

Proceedings of the  
COVID-19 and Lymphoma Panel:  
October 19, 2021

A LYMPHOMA RESEARCH FOUNDATION WHITE PAPER

## Introduction

On October 19, 2021, the Lymphoma Research Foundation convened an expert panel of medical and scientific advisors as part of a monthly meeting series, to discuss the current state of research regarding the COVID-19 vaccine and people with lymphoma. The panel discussed recommendations for oncologists caring for people with these cancers, as well as related scientific research and education programming.

This white paper reflects the panel discussion and the state of research as of the date of the above. Oncologists and other healthcare providers are encouraged to consult the most recent guidance from the Centers for Disease Control and Prevention (CDC) and other federal healthcare agencies when making treatment recommendations. Patients should consult with their own healthcare providers when making treatment decisions.

For additional information, members of the lymphoma community are also encouraged to visit the Lymphoma Research Foundation's COVID-19 Learning Center at [lymphoma.org/covid19](https://lymphoma.org/covid19) and/or contact the LRF Helpline at 800-500-9976 or [helpline@lymphoma.org](mailto:helpline@lymphoma.org).

The Foundation is grateful to the friends and family of Dr. Robert Schroeder whose support made this program possible.

## Presentations

### **Introduction**

Panel Chair Dr. Andrew Zelenetz of Memorial Sloan Kettering Cancer Center (MSKCC) opened the meeting by providing a recap of the previous Lymphoma Research Foundation (LRF) COVID-19 panel meeting, highlighting that many lymphoma patients, particularly those exposed to B cell-depleting therapies, do not mount a humoral immune response to vaccination and remain unprotected against COVID-19. Additional data on T cell responses and their implications for immunity are pending. Many lymphoma patients feel trapped and disconnected from friends and family, and it is important to identify novel strategies to help protect these patients.

### **PROVENT Trial Results**

Dr. Zelenetz provided a brief summary of the results of the phase III PROVENT trial presented by AstraZeneca at Infectious Disease Week 2021.<sup>1</sup> The PROVENT trial was a large, randomized trial that examined the efficacy of an antibody cocktail (AZD7442) as pre-exposure prophylaxis therapy (n=3460 patients) compared with placebo control (n=1737) in patients considered high-risk for COVID-19. Participants were accrued in late 2020, before the widespread availability of COVID-19 vaccines. The AZD7442 cocktail contains two antibodies that have been Fc engineered to prevent binding to the Fc receptor (FcR) and to maintain a longer half-life.

The estimated effective serum coverage after 1 dose was approximately 12 months, and the antibody cocktail was found to have high levels of neutralization against the Alpha, Beta, and Delta SARS-CoV-2 variants. The primary endpoint in the trial was symptomatic COVID-19, which occurred in 8 (0.002%) of AZD7442-treated participants and 17 (0.01%) of placebo-treated participants (relative risk reduction, 77%). No significant safety signal was observed. Severe COVID-19 was uncommon in the study population, occurring in 0 participants in the AZD7442 group and 3 participants in the placebo group. Two participants died from severe COVID-19.

The major limitation of the PROVENT trial was that it was ultimately conducted in the “wrong” population. The goal of the study was to examine the efficacy of pre-exposure prophylaxis in a group of patients that were less likely to respond to COVID-19 vaccination, and thus included a high proportion of patients over 65 years of age. People in this age group typically have an attenuated response to vaccination, but that is not the case following COVID-19 vaccination. Instead, only 3.8% of the study population was what panelists would consider truly immunosuppressed due to exposure to B cell-depleting therapy. It is expected that AZD7442 will be submitted to the United States Food and Drug Administration (FDA) for emergency use authorization (EUA) based on the results of this trial, but more data are needed to demonstrate that immunosuppressed patients can be expected to receive the same level of protection from this or other types of antibody-mediated pre-exposure prophylaxis therapy.

## Discussion

### ***Antibody Therapies in Hematologic Malignancies***

Dr. Zelenetz noted that AstraZeneca is very interested in conducting a study of AZD7442 in high-risk patients with hematologic malignancies and invited interested panelists to connect with the company if they are interested in participating. Dr. Bruce Cheson of The Center for Cancer and Blood Disorders said that their institution will be involved. Dr. Zelenetz indicated that a competing trial of a different Fc-engineered antibody is already being organized at MSKCC. The antibody, developed by The Rockefeller University and purchased by Bristol Myers Squibb (BMS), will be tested in a broad population of patients with hematologic malignancies to examine the ability of these patients to develop neutralizing antibodies and determine how long protection will last.

