The Impact of Chemotherapy and Immunotherapy on the Efficacy of COVID-19 Vaccination

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The presenter has no financial interests to disclose.

Overview

- Introduction
- Study design
- Results
- Discussion
- Conclusion

Introduction

- 986,000 people have died in the USA from SARS-CoV-2 viral infection (COVID-19) since JAN2020 with 6.2 million deaths world wide
- Patients with cancer have a higher risk of dying from COVID-19 than patients without cancer
- Both the National Comprehensive Cancer Network and American Society of Clinical Oncology have advised vaccination against SARS-CoV-2 for patients undergoing cancer-targeted therapies
- It is estimated that COVID-19 vaccinations have prevented over 100,000 deaths in the US

Introduction

- COVID-19 vaccine serum titers have been measured in specific subtypes of cancer (CLL), however data on vaccine effectiveness is wanting in landscapes:
  - General oncology clinic, multiple modality chemotherapy, solid malignancies
  - Titer level correlate to degree of protection
  - Degree of protection against variants and other coronavirus strains

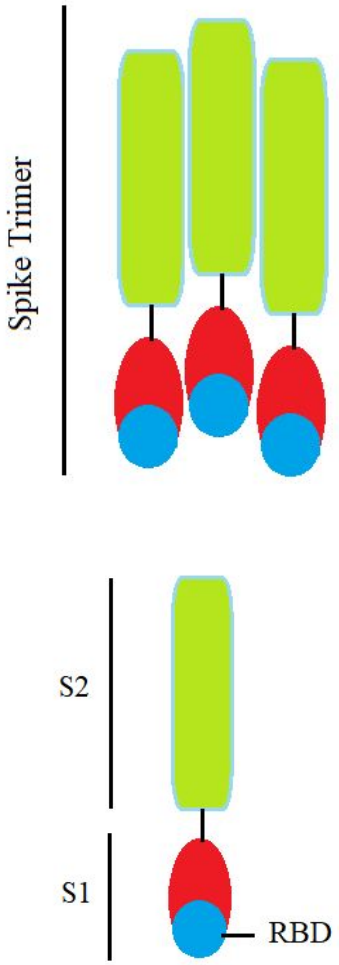
Objectives

- Primary
  - Evaluate COVID-19 vaccine titer levels in patients vaccinated while receiving chemotherapy and immunotherapy
  - Correlate titer levels with degree of serum neutralization

- Secondary
  - Determine if vaccine response differs depending on:
    - B-cell malignancies
    - Degree of protection against variants
    - Degree of protection against other strains of coronavirus
    - Characterize COVID-19 breakthrough infections and potential vulnerable population

Study Design

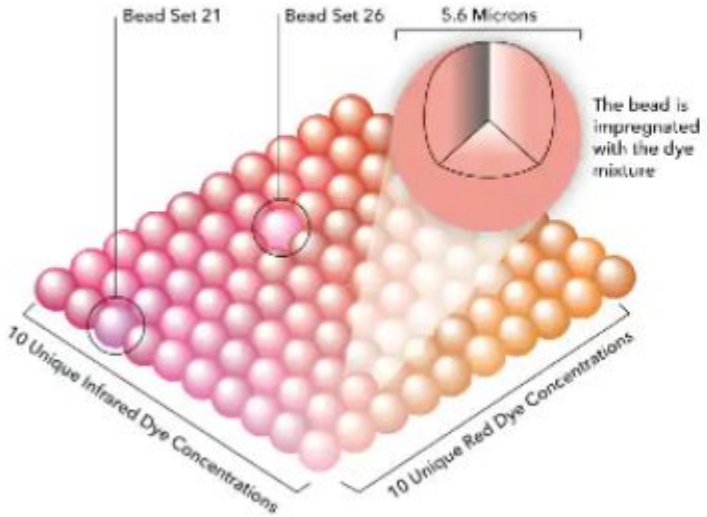
- Prospective observational study assessing titer response to COVID-19 vaccination in patients 18 and older receiving chemotherapy or immunotherapy
  - Excluded: Bone marrow transplants, primary immunodeficiency, acute myeloid leukemia
- Vaccination against SARS-CoV-2 via two doses of mRNA-1273 (Moderna), two doses of BNT162b2 (Pfizer), or single dose of Ad26.COV2 (Janssen)
- Serum obtained at 1, 3, and 6 months after COVID-19 Vaccination
- Measured anti-SARS-CoV-2 antibodies from the initial Wuhan strain for:
  - Spike trimer, Spike S1 subunit, Spike receptor binding domain (RBD), and the Nucleocapsid protein
    - Ratio of patient titers: negative control >1.3 indicative of titer presence
  - Antibody titers to SARS-CoV-2 spike protein variants: B.1.1.7 (α), B.1.351 (β) and P.1 (γ)



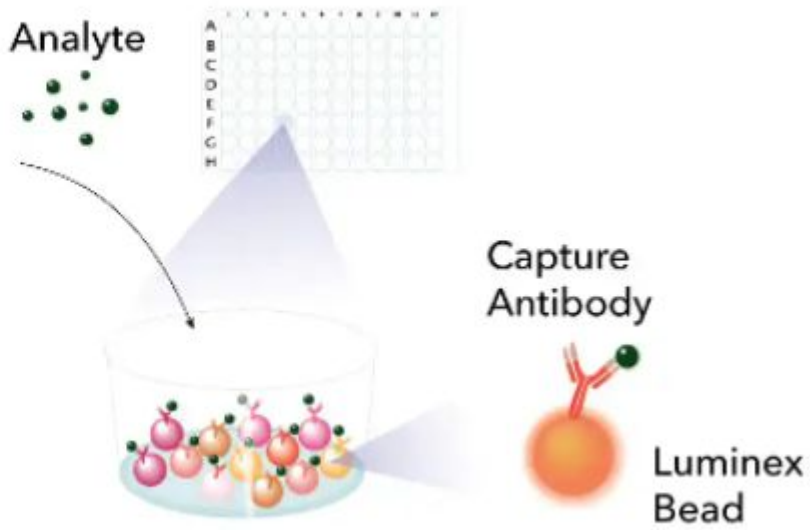
Study Design-Antibody Assessment

- 11 proteins and a negative control are assessed in a single well per sample
  - Mean fluorescent intensity (MFI) values from standards were utilized to generate a standard curve
  - A negative control which was established based on 160 healthy PCR negative and 69 PCR positive SARS-CoV-2 samples was run with each kit
  - The ratio of subjects antibody level compared to the negative control was calculated (Ratio = MFI of the sample / MFI of the low control)
    - Ratio > 1.3 = Ig is present
    - Ratio between 1 – 1.3 = indeterminate result
    - Ratio of < 1 corresponds = Ig that is absent for that given protein

