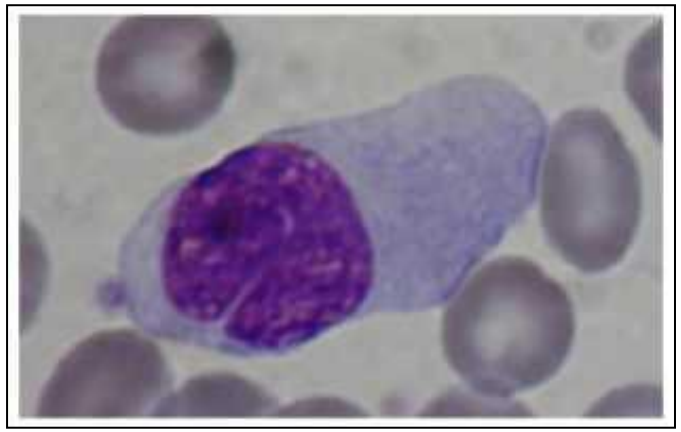
- Based upon resistance acquired during life
- Relies on genetic events and cellular growth
- Responds more slowly, over few days
- Is specific
  - each cell responds to a single epitope on an antigen
- Has anamnestic memory
  - repeated exposure leads to faster, stronger response
- Leads to clonal expansion

Adaptive Immunity: active and passive

	Active Immunity	Passive Immunity
Natural	clinical, sub-clinical infection	via breast milk, placenta
Artificial	Vaccination: Live, killed, purified antigen vaccine	immune serum, immune cells

Adaptive immunity: mechanisms

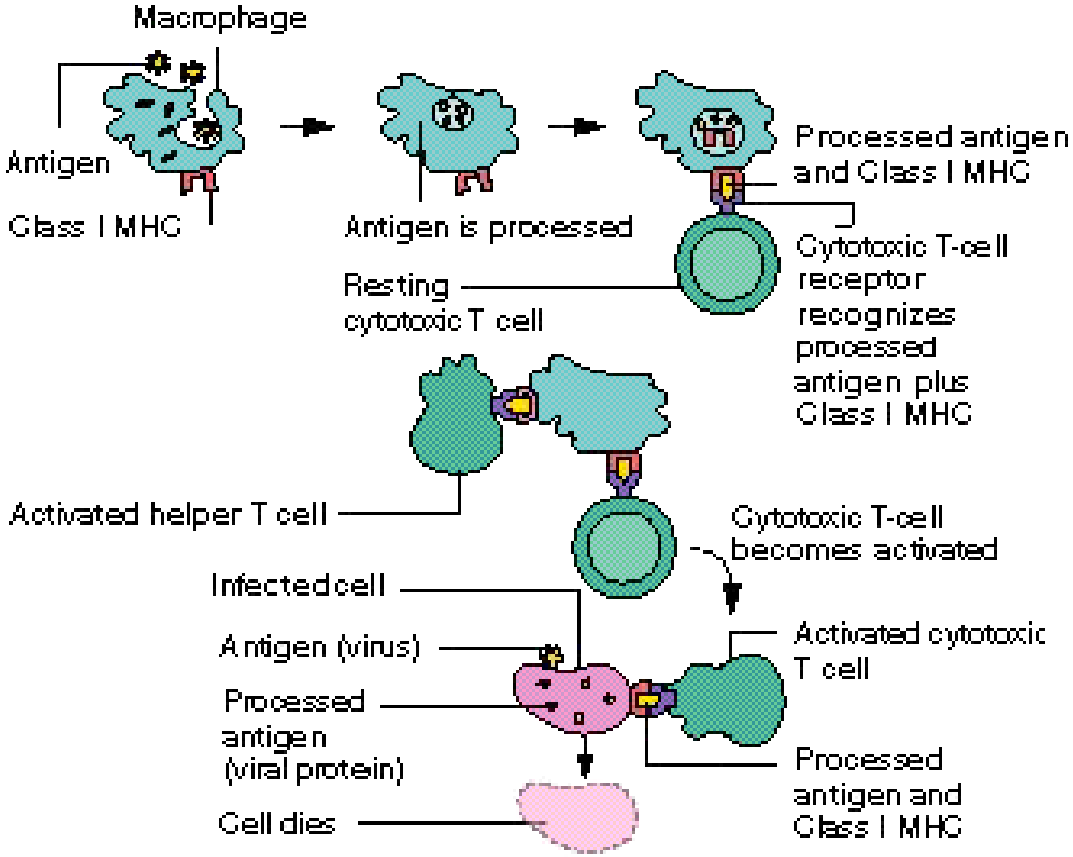
- Cell-mediated immune response (CMIR)
  - T-lymphocytes
  - Eliminate intracellular microbes that survive within phagocytes or other infected cells
- Humoral immune response (HIR)
  - B-lymphocytes
  - Mediated by antibodies
  - Eliminate extra-cellular microbes and their toxins



Plasma cell
(Derived from B-lymphocyte, produces antibodies)

Cell-mediated immune response

- T-cell
  - recognizes peptide antigen on macrophage in association with major histo-compatibility complex (MHC) class
  - identifies molecules on cell surfaces
  - helps body distinguish self from non-self
- T-cell goes into effectors cells stage that is able to kill infected cells

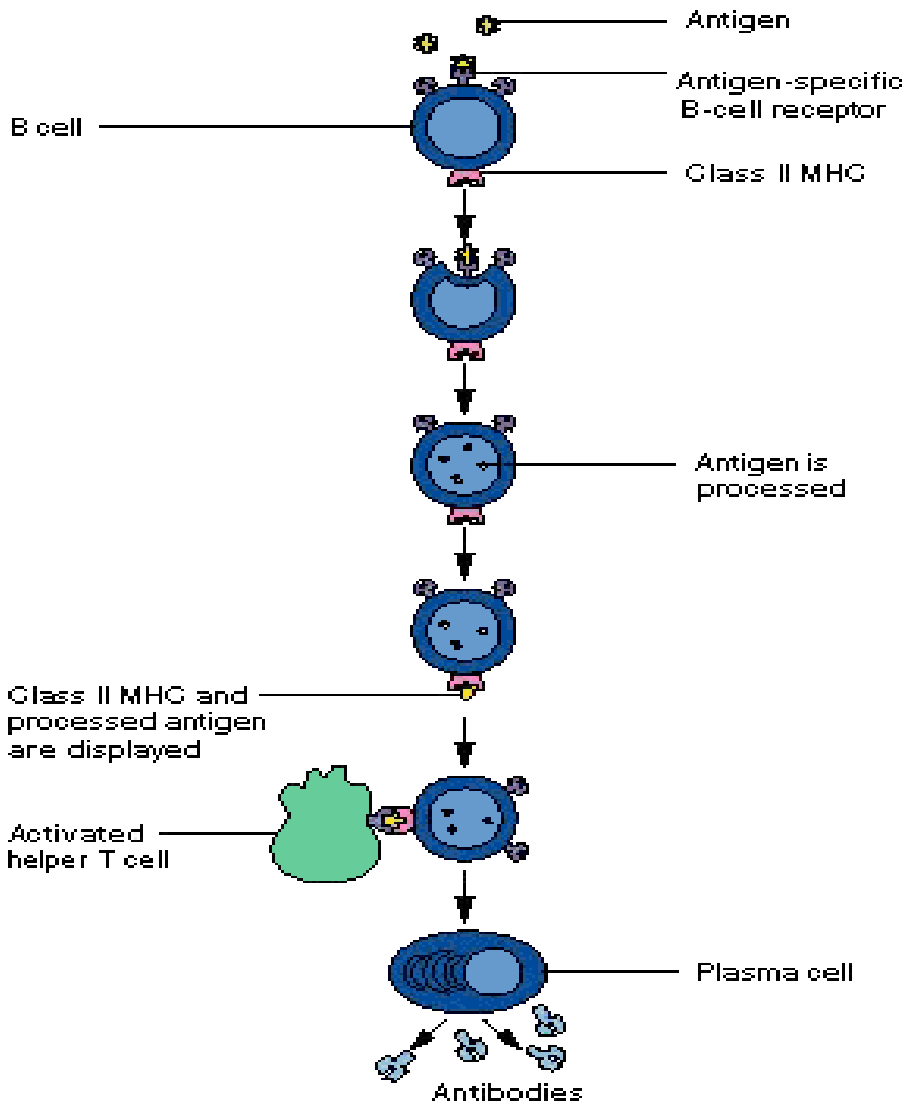


Cell mediated immune response

- Primary response
  - Production of specific clones of effector T cells and memory clones
  - Develops in several days
  - Does not limit the infection
- Secondary response
  - More pronounced, faster
  - More effective at limiting the infection
- Example - cytotoxic reactions against intracellular parasites, delayed hypersensitivity (e.g., Tuberculin test) and allograft rejection

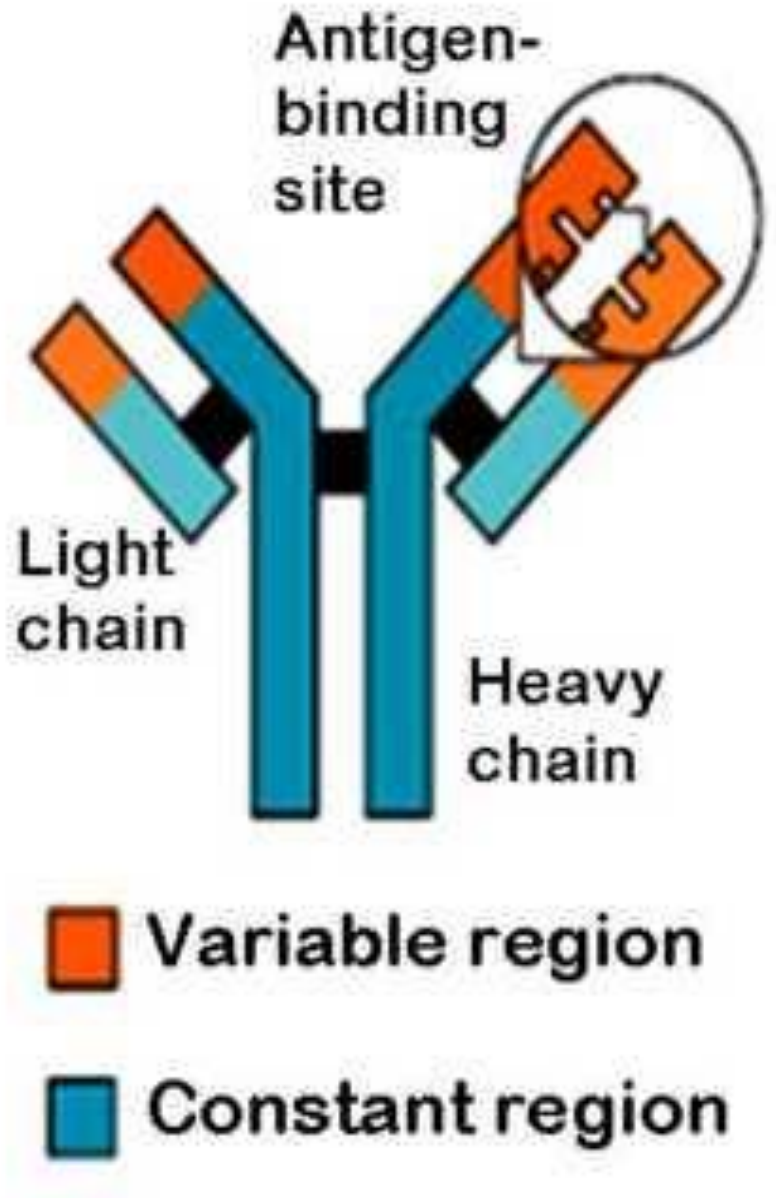
Humoral immune response

- B lymphocytes recognize specific antigens
  - proliferate and differentiate into antibody-secreting plasma cells
- Antibodies bind to specific antigens on microbes; destroy microbes via specific mechanisms
- Some B lymphocytes evolve into the resting state - memory cells