Dr. David Knorr added that a key factor when considering trials of pre-exposure prophylactic antibody therapy in hematologic malignancies is the abrogated FcR engagement with the AZD7442 antibodies. This activity was blocked in an effort to prevent potential antibody-dependent enhancement of disease, which was a possible concern when the antibodies were engineered. However, it has been repeatedly demonstrated, including with COVID-19 antibodies, that loss of FcR binding reduces the efficacy of passive antibody therapies.<sup>2</sup> Neutralization can still occur, but even with a long half-life, the impact of treatment will be reduced. Other investigational antibodies, such as those from BMS and Regeneron, still retain FcR-binding capacity and should in theory provide better protection. When considering a trial in populations that are expected to have limited effector-mediated activity to begin with, this is a key difference in these antibodies to consider.

### ***T Cell Responses***

Panelists shared their experiences and frustrations identifying which patients will respond well to vaccination. Anecdotally, panelists reported that approximately 20% of chronic lymphocytic leukemia (CLL) patients develop robust antibody responses after vaccination, but it is unclear what differentiates these individuals from the majority of CLL patients who do not have any response. No trends have been observed with regard to type of therapy or disease response. Panelists emphasized that anecdotal observations are irrelevant unless they are able to capitalize on understanding what makes these patients different from non-responders but are unsure how to proceed.

For patients who do not develop humoral responses to vaccination, T cell responses may be an important consideration. For CLL patients, it is unsurprising that humoral responses aren't observed given the types of drugs these patients are often treated with, but many patients may have more protection than expected based on T cell responses. In solid organ transplant recipients who did not develop any detectable antibody response to COVID-19 vaccination, 46.2% developed a positive T cell response.<sup>3</sup> However, it is unclear what this means clinically, and the clinical implications of these T cell populations for SARS-CoV-2 protection remain to be elucidated.

A variety of assays are under investigation to detect and monitor T cell responses post-vaccination. Traditional assays such as tetramer stimulation assays can be used but require a pre-exposure sample. Dr. Zelenetz reported that Dr. Peter Maslak at MSKCC has developed a flow-based assay looking for T cell responses characteristic of COVID-19 infection and vaccination and is currently collecting additional data for approval for use in New York state. A flow-based assay provides the advantage of being relatively inexpensive compared with other emerging options, such as an adapted ClonoSEQ assay from Adaptive which is under development. Clinically, however, monitoring of T cell responses is not currently done and more data are needed before any of these assays can be used in this setting.

Although the PROVENT study did not examine T cell responses, panelists agree that in theory the protective capacity of pre-exposure prophylaxis with antibody therapies may be related to stimulation of T cell responses. If enough antibody is present to neutralize the virus, antigen-antibody complexes will stimulate potent T cell responses. Formation of these immunocomplexes, however, would only occur after exposure to the viral antigen, such as via exposure or vaccination. Panelists do not recommend concurrent vaccination with passive antibody therapy at this time.

### **Methodological Pitfalls**

Dr. Lindsay Morton of the National Cancer Institute emphasized that there is still a need for rigorous data to address key research questions related to COVID-19 vaccination and protection in lymphoma patients. While much of the literature available suggests that cancer patients are unprotected by vaccination, many of these studies contain significant methodological flaws. The biggest issues are related to the selection of patients and the availability of supporting clinical data. For example, many studies contain highly selective populations of patients, and most do not address many of the factors that are known to affect COVID-19 exposure and severity, such as obesity, smoking status, race/ethnicity, age, or other comorbidities. Additionally, one of the biggest challenges is the heterogeneity of cancer patients, particularly with regard to the type of cancer and treatment. Therefore, there isn't a well-defined correlate of immune function or metric of antibody response in this broad population. How to generate rigorous data to answer the key questions related to protection of these patients remains a point of discussion in the field of cancer epidemiology.

### **Key Research Questions**

Dr. Zelenetz highlighted two general approaches that can be used to ensure lymphoma patients are protected from COVID-19: augmenting active immunity, and providing passive immunity. To support these broader goals, panelists identified two key questions that can be addressed with support from the Lymphoma Research Foundation:

- For patients who are B cell-depleted who fail to mount a humoral response to vaccination, can pre-exposure prophylactic antibody therapy provide protection from COVID-19?
- What levels of humoral and/or cellular immunity correlate with protection against COVID-19?

Clinical trials require significant mobilization, so panelists recommended prioritizing trial efforts where there is the most clear-cut need, which is the identification of therapeutic strategies to protect patients who are B cell-depleted who fail to mount an antibody response. Correlation between humoral and cellular immunity and protection may be readily addressed using or augmenting existing systematic datasets.