Luminex Bead Spectrum

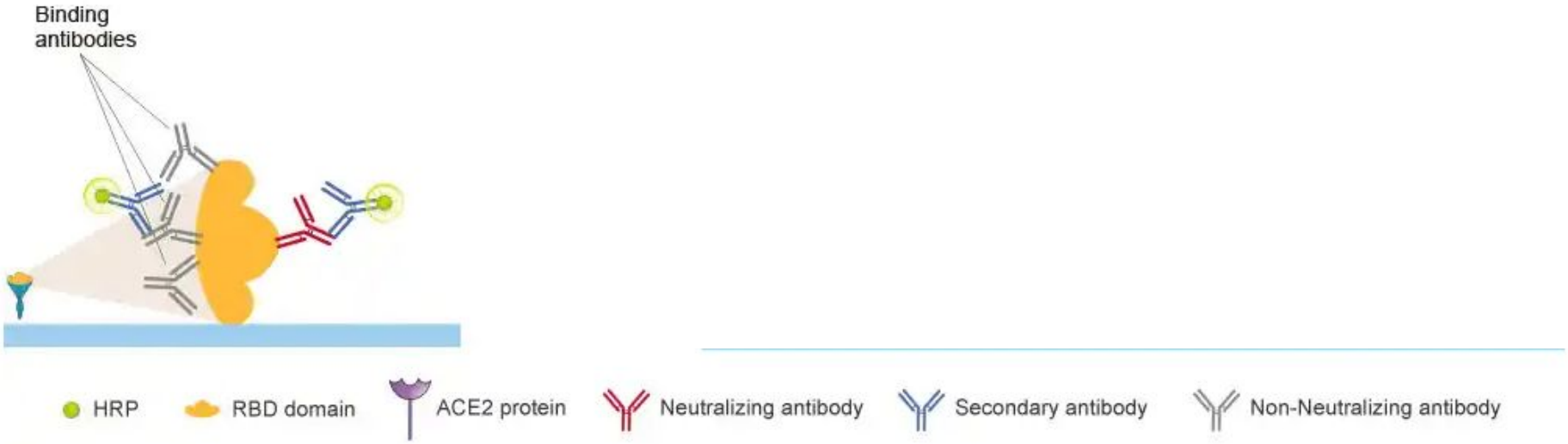


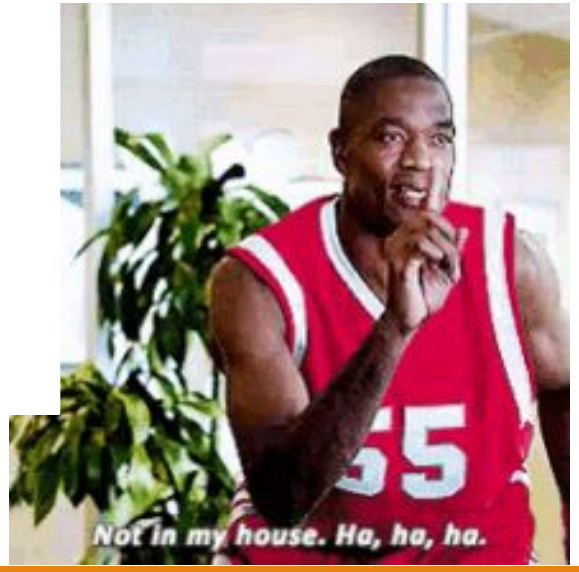
Luminex Assay Principle



Study Design

- Serum Neutralization Assay correlates performed using 10 serum samples from “low” titers, 10 from “intermediate” titers and 20 from “high” titer
- 20 % neutralization indicated a protective titer level from infection
  - Defined based on screening of 160 healthy (negative for SARS-CoV2) samples and correlated to a 50% plaque reduction in virus culture samples