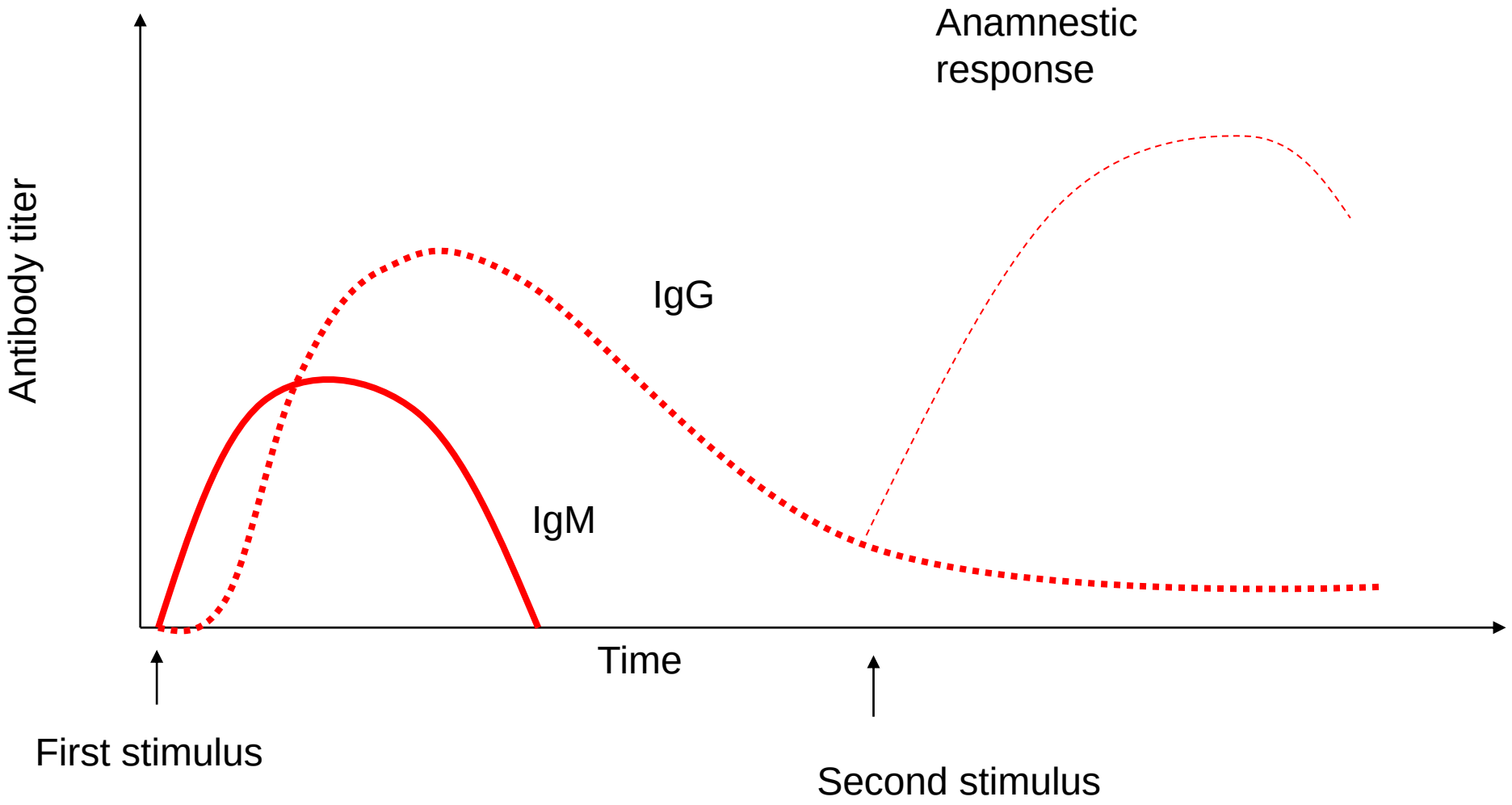


Antibodies

- Belong to the gamma-globulin fraction of serum proteins
- Y-shaped or T-shaped polypeptides
  - 2 identical heavy chains
  - 2 identical light chains
- Five kinds of antibodies
  - IgG, IgM, IgA, IgD, IgE



IgM – IgG sequential response



Case Fatality Rate

- Case fatality ratio (CFR) is the proportion of individuals diagnosed with a disease who die from that disease and is therefore a measure of severity among detected cases:

$$Case\ Fatality\ ratio\ (CFR, in\%) = \frac{Number\ of\ deaths\ from\ disease}{Number\ of\ confirmed\ cases\ of\ disease} \times 100$$

- **Assumption 1: The likelihood of detecting cases and deaths is consistent over the course of the outbreak.**
  - Early in an outbreak, surveillance tends to focus more on symptomatic patients who seek care, so milder and asymptomatic cases are less likely to be detected, leading to overestimation of CFR; this overestimation may decrease as testing and active case finding increase. One method to account for this is to remove from the analysis those cases that occurred before the establishment of robust surveillance, including application of clear case definitions (a method called left censoring).
- **Assumption 2: All detected cases have resolved (that is, reported cases have either recovered or died).**
  - During an ongoing epidemic, some of the active cases already detected may subsequently die, leading to underestimation of CFR estimated before their death. This effect is accentuated in fast-growing epidemics (e.g. during the exponential growth phase of COVID-19).

Original Investigation

FREE

October 28, 2021

Evaluation of COVID-19 Mortality and Adverse Outcomes in US Patients With or Without Cancer

Mariana Chavez-MacGregor, MD, MSC[1,2]; Xiudong Lei, PhD[1]; Hui Zhao, PhD[1]; Paul Scheet, PhD[3]; Sharon H. Giordano, MD, MPH[1,2]

Author Affiliations | Article Information

[1]Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston

[2]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston

[3]Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston

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Key Points

Question What are the rates of death, mechanical ventilation, intensive care unit stay, and hospitalization among patients with COVID-19 with or without cancer?

Findings In this cohort study of 507 307 patients with COVID-19, those with cancer who received anticancer treatment within 3 months before COVID-19 diagnosis had an increased risk of death, intensive care unit admission, and hospitalization. Patients without recent cancer treatment had similar or better outcomes than patients without cancer.

Meaning The results of this study have risk stratification and resource use implications for patients, clinicians, and health care systems.

Abstract

Importance As the COVID-19 pandemic continues, understanding the clinical outcomes of patients with cancer and COVID-19 has become critically important.

Objective To compare the outcomes of patients with or without cancer who were diagnosed with COVID-19 and to identify the factors associated with mortality, mechanical ventilation, intensive care unit (ICU) stay, and hospitalization.

Design, Setting, and Participants This cohort study obtained data from the Optum de-identified COVID-19 electronic health record data set. More than 500 000 US adults who were diagnosed with COVID-19 from January 1 to December 31, 2020, were analyzed.

Exposures The patient groups were (1) patients without cancer, (2) patients with no recent cancer treatment, and (3) patients with recent cancer treatment (within 3 months before COVID-19 diagnosis) consisting of radiation therapy or systemic therapy.

Main Outcomes and Measures Mortality, mechanical ventilation, ICU stay, and hospitalization within 30 days of COVID-19 diagnosis were the main outcomes. Unadjusted

Table 1. Characteristics of Patients Diagnosed With COVID-19 in the Optum Data Set

Variable	No. (%)			*P* value
	Patient without cancer	Patient with cancer		
		With no recent treatment	With recent treatment	
No. of patients (N = 507 307)	493 020	9991	4296	
Diagnosis period in 2020, calendar quarters				
January-March	27 391 (5.6)	627 (6.3)	445 (10.4)	<.001
April-June	139 390 (28.3)	3468 (34.7)	1723 (40.1)	
July-September	124 409 (25.2)	2297 (23.0)	838 (19.5)	
October-December	201 830 (40.9)	3599 (36.0)	1290 (30.0)	
Age, y				
Median (IQR)	48 (32-61)	68 (59-77)	66 (57-75)	<.001
18-39	181 888 (36.9)	482 (4.8)	208 (4.8)	
40-49	81 532 (16.5)	645 (6.5)	371 (8.6)	
50-54	45 147 (9.2)	609 (6.1)	331 (7.7)	
55-59	45 555 (9.2)	960 (9.6)	406 (9.5)	
60-64	41 818 (8.5)	1343 (13.4)	553 (12.9)	
65-69	31 454 (6.4)	1435 (14.4)	702 (16.3)	
70-74	23 582 (4.8)	1407 (14.1)	636 (14.8)	
75-79	16 174 (3.3)	1303 (13.0)	459 (10.7)	
80-84	11 398 (2.3)	965 (9.7)	347 (8.1)	
≥85	14 472 (2.9)	842 (8.4)	283 (6.6)	
Sex				
Female	273 727 (55.5)	5041 (50.5)	2397 (55.8)	<.001
Male	219 293 (44.5)	4950 (49.5)	1899 (44.2)	
Race and ethnicity[a]				
Hispanic	58 013 (11.8)	625 (6.3)	321 (7.5)	<.001
Non-Hispanic				
Black	74 440 (15.1)	1696 (17.0)	726 (16.9)	
White	295 733 (60.0)	7145 (71.5)	2961 (68.9)	
Other or unknown	64 834 (13.2)	525 (5.3)	288 (6.7)	
Severe obesity: BMI ≥40				
No	442 905 (89.8)	8901 (89.1)	3839 (89.4)	.03
Yes	50 115 (10.2)	1090 (10.9)	457 (10.6)	
Charlson-Deyo Comorbidity Index score[b]				
0	342 637 (69.5)	2890 (28.9)	1060 (24.7)	<.001
1	78 433 (15.9)	2131 (21.3)	817 (19.0)	
≥2	71 950 (14.6)	4970 (49.7)	2419 (56.3)	
SNF stay				
No	489 736 (99.3)	9713 (97.2)	4103 (95.5)	<.001
Yes	3284 (0.7)	278 (2.8)	193 (4.5)	
Insurance type				
Commercial	274 397 (55.7)	4731 (47.4)	2115 (49.2)	<.001
Medicare	55 672 (11.3)	3374 (33.8)	1409 (32.8)	
Medicaid	35 733 (7.2)	417 (4.2)	289 (6.7)	
Uninsured or unknown	127 218 (25.8)	1469 (14.7)	483 (11.2)	
Region				
Midwest	264 363 (53.6)	5801 (58.1)	2349 (54.7)	<.001
Northeast	104 328 (21.2)	2478 (24.8)	1327 (30.9)	
South	80 146 (16.3)	1221 (12.2)	315 (7.3)	
West	22 697 (4.6)	290 (2.9)	200 (4.7)	
Other or unknown[c]	21 486 (4.4)	201 (2.0)	105 (2.4)	

Abbreviations: BMI, body m
(calculated as weight in kilo
divided by height in meters
SNF, skilled nursing facility.