### *Pre-Exposure Prophylaxis Clinical Trial Design*

- **Study population:** Although the results from the PROVENT trial were promising, a trial in a large population of truly immunosuppressed patients is needed to understand the benefits of pre-exposure prophylaxis. Panelists suggested that the trial population include patients who failed or who are expected to fail to mount a humoral response based on B cell depletion. If trial participation is limited to patients who have definitively failed to mount a humoral response, important information may be missed, such as the effect of active vs post-therapy. Stratification can be performed based on those who do and don't mount an immune response, and humoral response should be considered as a parameter, but not a selection criterion. Vaccination should also not be a requirement for enrollment.
- **Randomization:** With pending EUA expected, pre-exposure prophylactic antibody therapy may be standard of care in some instances, which may make a randomized trial infeasible. Given the urgent nature of the situation, panelists agreed that randomization may not be needed or be the best approach. However, if the trial isn't randomized, substantial supporting data will need to be collected and adjusted for.
- **Endpoints:** While likely the most clinically relevant, occurrence of severe COVID-19 infection may be a complicated endpoint to rigorously assess, and the expected statistical power of the trial may make it infeasible. Symptomatic disease or potentially test positivity may be more appropriate endpoints. Regardless of what endpoint is chosen, it is important that it is assessed consistently and systematically across patients.

An intervention trial will require both industry and institutional partners. Panelists felt that amongst themselves, enough institutions were represented to cover a sufficiently large number of patients, with additional education efforts supported by the Lymphoma Research Foundation.

### ***Correlating Immune Responses with Protection***

To support the results of the interventional trial described, additional studies are needed to identify patients who are truly unprotected (i.e., exhibit inadequate B or T cell responses to vaccination). At present, though, “adequate” responses have yet to be defined, and it can only be determined whether or not an antibody response has been generated. As discussed in the first meeting, not all antibody responses are created equal, and even among those who generate a response, it still cannot be reliably determined whether patients are protected. This extends not only to lymphoma patients, but across all individuals, including diverse groups of immunosuppressed patients. Therefore, a study is needed to broadly correlate humoral and cellular immune responses with level of protection, which may include a variety of immunosuppressed patients, preferably with hematological malignancies. Systematic datasets that are already being collected, such as those from Israel, may be leveraged to answer these questions. Such a study may help define patients who will clearly benefit from pre-exposure prophylaxis, as well as a subset of patients who may not be fully protected by vaccination and require additional intervention.

Some limitations to consider when designing such a study:

- While individual datasets suggest that thresholds may exist that are predictive of immunity,<sup>4</sup> there are many different antibody tests available, and cutoffs determined using a single test will not be universal.
- The free availability of booster vaccines, and potentially pre-exposure prophylaxis antibody therapy in the future, may make it challenging to address these questions. However, there are likely to be geographic areas of the country where this will not be as much of an issue (e.g., areas where booster vaccine availability is limited) that can be leveraged.

## Recommendations

An interventional trial examining the efficacy of pre-exposure prophylactic antibody therapy in high-risk immunosuppressed patients with a known or expected lack of humoral response was identified as critical need for lymphoma patients at this time. A proposal will be circulated amongst panelists for response and critique. The goal will be the development of a topline trial design and identification of potential endpoints of interest. The proposal will be discussed in detail at the next meeting (November 30, 2021), with the goal of developing it into a Letter of Intent to a potential partner. The Lymphoma Research Foundation will support the efforts and ensure that all necessary information is considered during these discussions.

In the interim, Dr. Cheson also emphasized that there is a need to support patients who have questions now, who cannot wait a year for trial results. A resource such as LRF's online COVID-19 Learning Center must be kept operational as it is needed to answer key questions that patients and providers have about what is currently known and what remains to be answered about immune responses to vaccination. In addition to supporting trial development, the Foundation may consider developing such a resource to support patients and/or clinicians.

## References

1. AstraZeneca COVID-19 and RSV presentations at IDWeek 2021 will showcase scientific progress in infectious diseases [press release]. September 27, 2021 2021.
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3. Hall VG, Ferreira VH, Ierullo M, et al. Humoral and cellular immune response and safety of two-dose SARS-CoV-2 mRNA-1273 vaccine in solid organ transplant recipients. *Am J Transplant*. 2021.
4. Chung DJ, Shah GL, Devlin SM, et al. Disease and therapy-specific impact on humoral immune responses to COVID-19 vaccination in hematologic malignancies. *Blood Cancer Discovery*. 2021:bloodcandisc.0139.2021.



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