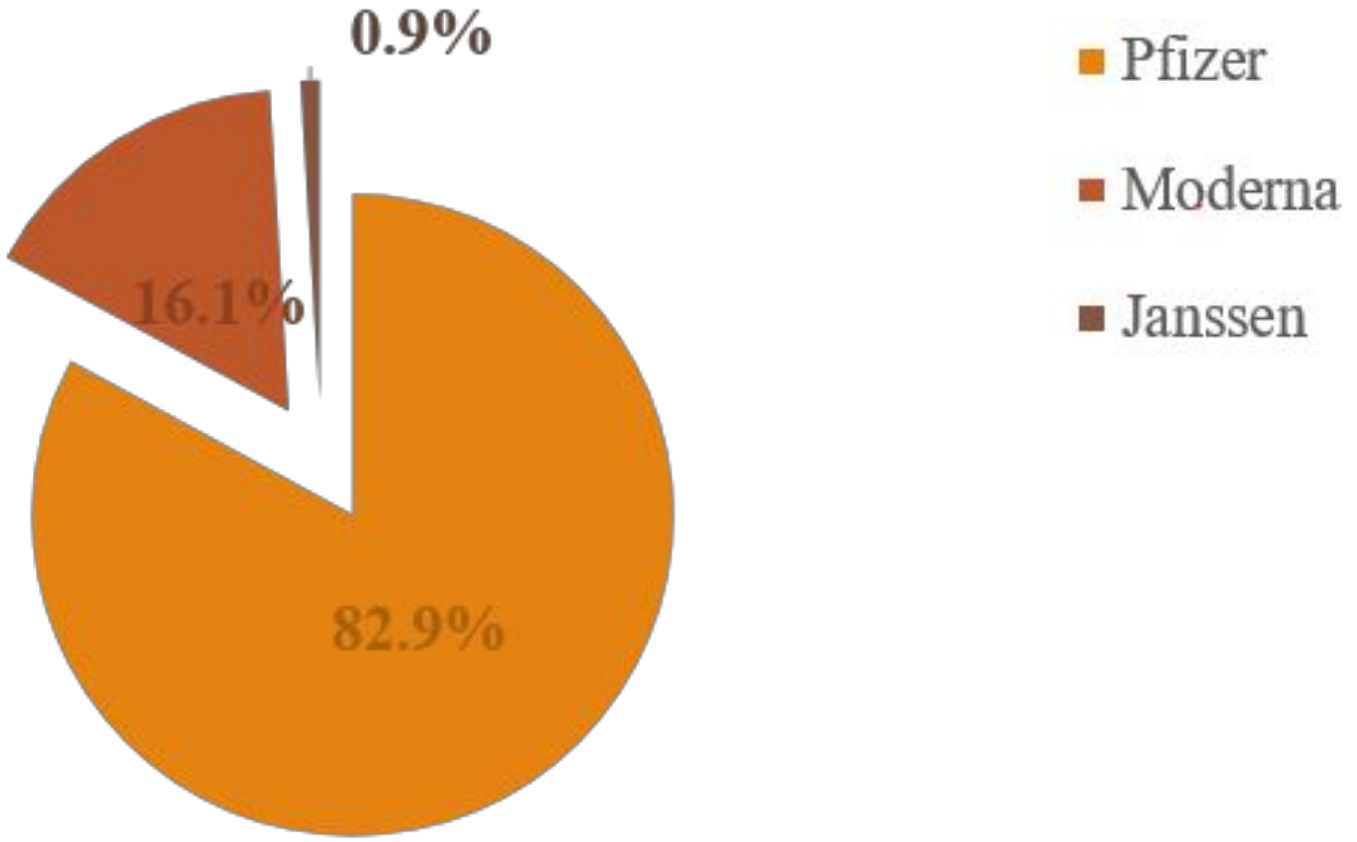




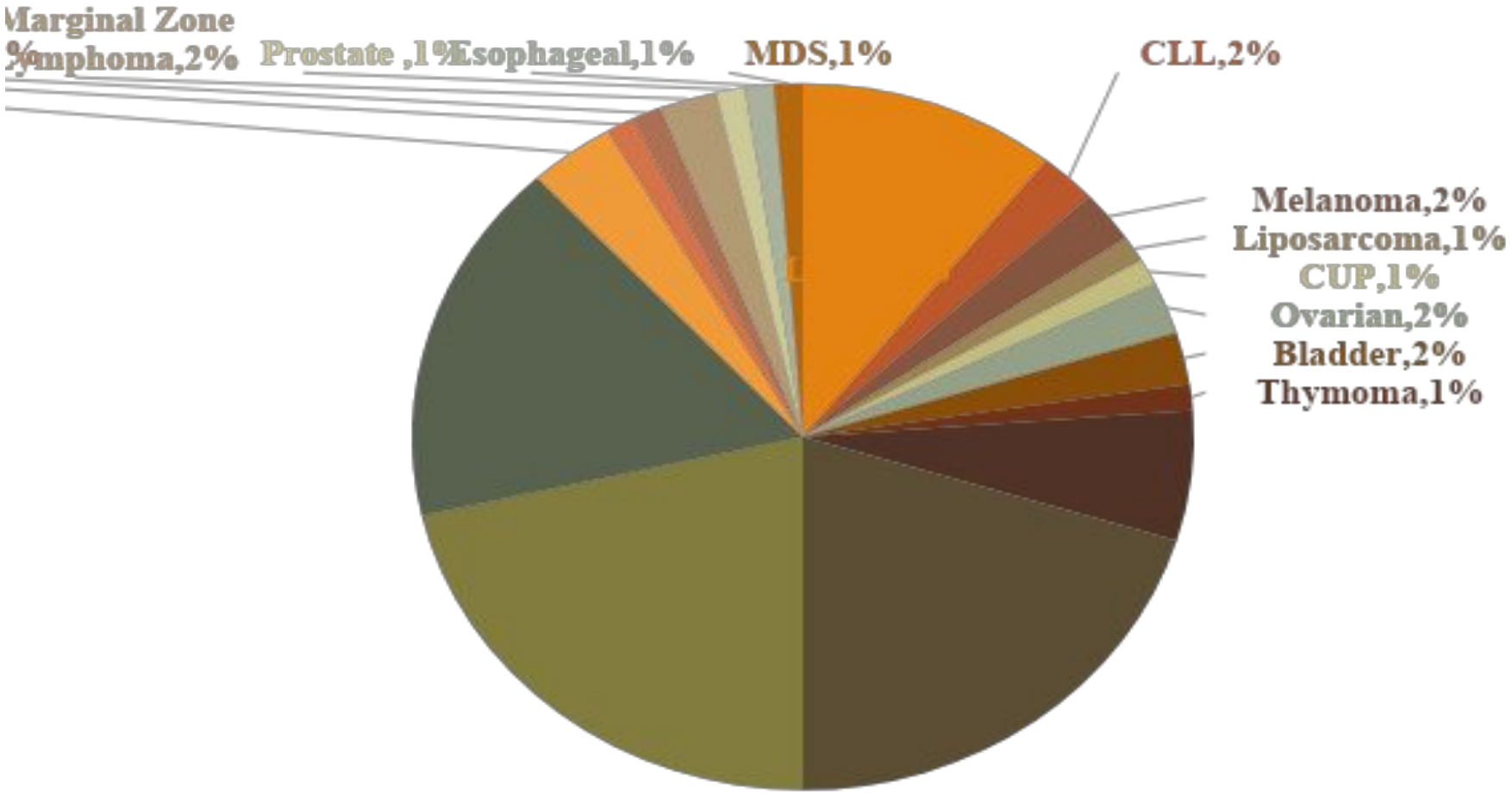
Demographics

- 120 total patients enrolled in first half of this study (not including booster data)
  - 28 dropped out
- 92 patients assessed: 57% Female, 43% male
- Age range 23-84, median 64
- 24% from patients with B-cell malignancies
- 48.9% Stage IV cancer