[a] Race and ethnicity were
self-reported in the Optun
and other category includ
other, or unknown. Furthe
other category was unava

[b] Score range: 0 to ≥2, with
highest score indicating a
number of comorbidities.

[c] Other category was not de
the Optum EHR.

Table 2. Logistic Regression Models of Adverse Outcomes Among Patients Diagnosed With COVID-19[a]

	30-d Mortality		30-d Mechanical ventilation		30-d ICU stay		30-d Hospitalization	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Patient group								
Without cancer	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
With no recent treatment	0.93 (0.84-1.02)	.12	0.61 (0.54-0.68)	<.001	0.98 (0.91-1.06)	.61	0.79 (0.75-0.83)	<.001
With recent treatment	1.74 (1.54-1.96)	<.001	1.00 (0.88-1.13)	.94	1.69 (1.54-1.87)	<.001	1.19 (1.11-1.27)	<.001
Age, y								
18-39	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
40-49	2.83 (2.37-3.39)	<.001	2.22 (2.02-2.45)	<.001	1.71 (1.60-1.82)	<.001	1.11 (1.07-1.14)	<.001
50-54	4.59 (3.83-5.49)	<.001	3.19 (2.89-3.53)	<.001	2.1 (1.95-2.25)	<.001	1.39 (1.34-1.44)	<.001
55-59	6.10 (5.15-7.23)	<.001	4.20 (3.82-4.61)	<.001	2.62 (2.45-2.81)	<.001	1.71 (1.66-1.77)	<.001
60-64	9.86 (8.40-11.57)	<.001	5.30 (4.84-5.81)	<.001	2.89 (2.70-3.08)	<.001	2.03 (1.97-2.10)	<.001
65-69	15.90 (13.58-18.61)	<.001	6.80 (6.19-7.46)	<.001	3.48 (3.25-3.73)	<.001	2.67 (2.58-2.76)	<.001
70-74	22.52 (19.23-26.37)	<.001	7.44 (6.75-8.20)	<.001	4.15 (3.86-4.47)	<.001	3.28 (3.16-3.41)	<.001
75-79	33.88 (28.92-39.69)	<.001	8.31 (7.50-9.21)	<.001	4.65 (4.30-5.02)	<.001	4.11 (3.94-4.28)	<.001
80-84	52.07 (44.43-61.02)	<.001	7.09 (6.34-7.94)	<.001	5.31 (4.89-5.76)	<.001	5.10 (4.87-5.34)	<.001
≥85	94.65 (81.10-110.48)	<.001	4.84 (4.31-5.44)	<.001	6.69 (6.19-7.22)	<.001	6.50 (6.22-6.78)	<.001
Sex								
Female	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Male	1.70 (1.62-1.78)	<.001	1.98 (1.90-2.06)	<.001	1.51 (1.46-1.56)	<.001	1.25 (1.23-1.28)	<.001
Race and ethnicity[b]								
Hispanic	1.20 (1.10-1.31)	<.001	1.78 (1.67-1.9)	<.001	1.56 (1.48-1.64)	<.001	1.92 (1.87-1.97)	<.001
Non-Hispanic								
Black	0.98 (0.92-1.05)	.56	1.33 (1.27-1.4)	<.001	1.39 (1.33-1.45)	<.001	1.66 (1.62-1.70)	<.001
White	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Other	1.36 (1.27-1.47)	<.001	1.81 (1.70-1.92)	<.001	1.12 (1.06-1.18)	<.001	1.29 (1.26-1.33)	<.001
Severe obesity: BMI ≥40								
No	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Yes	1.61 (1.50-1.73)	<.001	1.82 (1.72-1.92)	<.001	1.41 (1.35-1.48)	<.001	1.64 (1.60-1.68)	<.001
Charlson-Deyo Comorbidity Index score[c]								
0	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
1	1.91 (1.78-2.05)	<.001	2.30 (2.17-2.44)	<.001	2.39 (2.28-2.49)	<.001	1.97 (1.92-2.01)	<.001
≥2	3.49 (3.29-3.70)	<.001	4.83 (4.59-5.09)	<.001	3.86 (3.70-4.02)	<.001	3.22 (3.15-3.29)	<.001
Region								
Midwest	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Northeast	1.21 (1.14-1.28)	<.001	0.98 (0.93-1.02)	.32	0.56 (0.54-0.59)	<.001	1.48 (1.44-1.51)	<.001
South	1.86 (1.75-1.96)	<.001	1.03 (0.97-1.09)	.39	0.85 (0.81-0.89)	<.001	1.55 (1.51-1.59)	<.001
West	1.50 (1.34-1.67)	<.001	1.26 (1.15-1.38)	<.001	2.77 (2.62-2.93)	<.001	1.38 (1.33-1.44)	<.001
Other[d]	1.25 (1.10-1.42)	<.001	1.01 (0.91-1.12)	.92	1.03 (0.95-1.12)	.46	1.10 (1.05-1.15)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ICU, intensive care unit; OR, odds ratio.

[a] Variables in the model also included COVID-19 2020 diagnosis period, skilled nursing facility stay within 3 months before COVID-19 diagnosis, and insurance type.

[b] Race and ethnicity were self-reported in the Optum EHR, and other category included Asian, other, or unknown. Further detail on other category was unavailable.

[c] Score range: 0 to ≥2, with the highest score indicating a higher number of comorbidities.

[d] Other category was not defined in the Optum EHR.

Review

FREE

September 2, 2021

COVID-19 and Cancer

A Review of the Registry-Based Pandemic Response

Aakash Desai, MD, MPH[1,2]; Turab J. Mohammed, MD[3]; Narjust Duma, MD[4]; Marina C. Garassino, MBBS[5]; Lisa K. Hicks, MD, MSc[6]; Nicole M. Kuderer, MD[7]; Gary H. Lyman, MD, MPH[8,9,10]; Sanjay Mishra, MS, PhD[11]; David J. Pinato, MD, MCRP, MRes, PhD[12,13]; Brian I. Rini, MD[11]; Solange Peters, MD, PhD[14]; Jeremy L. Warner, MD, MS[11]; Jennifer G. Whisenant, PhD[11]; William A. Wood, MD, MPH[15]; Michael A. Thompson, MD, PhD[16]

» Author Affiliations | Article Information

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COVID-19 Resource Center

Abstract

Importance The COVID-19 pandemic has had consequences for patients with cancer worldwide and has been associated with delays in diagnosis, interruption of treatment and follow-up care, and increases in overall infection rates and premature mortality.

Observations Despite the challenges experienced during the pandemic, the global oncology community has responded with an unprecedented level of investigation, collaboration, and technological innovation through the rapid development of COVID-19 registries that have allowed an increased understanding of the natural history, risk factors, and outcomes of patients with cancer who are diagnosed with COVID-19. This review describes 14 major registries comprising more than 28 500 patients with cancer and COVID-19; these ongoing registry efforts have provided an improved understanding of the impact and outcomes of COVID-19 among patients with cancer.

Conclusions and Relevance An initiative is needed to promote active collaboration between different registries to improve the quality and consistency of information. Well-designed prospective and randomized clinical trials are needed to collect high-level evidence to guide long-term epidemiologic, behavioral, and clinical decision-making for this and future pandemics.

Introduction

Despite increasing vaccine availability, the COVID-19 pandemic continues to pose a substantial threat worldwide. Patients with cancer are a distinctly vulnerable population[1]; they are often immunocompromised and are at an increased risk of experiencing COVID-19–associated complications.[2-6] Potential treatments for COVID-19 have been intensively studied. For example, the performance of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) clinical trial[7] in the United Kingdom (UK) and the pace of vaccine development and deployment have been impressive. Despite these successes, patients with cancer have largely been excluded from these studies. The RECOVERY study and 4 other prospective clinical trials[8-12] of corticosteroid therapy either did not include cancer as a comorbidity or were not adequately powered to determine efficacy or safety in the subset of patients with cancer. Most of the clinical trials of COVID-19 vaccines did not include patients who were actively receiving anticancer treatment or had a recent history of cancer.[13,14] Thus, well-designed registries and retrospective cohort studies remain important tools for increasing our collective understanding of the natural history and outcomes of COVID-19 among patients with cancer.[15]

Despite the many challenges that the pandemic has created, the global biomedical community has responded with an unprecedented level of investigation, collaboration,

Thoracic Cancers International COVID-19 Collaboration (TERAVOLT)

“The TERAVOLT36 is one of the first global registries aimed at understanding COVID-19 among patients with thoracic cancers, including small cell lung cancer, non–small cell lung cancer, mesothelioma, carcinoid or neuroendocrine tumors of thoracic origin, and thymic epithelial tumors. Garassino et al presented initial data from the TERAVOLT registry at the 2020 annual meeting of the American Association for Cancer Research; these data were collected from 200 patients who were primarily from European centers. Of those, 151 patients (76%) had non–small cell lung cancer, 148 patients (74%) were receiving active treatment for cancer, 152 patients (76%) required hospitalization, and 66 patients (33%) with thoracic cancer died. Previous or current smoking, older age (>65 years), treatment with chemotherapy alone, and the presence of comorbidities were independent factors significantly associated with an increased risk of death.36 Updated data from 400 patients were subsequently reported at the 2020 annual meeting of the American Society of Clinical Oncology (ASCO), revealing a 35.5% mortality rate.37 In addition, in September 2020, results from a study including a global population of 1012 patients38 were presented at the 2020 virtual conference of the European Society for Medical Oncology, confirming a mortality rate of 32% among 326 patients with thoracic cancer and COVID-19. An ECOG performance status of 2 or higher, older age (>65 years), smoking history, stage IV disease, receipt of more than 10 mg of steroid medication per day, treatment with chemotherapy alone, and no treatment were all found to be significantly associated with worse outcomes.38 It is notable that no specific information was available regarding the reasons for steroid use (ie, whether steroid medications were initiated for the treatment of certain comorbid conditions, such as chronic obstructive pulmonary disease or autoimmune disorders, or to reduce the severity of illness). Therefore, given the unmeasured and potential unknown sociodemographic confounders, randomized clinical trials remain the criterion standard to provide definitive answers regarding the efficacy of COVID-19 therapies, such as corticosteroid medications.”

Immunogenicity of the BNT162b2 COVID-19 mRNA vaccine and early clinical outcomes in patients with haematological malignancies in Lithuania: a national prospective cohort study

Kazimieras Maneikis, Karolis Šablauskas*, Ugnė Ringelevičiūtė, Vilmantė Vaitekėnaitė, Rita Čekauskienė, Lina Kryžauskaitė, Daniel Naumovas, Valdas Banys, Valdas Pečeliūnas, Tumas Beinortas†, Laimonas Griškevičius†*

Summary

Background Haematological malignancies and their treatments are likely to affect SARS-CoV-2 vaccine efficacy. We aimed to evaluate serological response to BNT162b2 vaccine in patients with haematological malignancies by type of treatment.