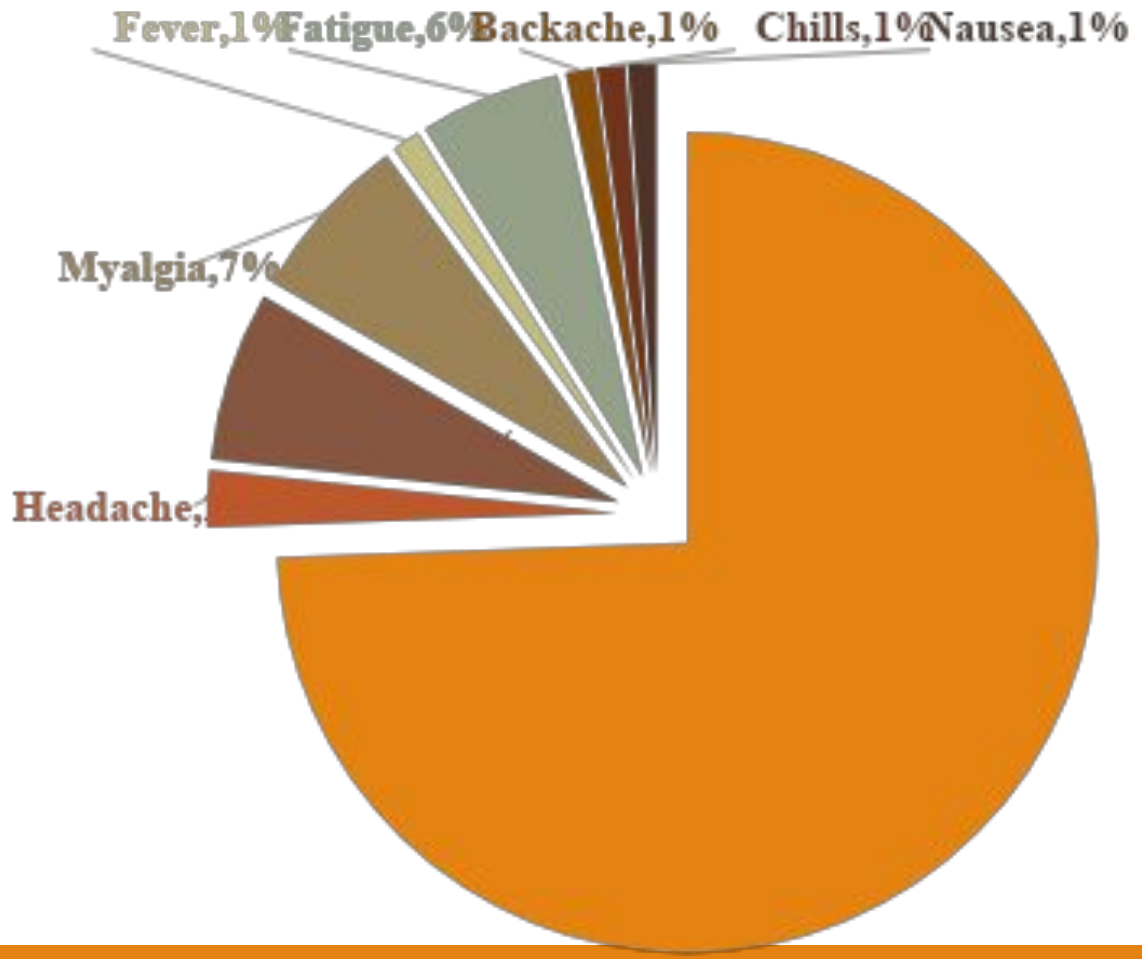
Vaccines Obtained



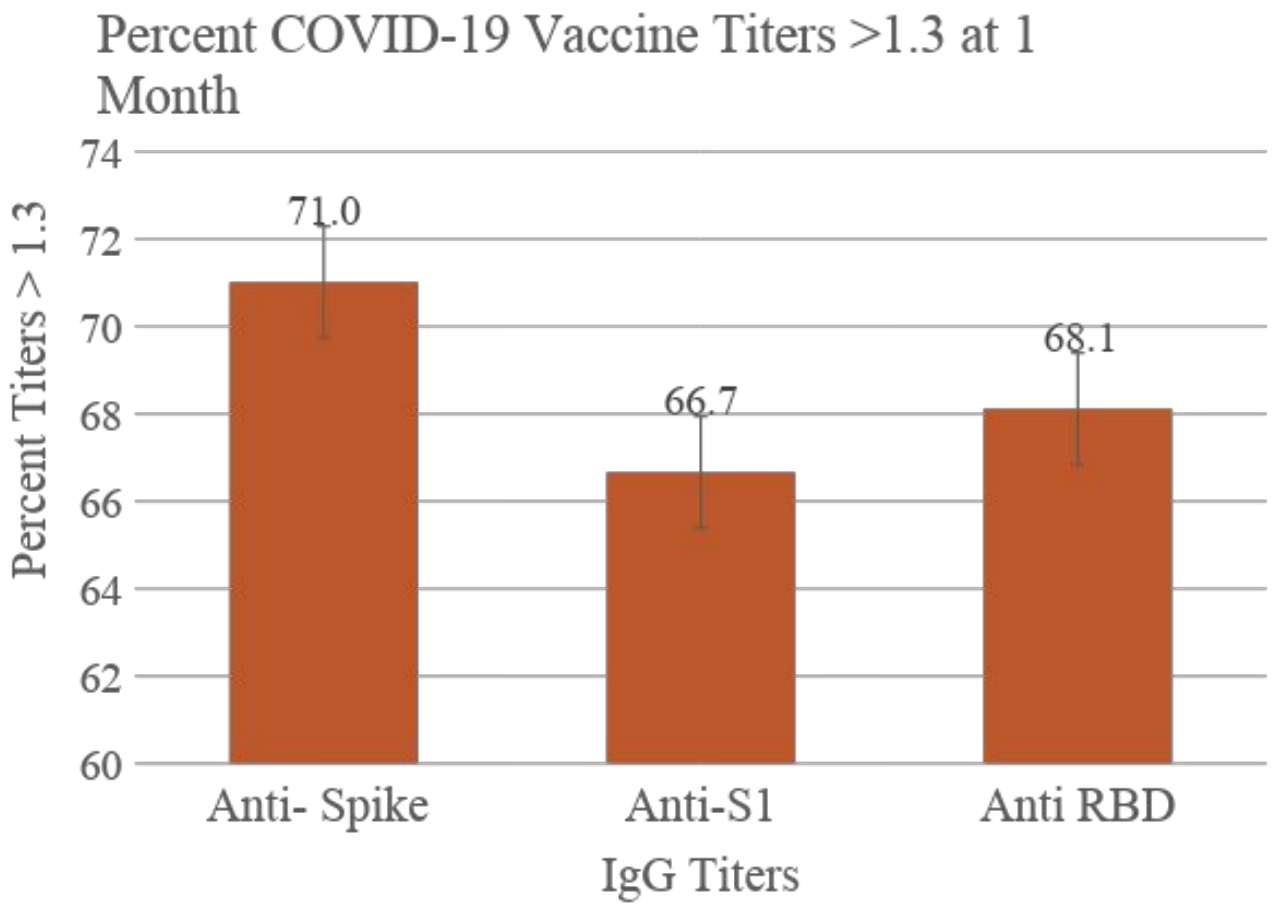
Malignancies



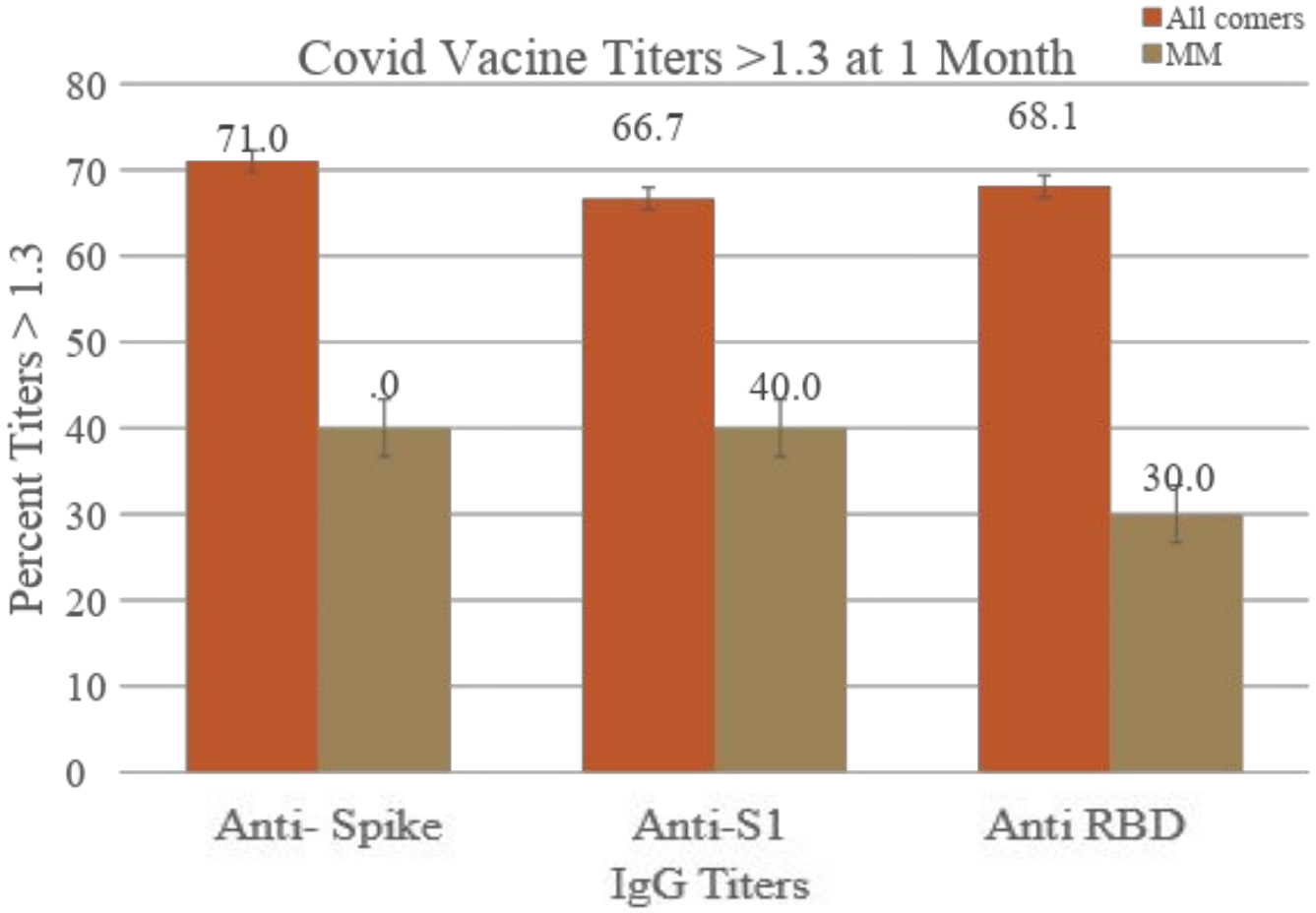
Vaccine Side Effect Profile



Detectable Titer Response at 1 Month

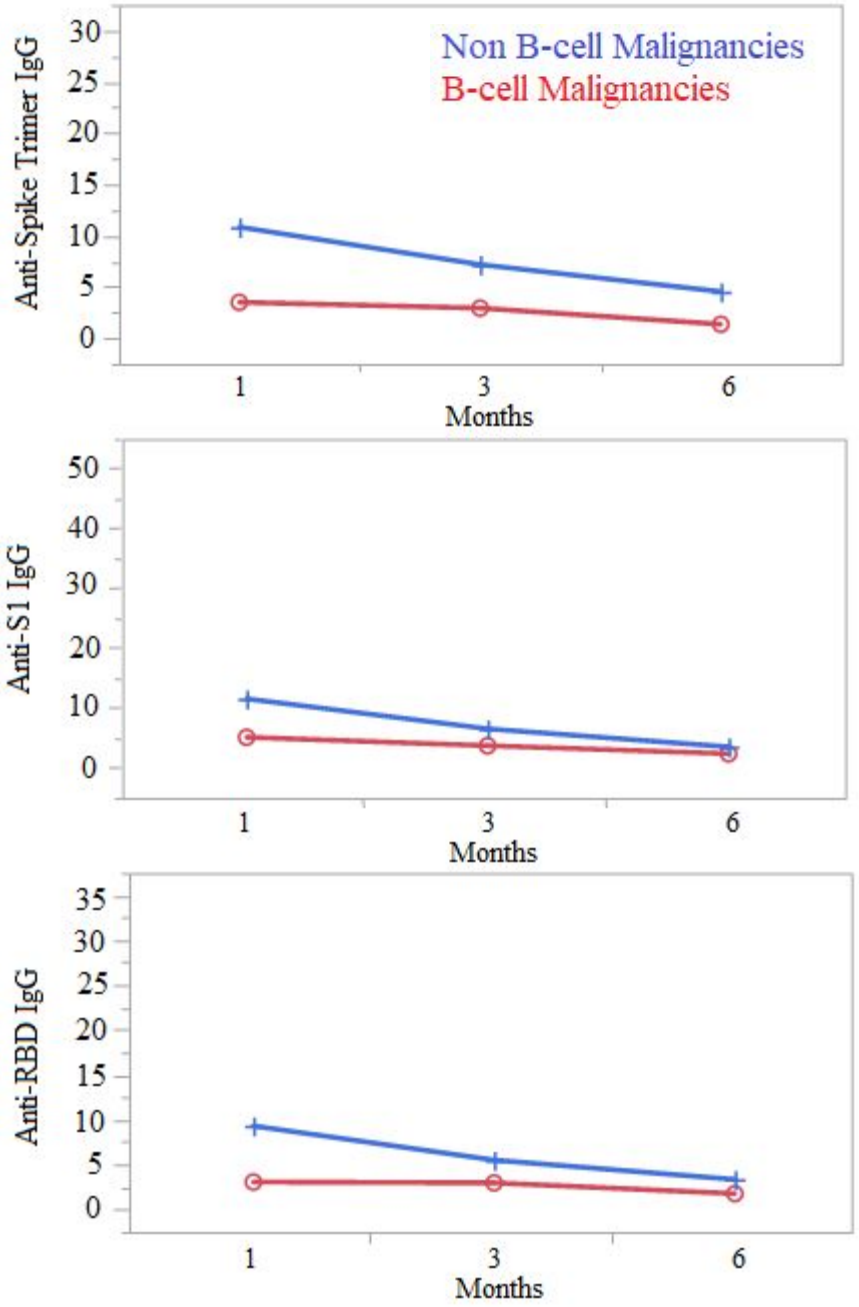


1 Month Titer Response in Multiple Myeloma



B-Cell Malignancies

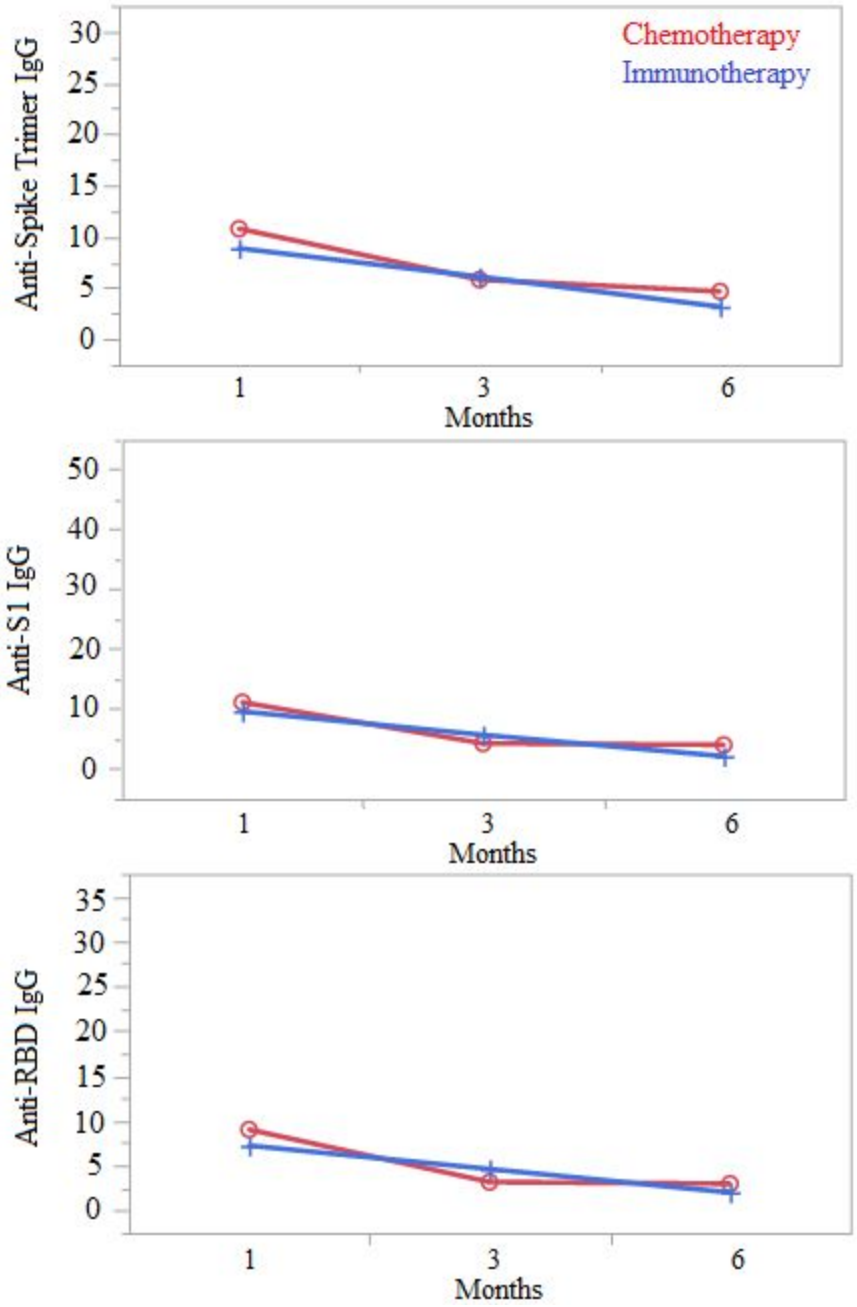
- Anti-spike, anti-S1 and anti-RBD titers decayed from 1-6 months for non-B cell malignancies (P<0.001)
- Statistically significant difference in titer levels at 1 and 3 months between B and non-B cell malignancies, but not at 6 months
- No significant decay amongst titers in patients with B cell malignancies
  - Too low at start



Chemotherapy vs. Immunotherapy

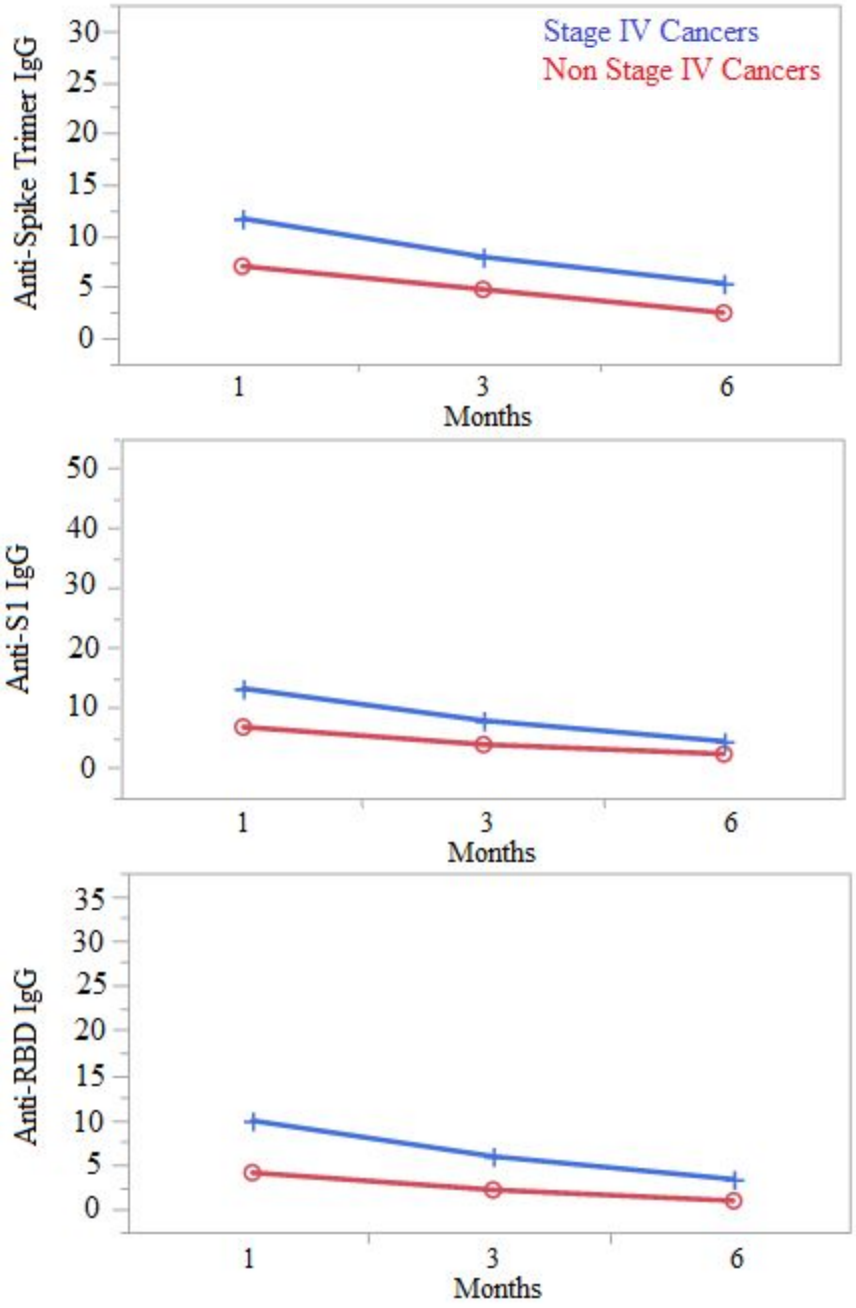
- No significant response difference at 1,3 and 6 months between chemotherapy (less B-cell malignancies) and immunotherapy