Methods Our national prospective cohort study was done in Lithuania and assessed serological response to one and two BNT162b2 (Comirnaty, Pfizer-BioNTech) vaccine doses in healthy health-care workers and in patients with haematological malignancies. Eligible participants were aged 18 years or older, had received both vaccine doses, and had available biobanked blood samples from before vaccination and after the second dose. Biobanked samples and health data were obtained from Vilnius University Hospital Santaros Klinikos Biobank. Abbott Architect SARS-CoV-2 IgG Quant II chemiluminescent microparticle assay was used to quantify serum anti-SARS-CoV-2-S1 IgG antibody (anti-S1 IgG antibody) concentrations 0–10 days before the first BNT162b2 vaccine, on the day of second immunisation (around day 21), and 7 to 21 days after the second immunisation. Adverse events were assessed by a standardised questionnaire. Breakthrough infections were characterised clinically and by SARS-CoV-2 genotyping whenever possible. This study is registered with ClinicalTrials.gov, NCT04871165.

Findings Between Jan 8 and April 21, 2021, 885 participants with haematological malignancies were included in the study. 857 patients were anti-S1 IgG seronegative at timepoint 0 and constituted the main analysis cohort. The age-matched comparison was made between 315 patients with haematological malignancies who were aged 18–60 years and 67 healthy health-care workers in the same age group. Patients aged 18–60 years with haematological malignancies had lower median anti-S1 IgG antibody responses after two BNT162b2 vaccine doses than did health-care workers of the same age group (median 6961 AU/mL [IQR 1292–20 672] *vs* 21 395 AU/mL [14 831–33 553]; p<0·0001). Compared with untreated patients with haematological malignancies (n=53; median 5761 AU/mL [629–16 141]), patients actively treated with Bruton tyrosine kinase inhibitors (BTKIs; n=44; 0 AU/mL [0–7]; p<0·0001), ruxolitinib (n=16; 10 AU/mL [0–45]; p<0·0001), venetoclax (n=10; 4 AU/mL [0–1218]; p=0·0005), or anti-CD20 antibody therapy (n=87; 17 AU/mL [1–2319]; p<0·0001) showed particularly poor anti-S1 IgG antibody responses following two BNT162b2 doses. Patients being treated with tyrosine kinase inhibitors (n=41; 10 537 AU/mL [IQR 2335–19 388]) or patients who received autologous haematopoietic stem-cell transplantation (HSCT; n=192; 6203 AU/mL [1451–16 834]) or allogeneic HSCT (n=122; 6304 AU/mL [1120–16 913]) were among the subgroups with the highest numerical responses. Nine SARS-CoV-2 infections and three COVID-19 deaths were observed among fully vaccinated patients with haematological malignancies.

Interpretation Patients with haematological malignancies mount blunted and heterogeneous antibody responses to the full course of BNT162b2 mRNA vaccination. Patients who are actively treated with BTKIs, ruxolitinib, venetoclax, or anti-CD20 antibody therapies seem to be the most negatively affected and might be left unprotected from SARS-CoV-2 infection. Breakthrough severe SARS-CoV-2 infections in fully vaccinated patients with haematological malignancies emphasise the importance of ongoing strict adherence to non-pharmacological interventions and household vaccination while SARS-CoV-2 is circulating in the community.

Funding Vilnius University Hospital Santaros Klinikos.

Lancet Haematol 2021; 8: e583–92

Published Online July 2, 2021 https://doi.org/10.1016/S2352-3026(21)00169-1

See **Comment** page e540

For the Lithuanian translation of the abstract see **Online** for appendix 1

*Contributed equally to the work

†Contributed equally to the work

Hematology, Oncology and Transfusion Medicine Center, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania (K Maneikis MD, K Šablauskas MD, U Ringelevičiūtė MD, V Vaitekėnaitė MD, R Čekauskienė MD, L Kryžauskaitė MD, D Naumovas MS, V Banys MD, V Pečeliūnas MD, Prof L Griškevičius MD); **Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania** (K Maneikis, K Šablauskas, U Ringelevičiūtė, V Vaitekėnaitė, V Pečeliūnas, Prof L Griškevičius); **Department of Haematology, Cambridge University Hospitals NHS trust, Cambridge, UK** (T Beinortas MBBCh); **Wellcome—MRC Cambridge Stem Cell Institute, Cambridge, UK** (T Beinortas)

Correspondence to: Dr Kazimieras Maneikis, Vilnius University Hospital Santaros Klinikos, Vilnius LT-08661, Lithuania **kazimieras.maneikis@santa.lt**

Introduction

Patients with haematological malignancies have a very high COVID-19 case fatality rate, reaching as high as 48% in some cohorts.[1–3] Therefore, protecting this group of people from COVID-19 is of particular importance. In clinical trials, vaccines against SARS-CoV-2 have been shown to induce efficient antibody and T-cell responses and to protect from symptomatic COVID-19 disease.[4,5] Immunological response to these vaccines might be reduced by the immunosuppressive nature of haematological malignancies themselves and their treatments. However, patients with active or recently treated

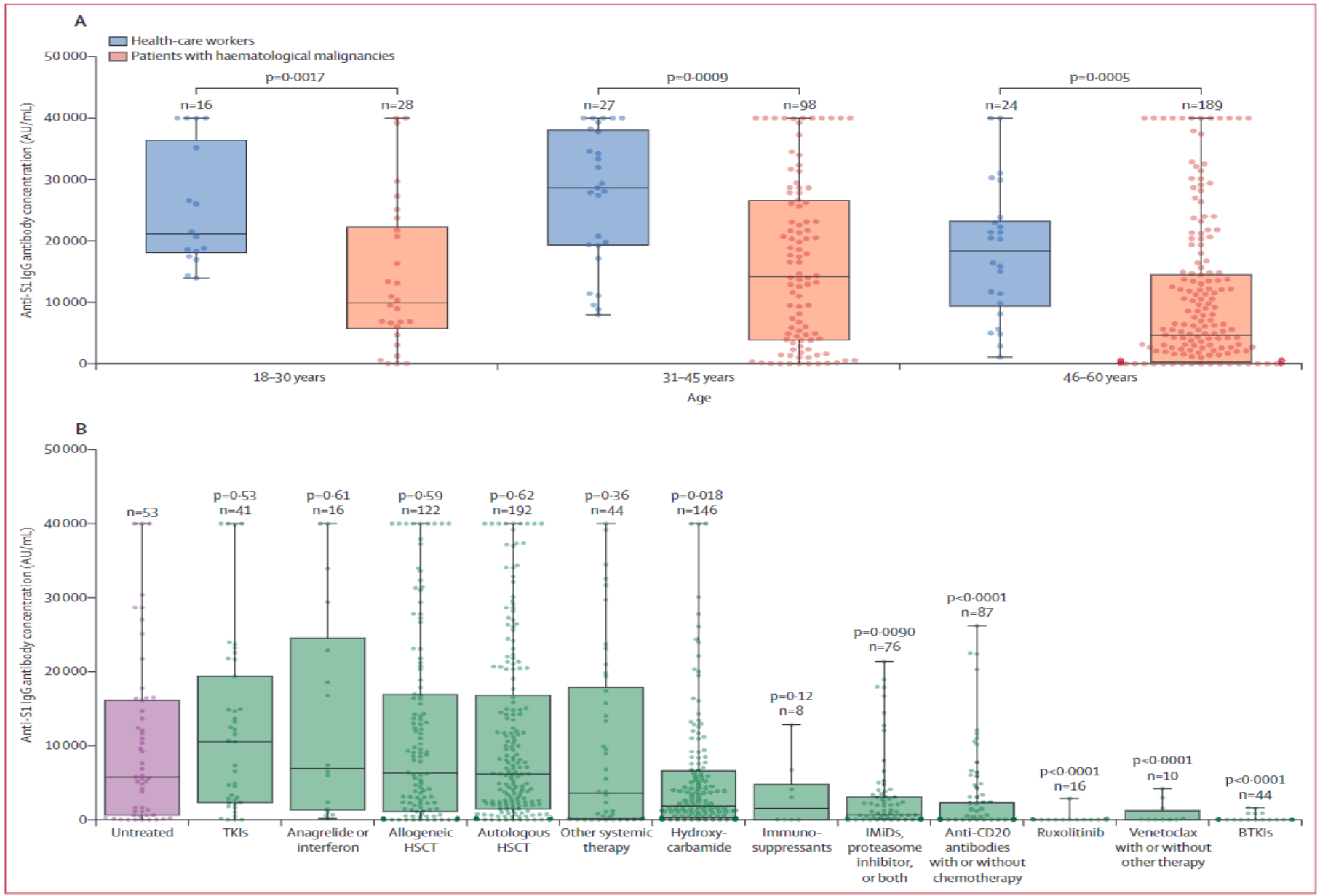


Figure 2: **Serological response to two doses of BNT162b2 mRNA vaccine**

The boxes show IQR, centre line shows the median, and whiskers show maximum and minimum values; the dots show individual participants. (A) Serological response to two doses of BNT162b2 in healthy individuals and in individuals with haematological malignancies grouped by age. (B) Serological response to two doses of BNT162b2 in treated patients compared with untreated patients with haematological malignancies; p values are for the comparison between the median anti-S1 IgG antibody concentration of each treatment group and the untreated group; the treatment regimens of each group are shown in the table. BTKIs=Bruton tyrosine kinase inhibitors. HSCT=haematopoietic stem-cell transplantation. IMiDs=immunomodulatory imide drugs. TKIs=tyrosine kinase inhibitors.