- Equivalent decay over time



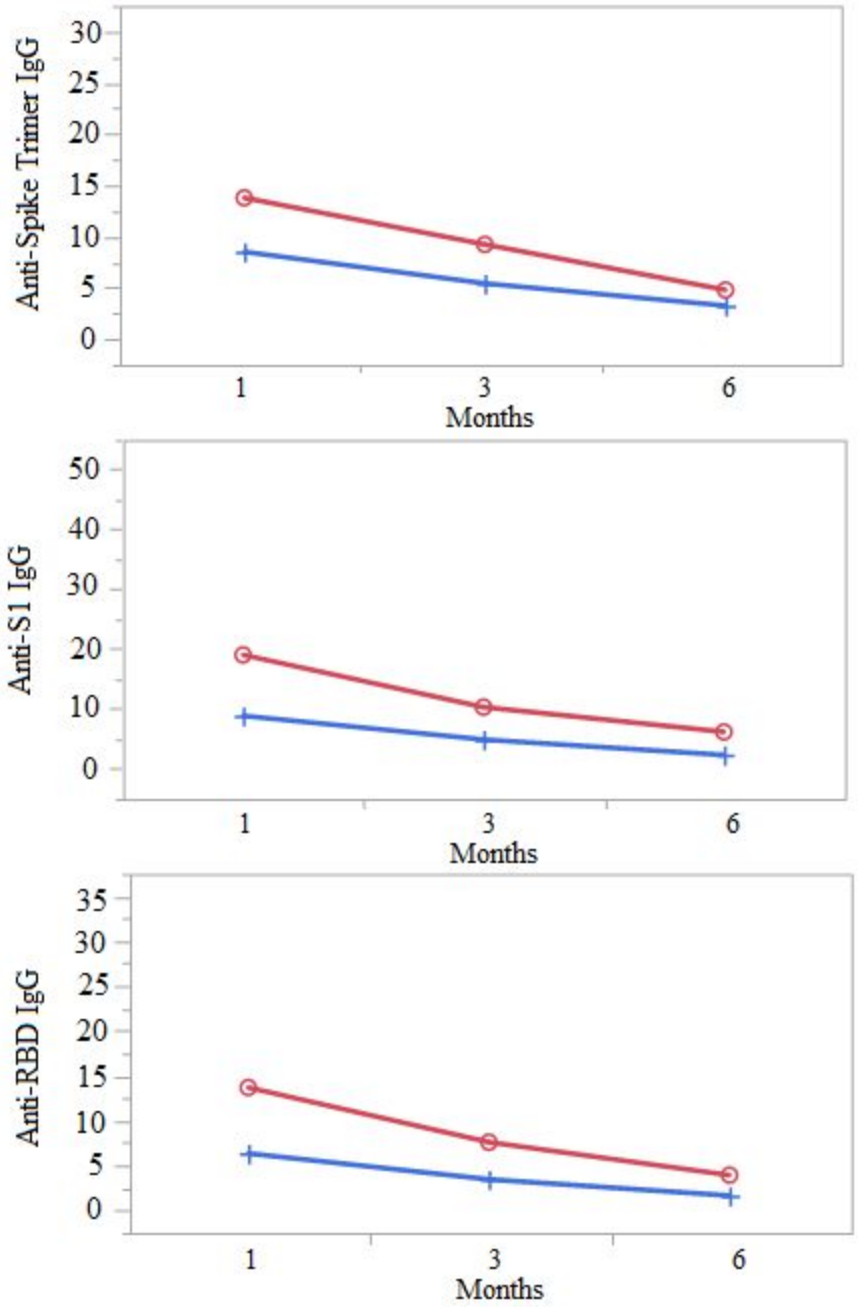
Stage IV Malignancies

- Statistically significant higher titer response for Spike trimer, S1 and RBD at 1 month, not 3 or 6 months ($P<0.0001$)
- Equivalent rate of titer decay between Stage IV and all others
- 50% of patients with stage IV malignancies on non-cytotoxic chemotherapies at 1 month after vaccination
  - Molecularly targeted therapies or single agent chemo

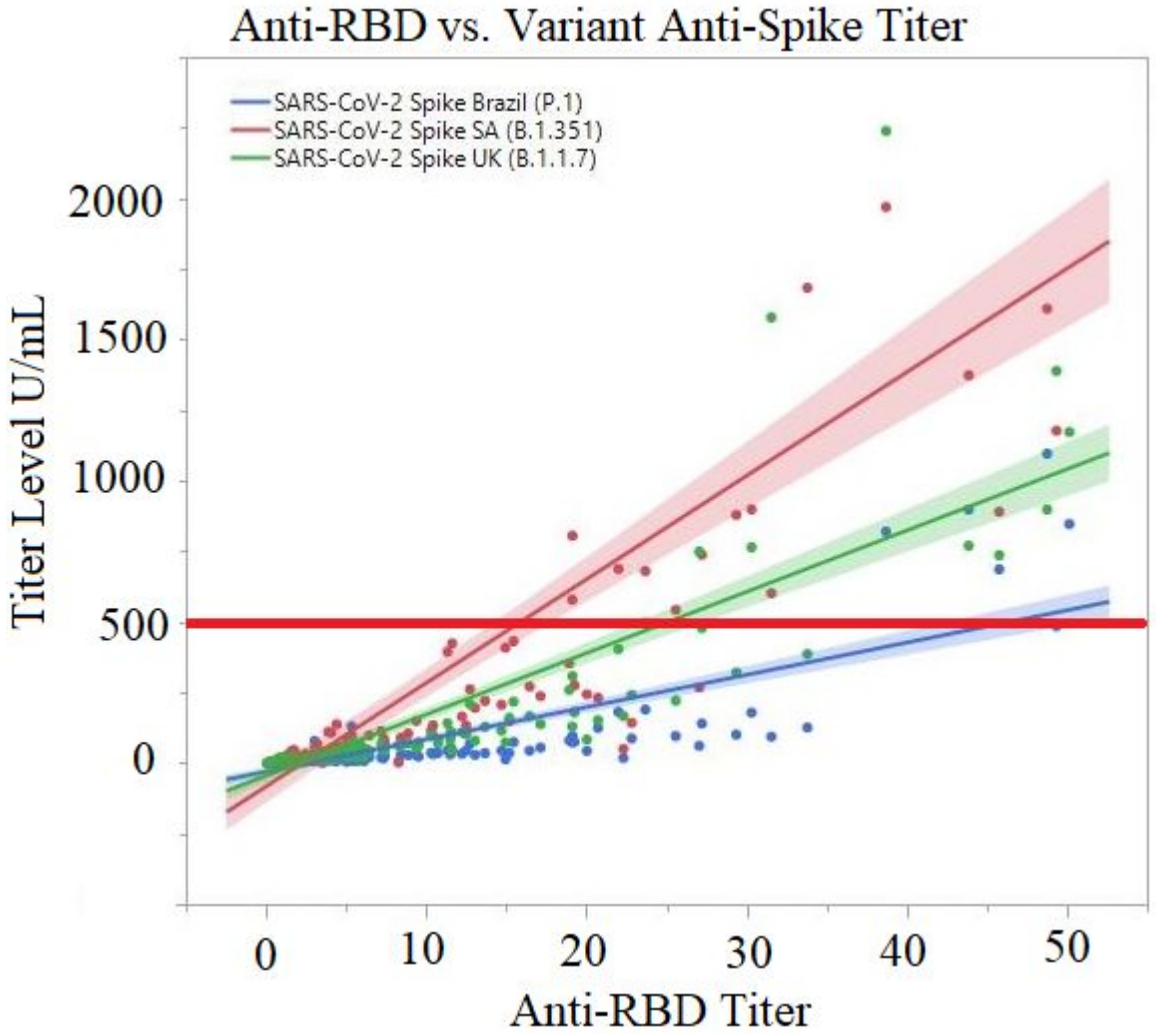


Response Rates for Moderna vs. Pfizer

- Higher titer response to Spike, S1 and RBD for Moderna vs. Pfizer at 1 month ($P<0.001$)
- No significance difference in titer levels at 3 and 6 months after vaccination