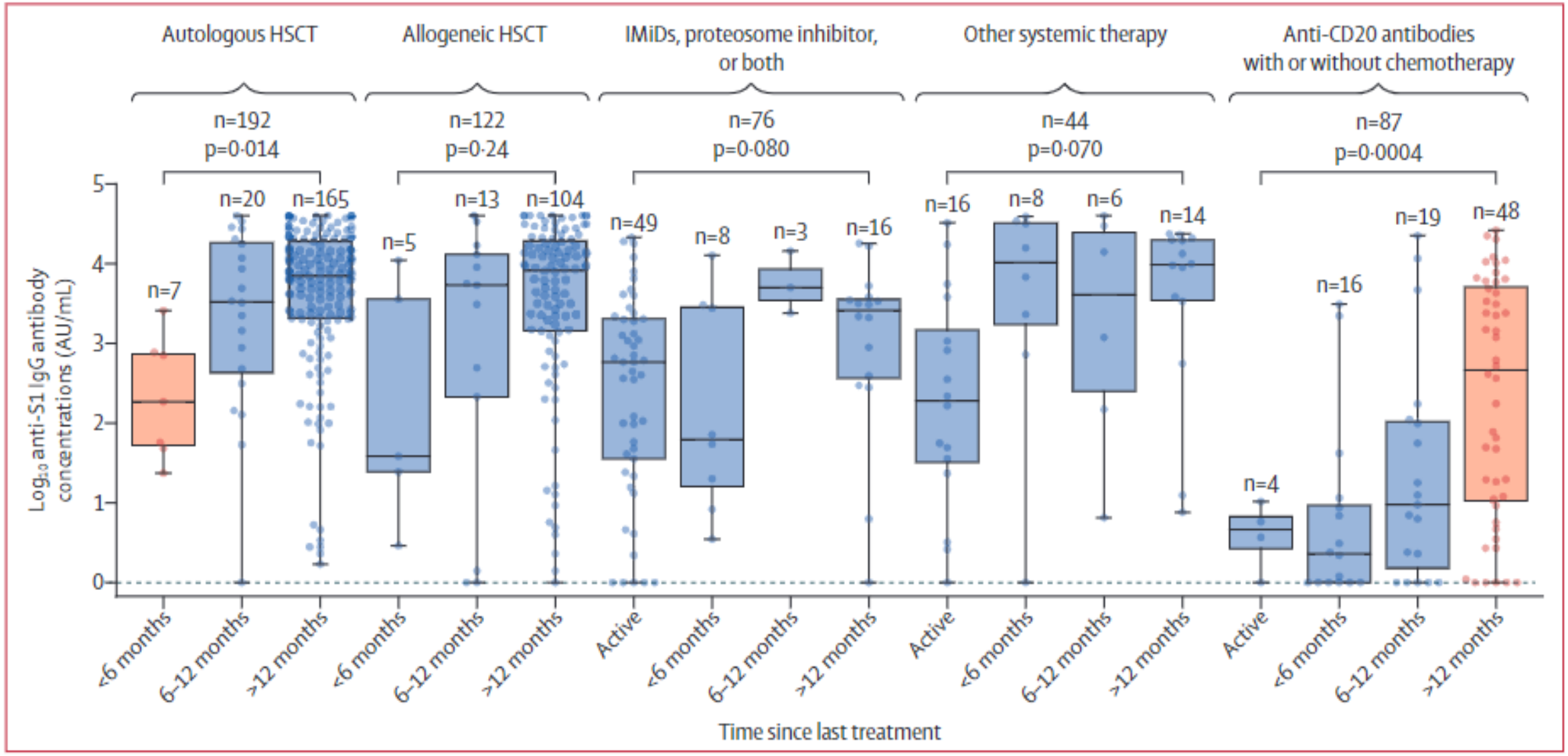


Figure 3: **Serological response after the second dose of vaccine stratified by time since treatment**

The boxes show IQR, centre line shows the median, and whiskers show maximum and minimum values; the dots show individual participants; and p values are for the comparisons of anti-S1 IgG antibody median values within each treatment group. The subgroup differing significantly from others within the treatment group is shown in orange. The treatment regimens of each group are shown in the table. HSCT=haematopoietic stem-cell transplantation. IMiDs=immunomodulatory imide drugs.

Moderna vaccine (mRNA-1273)

- mRNA vaccine at a dose of 100 mcg for primary series
    - Immunocompromised can get an additional dose of 100 mcg at least 4 weeks after primary series
    - Booster doses are at 50 mcg for all eligible patients
- Two doses- 4 weeks apart (28 days)
- 94.5% effective
- Authorized for 18+
- FDA fact sheet: https://www.fda.gov/media/144638/download

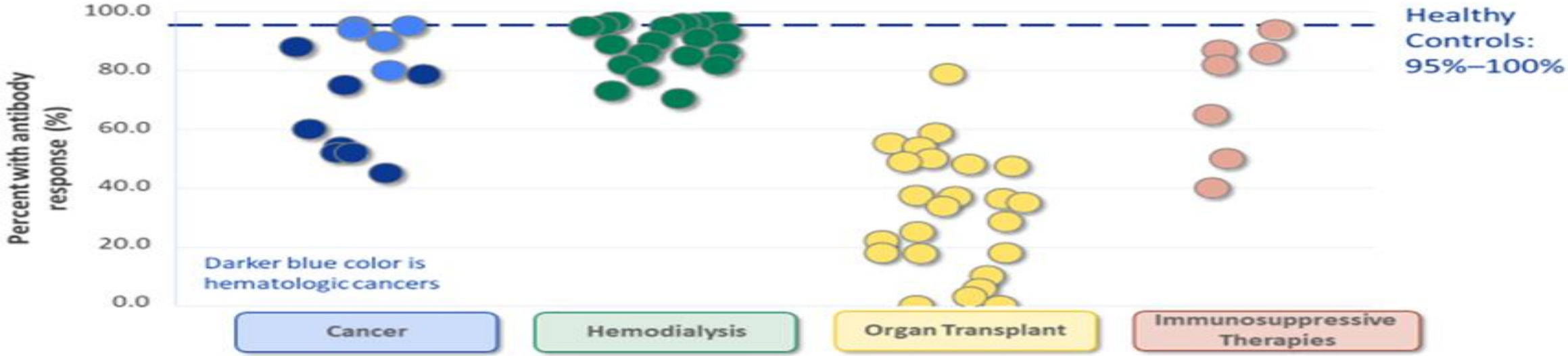
BioNTech/Pfizer (NT1622)

- mRNA vaccine
- Two doses -3 weeks apart (21 days)
- 95% effective
- Authorized for 12+ at a dose of 30 mcg
    - Booster doses at same dose
- Authorized for 5-11 at a dose of 10 mcg
- Extreme cold storage and shipping requirements have been changed.
- FDA fact sheet: https://www/fda.gov/media/144414/download

Johnson & Johnson/Janssen COVID Vaccine

- Non-replicating viral vector vaccine
- One dose
- In U.S. 72% effective in preventing moderate to severe/critical COVID-19 occurring 28 days after vaccination
- Stored at normal medication refrigerated temperatures 36°- 46 °F.
- FDA fact sheet: https://www.fda.gov/media/146305/download
- Janssen COVID Vaccine FAQ https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/janssen-covid-19-vaccine-frequently-asked-questions

Percent of subjects with antibody response after two mRNA vaccine doses by immunocompromising condition and study (n=63)



Comparing evidence 3rd mRNA COVID-19 vaccine dose in immunosuppressed people with seropositive response

Study	Patient Population	2nd Dose			3rd Dose Seronegative after 2nd dose		
		Sample Size	Seronegative N (%)	Seropositive N (%)	Sample Size	Seronegative N (%)	Seropositive N (%)
Kamar et al.	Recipients of solid-organ transplant	99	59 (60)	40 (40)	59	33 (56)	**26 (44)**
Werbel et al.	Recipients of solid-organ transplant	30	24 (80)	6 (20)	24	16 (67)	**8 (33)**
Longlune et al.	Patients on hemodialysis	82	13 (16)	69 (84)	12	7 (58)	**5 (42)**
Maxime et al.	Patients on hemodialysis	106	66 (62)	40 (38)	12	6 (50)	**6 (50)**

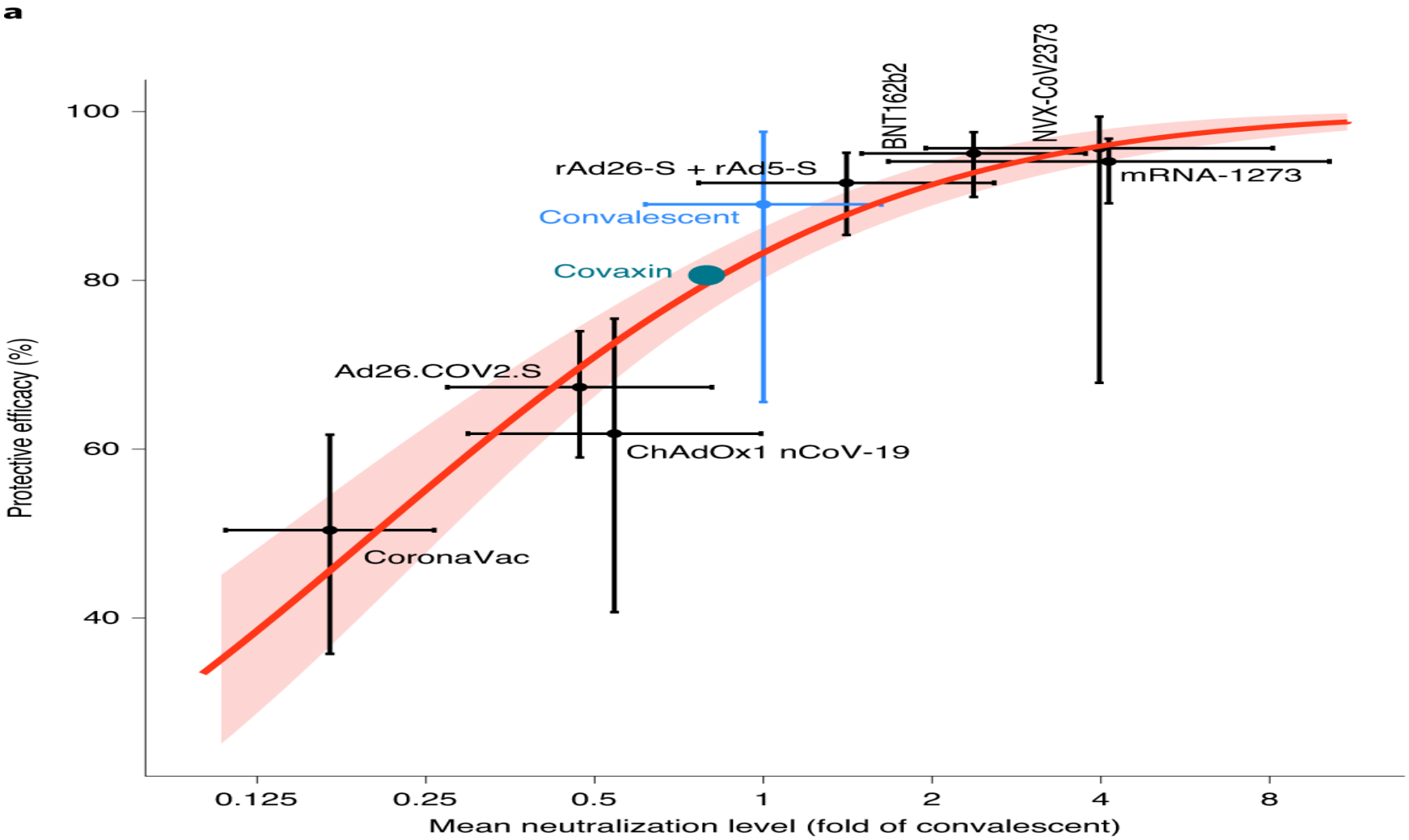
- Among those who had **no detectable antibody** response to an initial mRNA vaccine series, **33-50% developed an antibody response to an additional dose**

What are the levels of antibodies in sera that are protective?

Khory et al

Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection

Nature Medicine **volume 27**, pages1205–1211 (2021)



Editor's Note: This article was published on December 8, 2021, at NEJM.org.

ORIGINAL ARTICLE

BNT162b2 Vaccine Booster and Mortality Due to Covid-19

Ronen Arbel, Ph.D., Ariel Hammerman, Ph.D., Ruslan Sergienko, M.A., Michael Friger, Ph.D., Alon Peretz, M.D., Doron Netzer, M.D., and Shlomit Yaron, M.D.

December 23, 2021
N Engl J Med 2021; 385:2413-2420
DOI: 10.1056/NEJMoa2115624

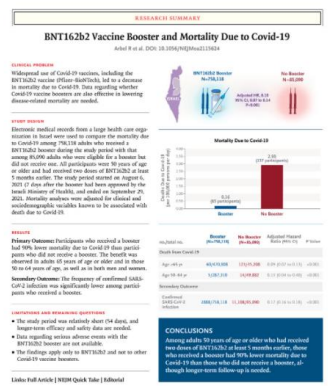
Abstract

BACKGROUND

The emergence of the B.1.617.2 (delta) variant of severe acute respiratory syndrome coronavirus 2 and the reduced effectiveness over time of the BNT162b2 vaccine (Pfizer–BioNTech) led to a resurgence of coronavirus disease 2019 (Covid-19) cases in populations that had been vaccinated early. On July 30, 2021, the Israeli Ministry of Health approved the use of a third dose of BNT162b2 (booster) to cope with this resurgence. Evidence regarding the effectiveness of the booster in lowering mortality due to Covid-19 is still needed.