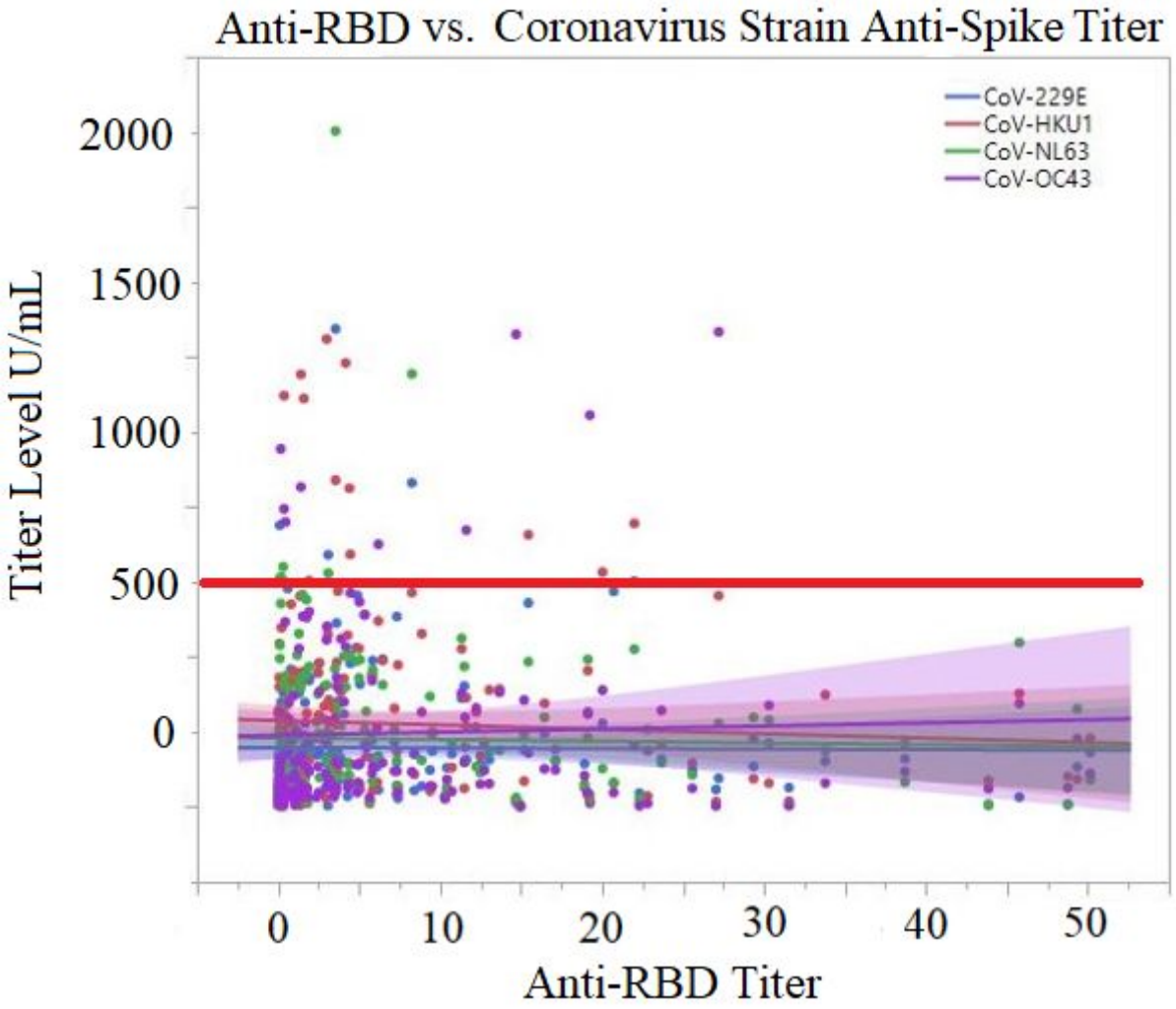


Anti-RBD Correlating to Variant Protection



- >500 U/ml manufacturer cutoff for high-titer
- Higher titer of RBD portended greater protection against:
  - B.1.351 (β) > B.1.1.7 (α) > P.1 (γ)
- Even at high anti-RBD titer, limited protection against gamma variant

Anti-RBD IgG vs. Neutralization of Coronavirus Strains



- Increasing anti-RBD IgG levels showed no significant improvement in protection against common coronavirus strains

Nominal Logistical Fit Analysis

- Determined threshold of anti-RBD IgG of 7.43 and above correlates to consistently >20% neutralization

X	Prob	1-Specificity	Sensitivity	Sens-(1-Spec)	
.	.	0.0000	0.0000	0.0000	
9.480000	1.0000	0.0000	0.9286	0.9286	
7.430000	1.0000	0.0000	1.0000	1.0000	*
3.540000	0.0000	0.0400	1.0000	0.9600	
0.040000	0.0000	1.0000	1.0000	0.0000	
0.040000	0.0000	1.0000	1.0000	0.0000	

Multivariate Correlation for Titer Levels to Serum Neutralization for Variants

Multivariate Correlations				
	SARS-CoV-2 N	SARS-CoV-2 Spike (Trimer)	SARS-CoV-2 S1	SARS-CoV-2 RBD
SARS-CoV-2 N	1	0.3283	0.2644	0.2716
SARS-CoV-2 Spike (Trimer)	0.3283	1	0.8621	0.8503
SARS-CoV-2 S1	0.2644	0.8621	1	0.97
SARS-CoV-2 RBD	0.2716	0.8503	0.97	1
SARS-CoV-2 Spike UK (B.1.1.7)	0.1887	0.6438	0.8243	0.819
SARS-CoV-2 Spike SA (B.1.351)	0.1211	0.5577	0.7534	0.6947
SARS-CoV-2 Spike Brazil (P.1)	0.2142	0.6065	0.8019	0.7323
CoV-OC43	-0.0141	0.0475	0.0227	0.0161
CoV-NL63	0.21	0.0098	-0.0231	-0.0099
CoV-229E	0.1407	0.0388	-0.0081	-0.0016
CoV-HKU1	0.1204	0.062	-0.0507	-0.0612

RBD Titer Correlation to Neutralization

X	Prob	1-Specificity	Sensitivity	Sens-(1-Spec)	
.	.	0.0000	0.0000	0.0000	
9.480000	1.0000	0.0000	0.9286	0.9286	
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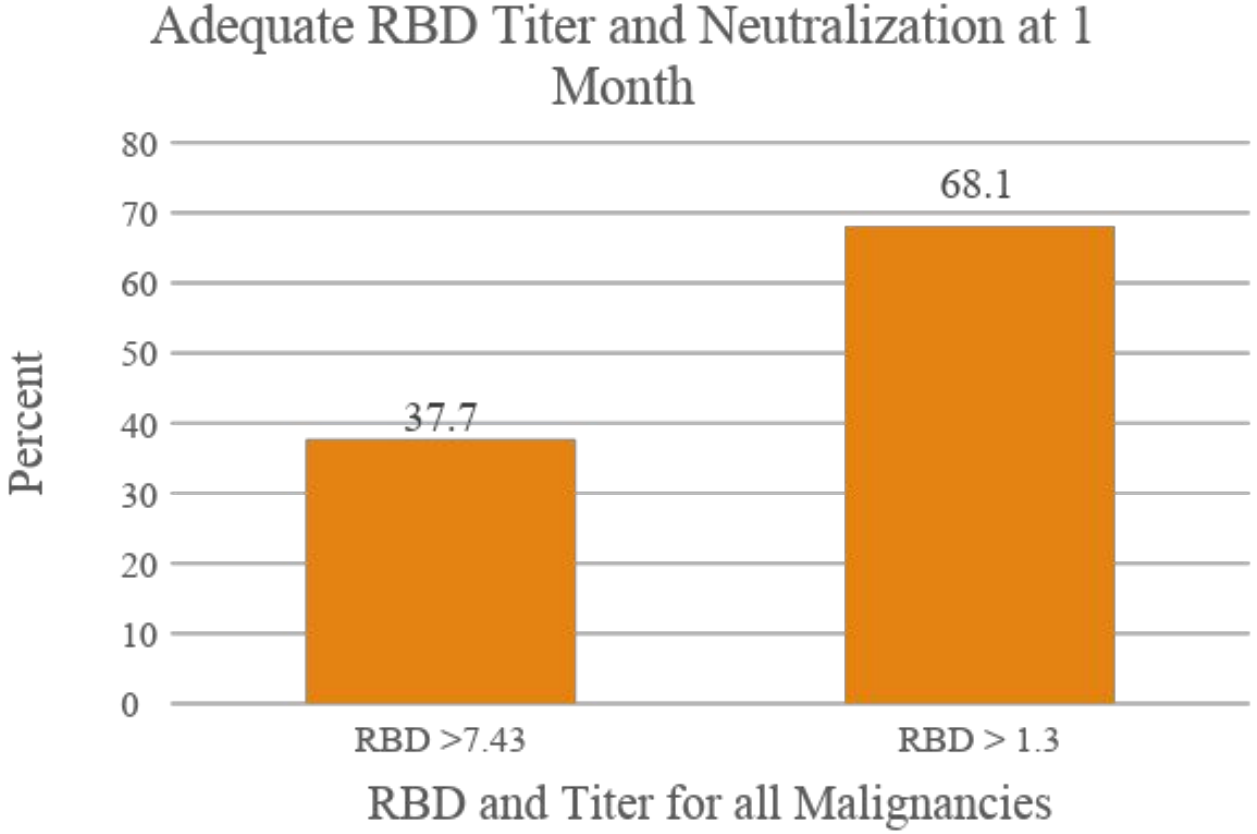
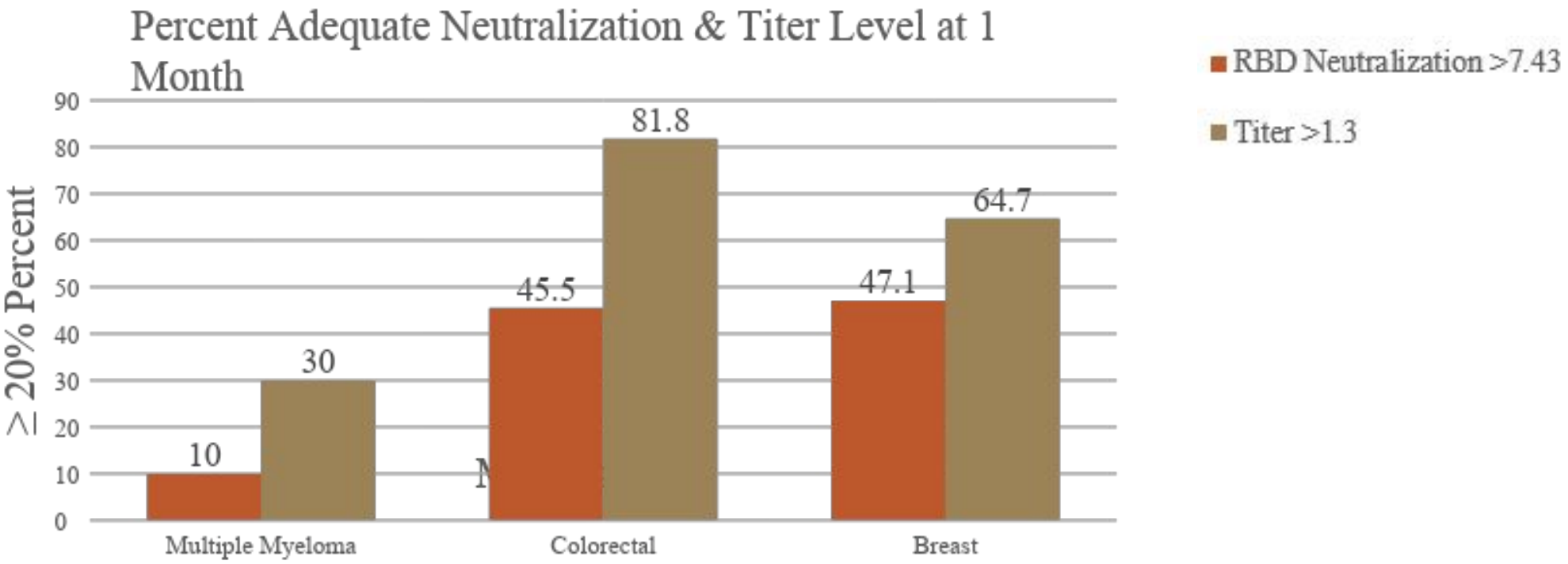
0.040000	0.0000	1.0000	1.0000	0.0000	
0.040000	0.0000	1.0000	1.0000	0.0000	