METHODS

We obtained data for all members of Clalit Health Services who were 50 years of age or older at the start of the study and had received two doses of BNT162b2 at least 5 months earlier. The mortality due to Covid-19 among participants who received the booster during the study period (booster group) was compared with that among participants who did not receive the booster (nonbooster group). A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association of booster status with death due to Covid-19, with adjustment for sociodemographic factors and coexisting conditions.


RESEARCH SUMMARY

BNT162b2 Vaccine Booster and Mortality Due to Covid-19

RESULTS

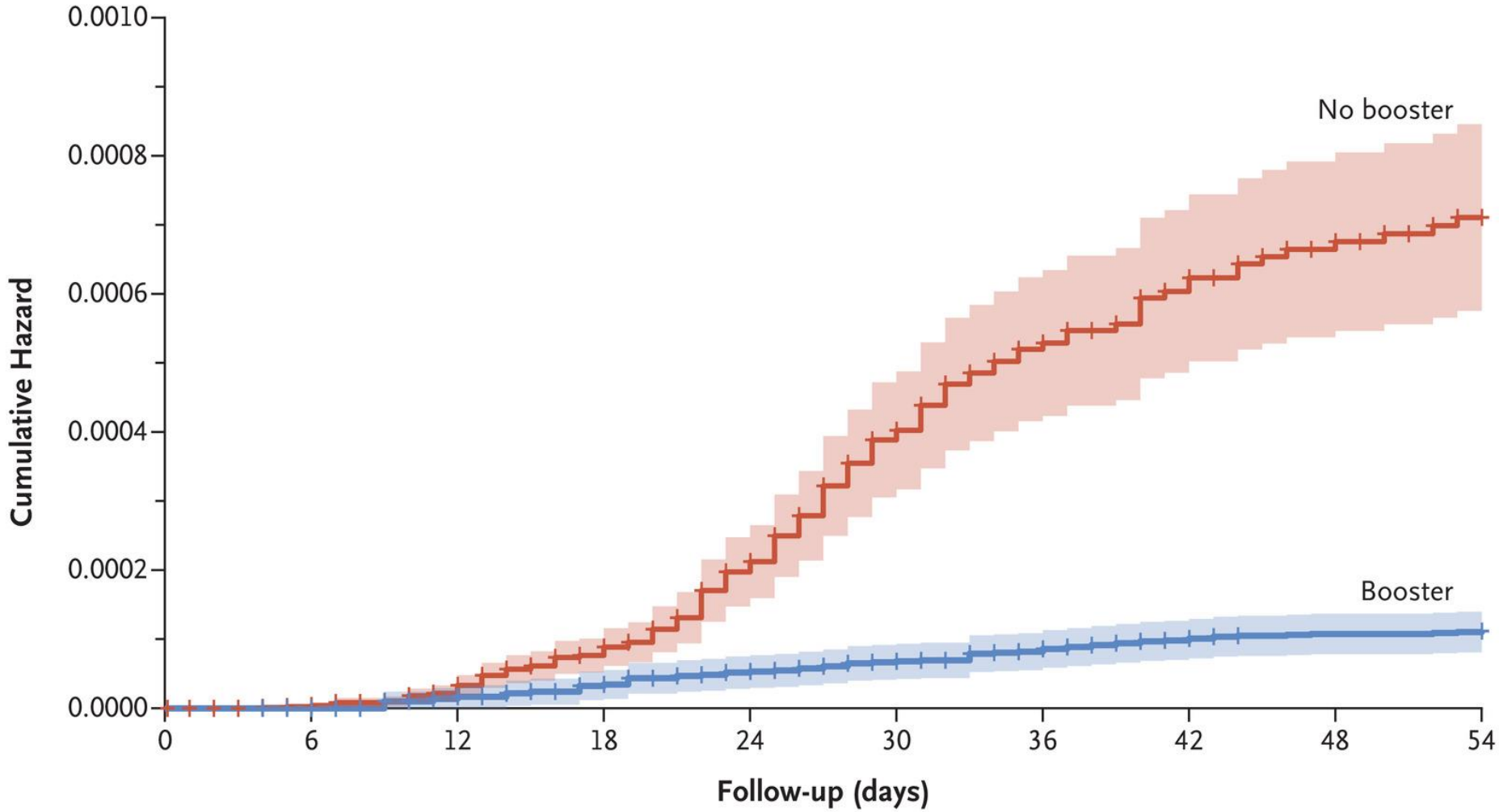
A total of 843,208 participants met the eligibility criteria,

Related Articles

EDITORIAL DEC 23, 2021
Booster Doses and Prioritizing Lives Saved
M.K. Patel

ORIGINAL ARTICLE DEC 23, 2021
Protection against Covid-19 by BNT162b2 Booster across Age Groups
Y.M. Bar-On and Others

CORRESPONDENCE FEB 9, 2022
BNT162b2 Vaccine Booster and Covid-19 Mortality



No. at Risk										
No booster	841,428	723,609	520,459	326,741	202,797	145,021	111,761	101,695	90,036	83,989
Booster	46,259	119,332	322,203	515,639	639,315	696,859	729,971	739,945	756,591	757,614
Cumulative No. of Events										
No booster	0	3	20	43	72	103	119	129	134	137
Booster	0	0	4	12	23	33	46	57	62	65

Table 2. Association of Confounding Variables with Death Due to Covid-19.*

Variable	Hazard Ratio for Death Due to Covid-19 (95% CI)	P Value
Booster received	0.10 (0.07–0.14)	<0.001
Age	1.10 (1.09–1.12)	<0.001
Male sex	2.49 (1.82–3.41)	<0.001
Socioeconomic status	0.98 (0.92–1.04)	0.45
Diabetes	1.29 (0.96–1.72)	0.09
Chronic obstructive pulmonary disease	1.31 (0.86–1.99)	0.22
Chronic kidney failure	2.27 (1.63–3.15)	<0.001
Ischemic heart disease	0.96 (0.69–1.32)	0.79
Chronic heart failure	1.41 (0.95–2.09)	0.09
Obesity	1.17 (0.87–1.58)	0.30
Lung cancer	3.20 (1.49–6.87)	0.003
History of cerebrovascular accident	1.54 (1.08–2.17)	0.02
History of transient ischemic attack	0.87 (0.50–1.51)	0.63
History of smoking	1.10 (0.82–1.49)	0.52

* Age was a continuous variable, and socioeconomic status was an ordinal variable; all other variables were dichotomous (present vs. absent). Covid-19 denotes coronavirus disease 2019.

ORIGINAL ARTICLE

Homologous and Heterologous Covid-19 Booster Vaccinations

Robert L. Atmar, M.D., Kirsten E. Lyke, M.D., Meagan E. Deming, M.D., Ph.D., Lisa A. Jackson, M.D., M.P.H., Angela R. Branche, M.D., Hana M. El Sahly, M.D., Christina A. Rostad, M.D., Judith M. Martin, M.D., Christine Johnston, M.D., M.P.H., Richard E. Rupp, M.D., Mark J. Mulligan, M.D., Rebecca C. Brady, M.D., et al., for the DMID 21-0012 Study Group*

January 26, 2022
DOI: 10.1056/NEJMoa2116414

Abstract

BACKGROUND

Although the three vaccines against coronavirus disease 2019 (Covid-19) that have received emergency use authorization in the United States are highly effective, breakthrough infections are occurring. Data are needed on the serial use of homologous boosters (same as the primary vaccine) and heterologous boosters (different from the primary vaccine) in fully vaccinated recipients.

METHODS

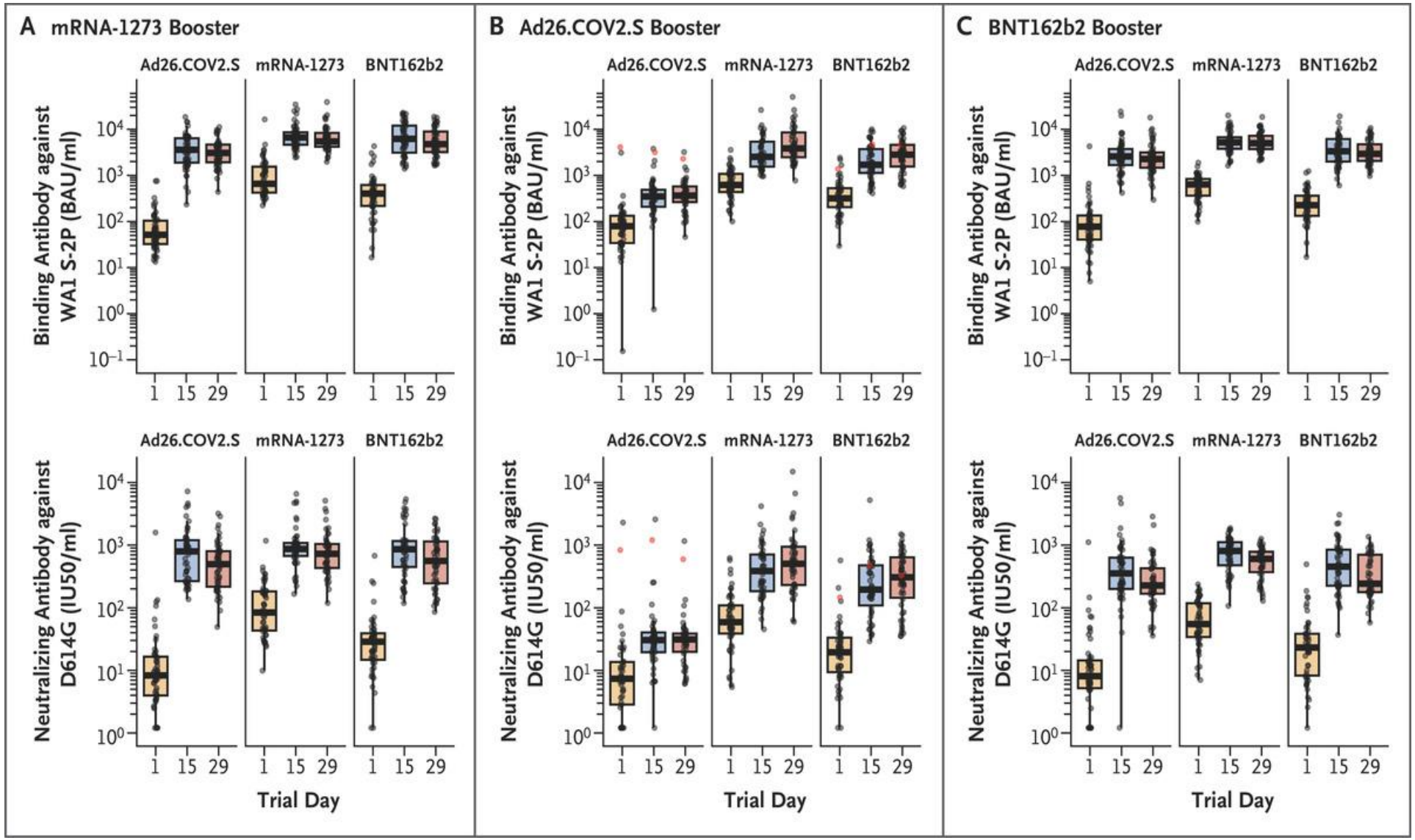
In this phase 1–2, open-label clinical trial conducted at 10 sites in the United States, adults who had completed a Covid-19 vaccine regimen at least 12 weeks earlier and had no reported history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection received a booster injection with one of three vaccines: mRNA-1273 (Moderna) at a dose of 100 μg, Ad26.COV2.S (Johnson & Johnson–Janssen) at a dose of 5×10^{10} virus particles, or BNT162b2 (Pfizer–BioNTech) at a dose of 30 μg. The primary end points were safety, reactogenicity, and humoral immunogenicity on trial days 15 and 29.

RESULTS

Of the 458 participants who were enrolled in the trial, 154 received mRNA-1273, 150 received Ad26.COV2.S, and 152 received BNT162b2 as booster vaccines; 1 participant did not receive the assigned

Related Articles

CORRESPONDENCE JAN 26, 2022
SARS-CoV-2 Omicron Variant Neutralization after mRNA-1273 Booster Vaccination
R. Pajon and Others

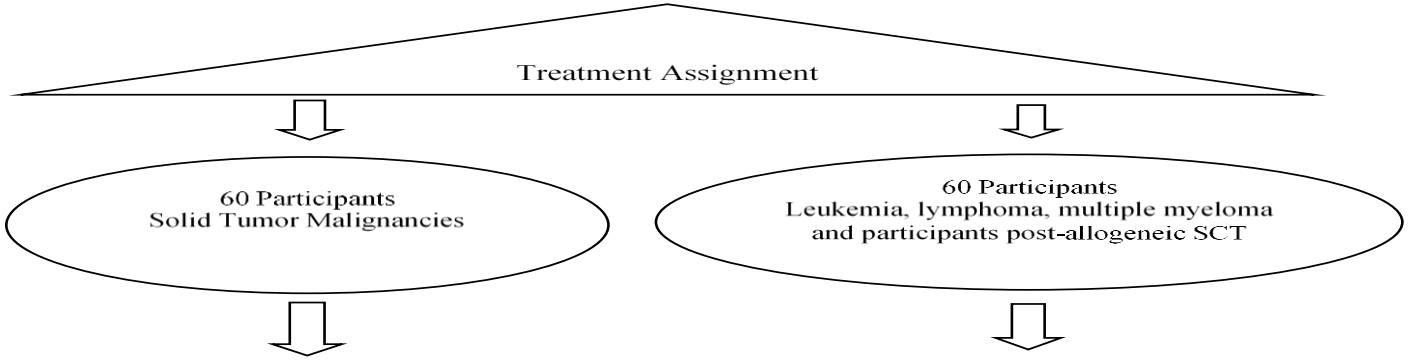

A mRNA-1273 Booster
B Ad26.COV2.S Booster
C BNT162b2 Booster
Ad26.COV2.S
mRNA-1273
BNT162b2
Binding Antibody against WA1 S-2P (BAU/ml)
Neutralizing Antibody against D614G (IU50/ml)
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
10^{4}
1 15 29
Trial Day

Protocol 000115-C from NCI

- Participants will get 2 doses of the mRNA-1273 vaccine if they have not been vaccinated already. It will be injected into a muscle in the arm on Days 1 and 29. They will be followed for 12 months after the second dose.
- Participants will have study visits at the Clinical Center on Days 1, 29, 36, 57, 209, and 394. Some visits will last about 4-6 hours.
- Patients will be able to get up to 2 doses of mRNA-1273 as a booster on trial if they have already completed a primary series of a vaccine. Participants who have already received a booster dose of vaccine will be able to enroll to receive an additional booster. It will be injected into a muscle in the arm on Day 1. Participants will be followed for 12 months after their last booster injection. Participants who receive booster doses will have study visits at the Clinical Center on Days 1, 29, 57, 180 and 360.
- Participants will give blood and saliva samples for research.
- Participation will last about 16 months.

Prior to Enrollment

Screening: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document eligibility criteria.



Day 1

Perform pregnancy test; collect blood for assays;

Administer Vaccine 100 µg (N=120)

Days 1-8

Clinical and AE assessment

Day 29

Screen participants by criteria; obtain interim history, document.
Perform pregnancy test; collect blood for assays;

Administer Vaccine 100 µg (N=120)

Days 29-36

Day 394, Final Study Visit Day

Assessment of Final Study Outcome Measures

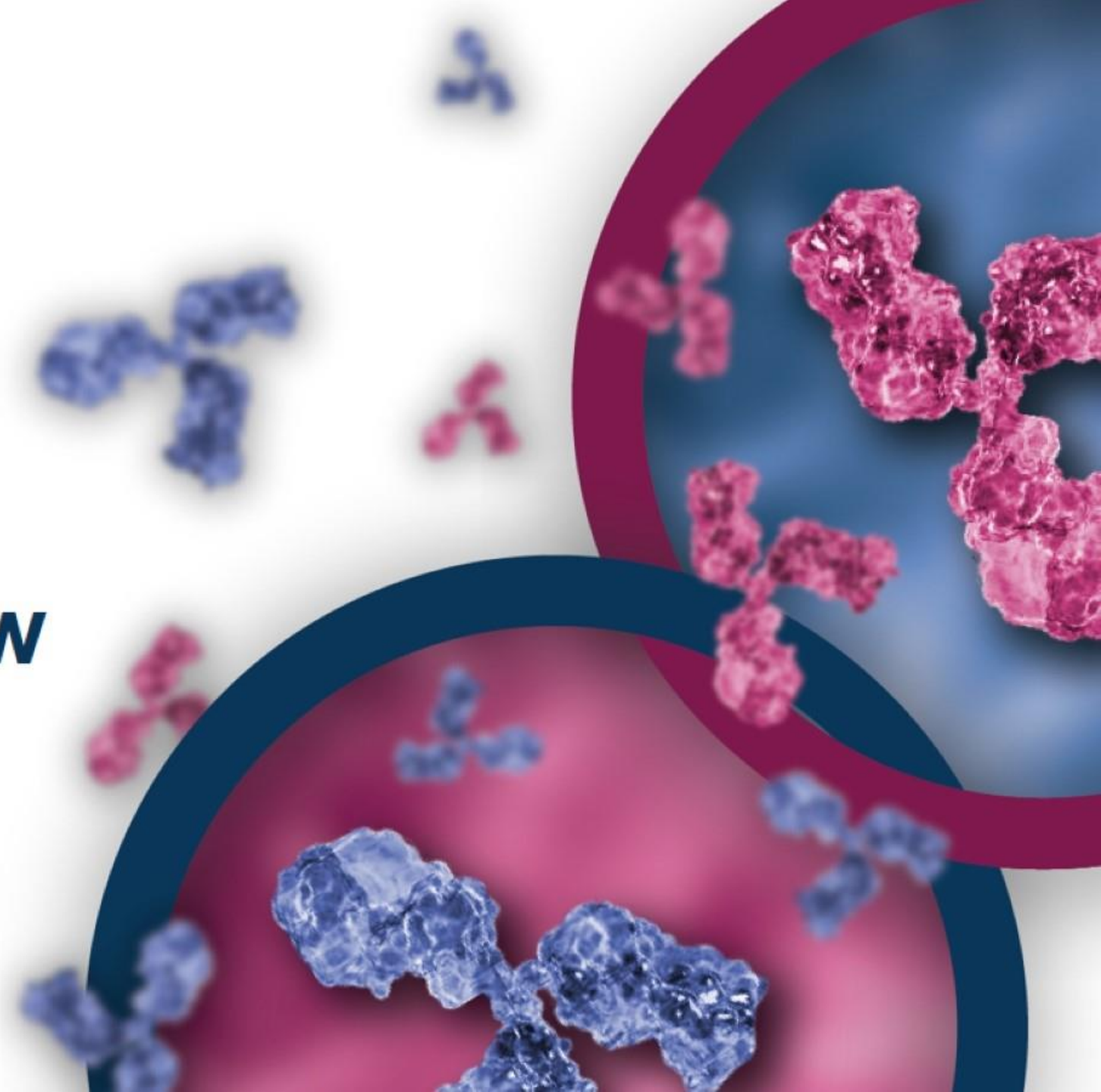
Cohorts

Cohort	Description	Arm	Sample Size	Intervention
1	Hematologic Low Immunosuppression	1	20	100 µg (0.5 mL) mRNA-1273 injection
2	Hematologic Intermediate Immunosuppression	1	20	100 µg (0.5 mL) mRNA-1273 injection
3	Hematologic High Immunosuppression	1	20	100 µg (0.5 mL) mRNA-1273 injection
4	Solid Tumor*	1	Up to 60	100 µg (0.5 mL) mRNA-1273 injection

*Solid tumor cohort is inclusive of all tumors for which PD1/PDL1 inhibitors are approved therapies, including Hodgkin Lymphoma or Primary Mediastinal B-Cell Lymphoma.

AstraZeneca

EVUSHELD™ (Tixagevimab Co-packaged with Cilgavimab) Product Overview



MARP ML-6003-US-0003 Approved 12/21

Emergency Use Authorization (EUA)

The US FDA has issued an EUA for the emergency use of the unapproved product EVUSHELD™ (tixagevimab co-packaged with cilgavimab) for the **pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):**

- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination **or**
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).
- EVUSHELD is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19.
- EVUSHELD is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of EVUSHELD under section 564(b)(1) of the Act, 21 U.S.C. §360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; US FDA = United States Food and Drug Administration

Fact sheet for healthcare providers. Emergency Use Authorization (EUA) of EVUSHELD™ (tixagevimab co-packaged with cilgavimab). 2021.

Emergency Use Authorization (continued)

Medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination include but are not limited to:

- Active treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)

Limitations of Authorized Use:

- EVUSHELD is **not** authorized for **treatment** of COVID-19 or **post-exposure prophylaxis**
- PrEP with EVUSHELD is not a substitute for vaccination in individuals where COVID-19 is vaccination is recommended
- In individuals who have received a COVID-19 vaccine, EVUSHELD should be administered ≥2 weeks after vaccination

COVID-19 = coronavirus disease 2019; PrEP = pre-exposure prophylaxis

Fact sheet for healthcare providers. Emergency Use Authorization (EUA) of EVUSHELD™ (tixagevimab co-packaged with cilgavimab). 2021.

Contraindications, Warnings and Precautions

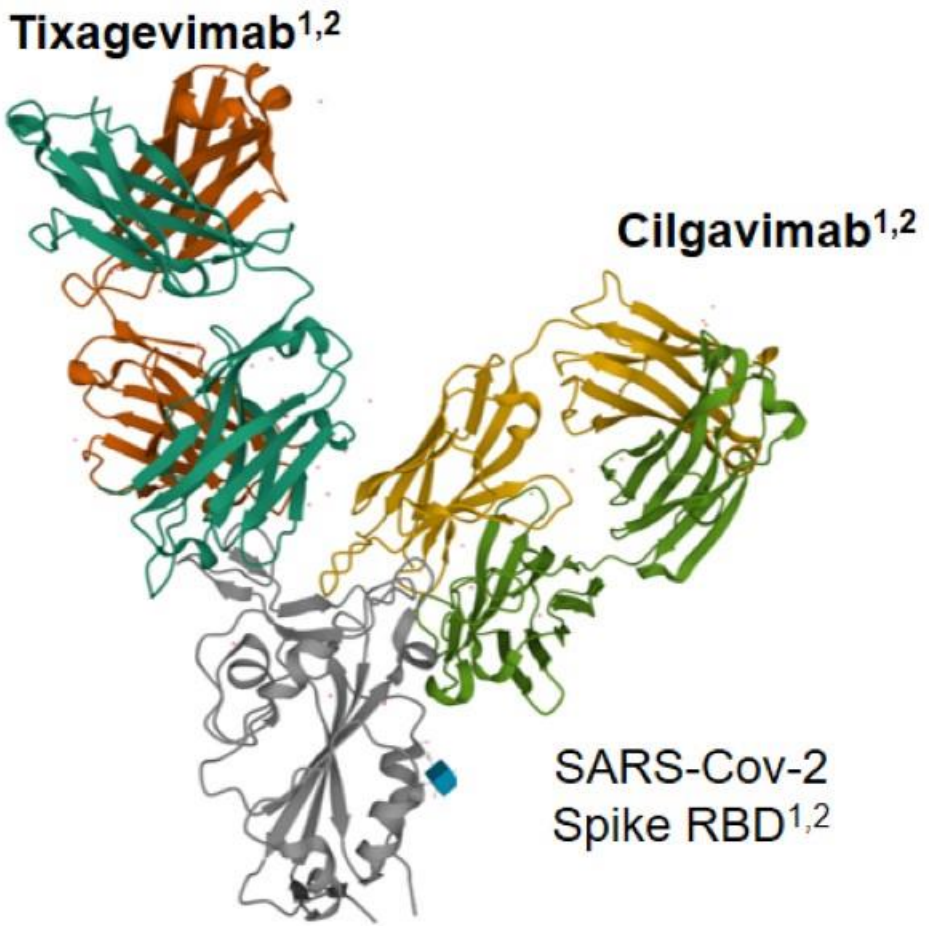
Contraindications

- EVUSHELD is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to any component of EVUSHELD.

Warning and Precautions

- There are limited clinical data available for EVUSHELD. Serious and unexpected adverse events may occur that have not been previously reported with EVUSHELD use.
- **Hypersensitivity Including Anaphylaxis:** Serious hypersensitivity reactions, including anaphylaxis, have been observed with IgG1 monoclonal antibodies like EVUSHELD. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy. Clinically monitor individuals after injections and observe for at least 1 hour.
- **Clinically Significant Bleeding Disorders:** As with any other intramuscular injection, EVUSHELD should be given with caution to individuals with thrombocytopenia or any coagulation disorder.
- **Cardiovascular Events:** A higher proportion of subjects who received EVUSHELD versus placebo reported myocardial infarction and cardiac failure serious adverse events. All of the subjects with events had cardiac risk factors and/or a prior history of cardiovascular disease, and there was no clear temporal pattern. A causal relationship between EVUSHELD and these events has not been established. Consider the risks and benefits prior to initiating EVUSHELD in individuals at high risk for cardiovascular events, and advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event.

Tixagevimab/Cilgavimab: LAAB Combination

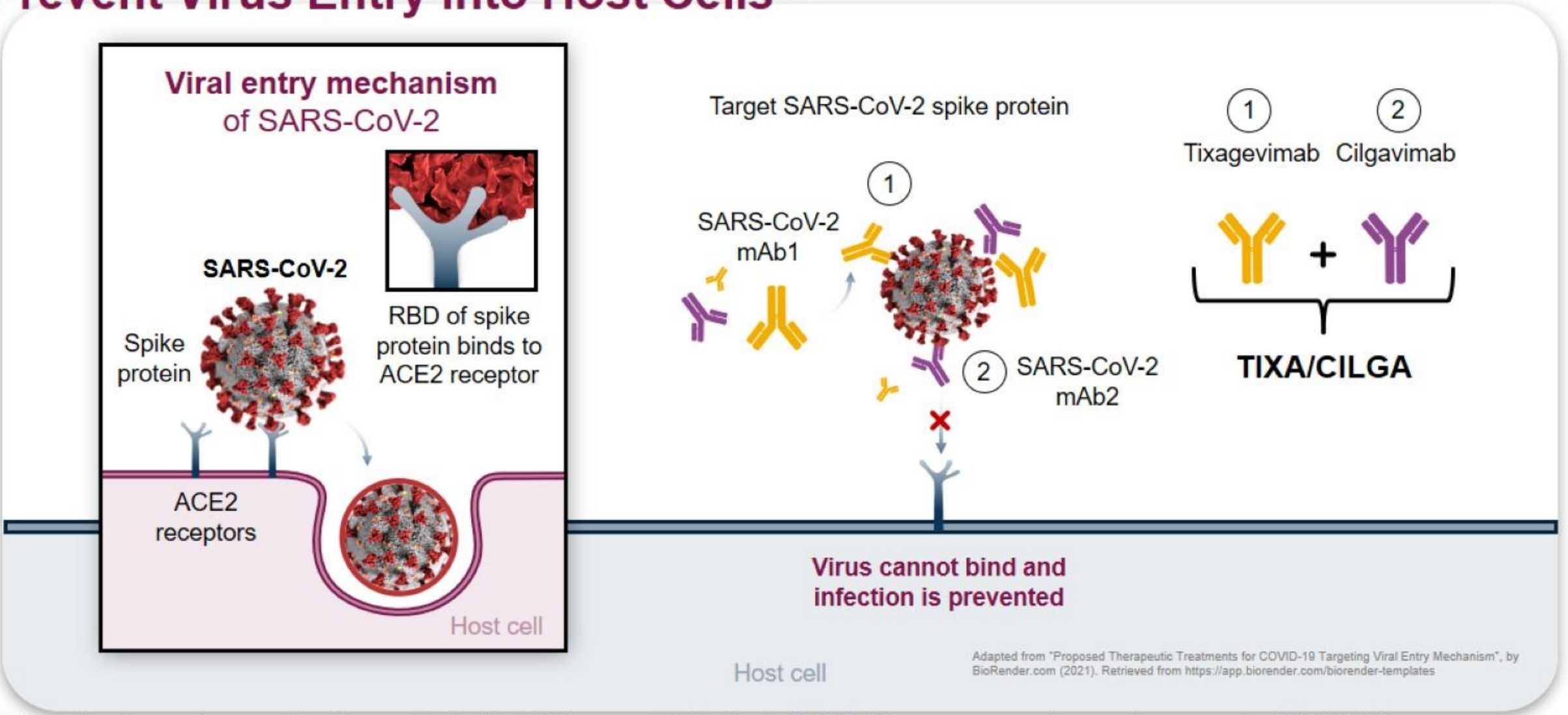


- 2 human mAbs binding 2 distinct epitopes[3]
- Highly potent[4]
- Retained neutralizing activity against variants of concern[3]
- Intramuscular administration[5]
- Extended half-life (YTE modification)[5]
- Reduced FcR or C1q binding (TM)[5]
- Favorable safety profile[5]
- Efficacy was shown for pre-exposure prophylaxis in high-risk populations[5]

Some of the information provided is based off a preprint research paper that has not been peer reviewed.
C1q = complement component 1q; mAb = monoclonal antibody; FcR = fragment crystallizable region; LAAB = long-acting antibody; RBD = receptor-binding domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TM = triple modification; YTE = M252Y/S254T/T256E.

1. Sehnal D et al. *Nucleic Acids Res*. 2021;49:W431-W437; 2. Protein Data Bank. https://www.rcsb.org/. 7L7E. Accessed November 10, 2021; 3. Loo YM et al. Preprint published online. *medRxiv*. 2021; 4. Zost SJ et al. *Nature*. 2020;584:443-4493. 5. Fact sheet for healthcare providers. Emergency Use Authorization (EUA) of EVUSHELD™ (tixagevimab co-packaged with cilgavimab). 2021.

Tixagevimab/Cilgavimab targets SARS-CoV-2 Spike Protein To Prevent Virus Entry Into Host Cells[1-4]



Adapted from "Proposed Therapeutic Treatments for COVID-19 Targeting Viral Entry Mechanism", by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates

ACE2 = angiotensin-converting enzyme 2; mAb = monoclonal antibody; RBD = receptor-binding domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TIXA/CILGA = tixagevimab/cilgavimab.

1. Cevik M et al. *BMJ*. 2020;371:m3862. https://dx.doi.org/10.1136/bmj.m3862. Accessed September 24, 2021; 2. Taylor PC et al. *Nat Rev Immunol*. 2021;21:382-393; 3. Zost SJ et al. *Nature*. 2020;584:443-449. 4. Fact sheet for healthcare providers. Emergency Use Authorization (EUA) of EVUSHELD™ (tixagevimab co-packaged with cilgavimab). 2021.

Therapies

- Statement on Anticoagulation in Hospitalized Patients
- Statement on Therapies for High-Risk, Nonhospitalized Patients
- **Statement on Paxlovid Drug-Drug Interactions**
- Statement on Patient Prioritization for Outpatient Therapies
- Antiviral Therapy
- Anti-SARS-CoV-2 Antibody Products
- Cell-Based Therapy
- Immunomodulators
- Antithrombotic Therapy
- Concomitant Medications
- Supplements

The COVID-19 Treatment Guidelines Panel's Statement on Potential Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications

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On December 22, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for ritonavir-boosted nirmatrelvir (Paxlovid) for the treatment of patients with mild to moderate COVID-19 who are within 5 days of symptom onset and at high risk of progression to severe disease.[1,2] The dose for patients with normal renal function is nirmatrelvir 300 mg (two 150 mg tablets) plus ritonavir 100 mg (one 100 mg tablet) orally twice daily for 5 days. For more information, see the COVID-19 Treatment Guidelines Panel's (the Panel) statement on treatment options for nonhospitalized patients with mild to moderate COVID-19.

Ritonavir-boosted nirmatrelvir (Paxlovid) has significant and complex drug-drug interaction potential, primarily due to the ritonavir component of the combination. Boosting with ritonavir, a strong cytochrome P450 (CYP) 3A inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. Ritonavir is an FDA-approved drug that has been used for more than 2 decades as a pharmacologic boosting agent for certain anti-HIV medications; therefore, there is a large body of literature describing its use with other drugs and its potential for serious and sometimes life-threatening drug-drug interactions. **Clinicians who are not experienced in prescribing ritonavir-boosted drugs should refer to resources such as the EUA fact sheet for ritonavir-boosted nirmatrelvir (Paxlovid) and the Liverpool COVID-19 Drug Interactions website for additional guidance.** Consultation with an expert (e.g., clinical pharmacist, HIV specialist, and/or the patient's specialist provider[s], if applicable) should also be considered.

Ritonavir is an inhibitor, inducer, and substrate of various drug-metabolizing enzymes and/or drug transporters. Most notably, as a strong inhibitor of CYP3A, it may increase concentrations of certain concomitant medications, thereby increasing the

Thank You

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- Email: sharone@mail.nih.gov
- Twitter: @EladSharonMD