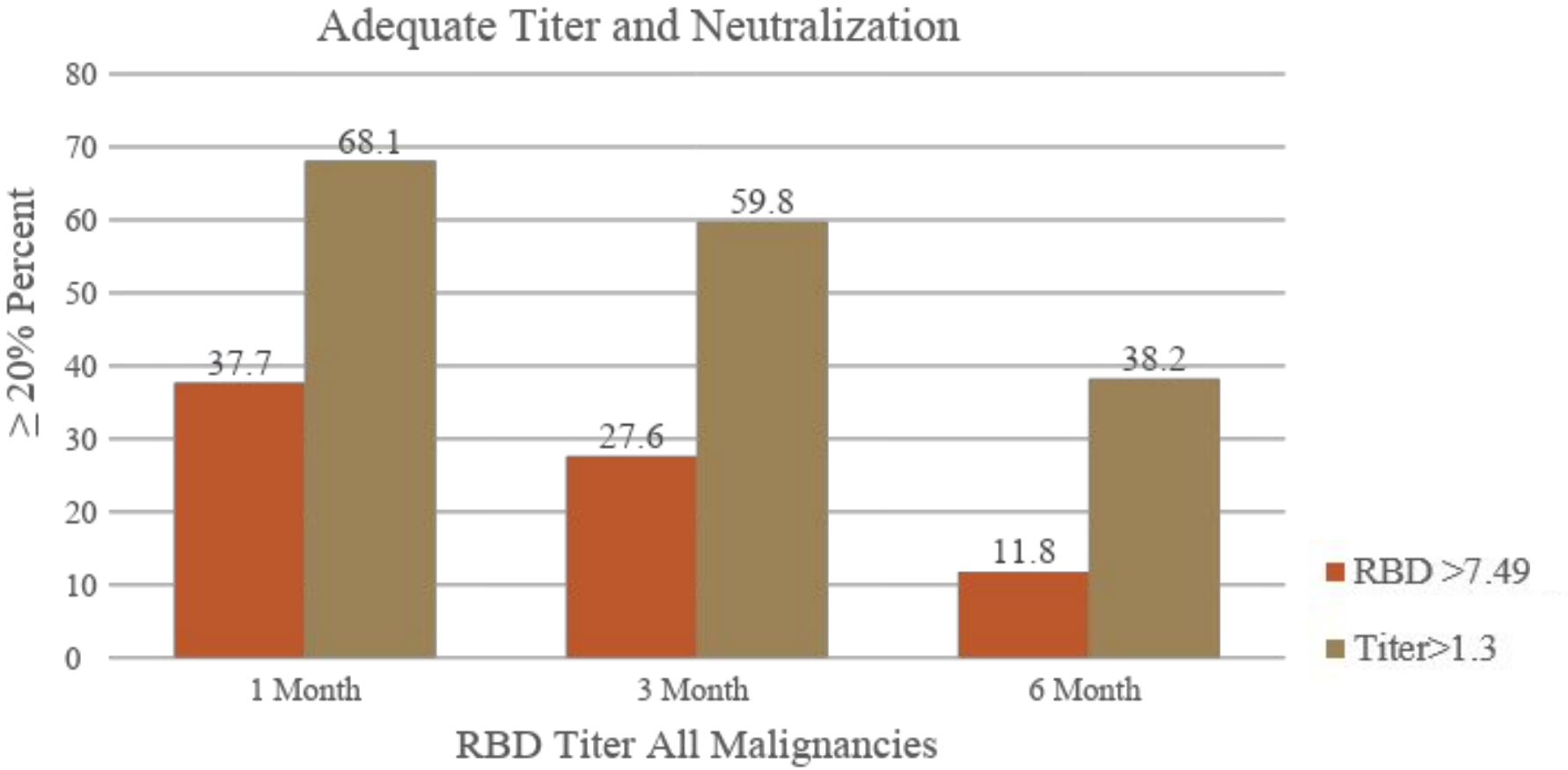
- 37.7% of all patients exhibited adequate titer response at month 1



Neutralization Correlating to Detectable RBD Titers at 1 Month



RBD Titer Correlation to Neutralization



Break Through Infections

Disease	Therapy	Vaccine	Time of Infection after vaccination
Multiple Myeloma	Daratumumab, dexamethasone	Pfizer	4 months
Multiple Myeloma	Daratumumab, bortezomib, dexamethasone	Pfizer	5 months
Multiple Myeloma	Daratumumab	Pfizer	5 months*
Primary Myelofibrosis	Ruxolitinib	Moderna	6 months
Waldenstrom Macroglobulinemia	Ibrutinib	Moderna	6 months*

*Patient died from COVID-19

Other Notable Non-Responders

Malignancy	Treatment	Number of Patients	Detectable Titers at 1 month
CLL	Ibrutinib	2	0
Breast	ddAC+T	4	0
Ewing Sarcoma	Irinotecan+ Temodar	1	0

Conclusion

- Vaccination against SARS-CoV-2 appears safe in patients with active malignancies undergoing cancer-targeted therapies

- Titers levels decay over six months but do not decay in patients with B-cell malignancies (due to limited response)

- Blunted response to vaccination were observed in patients receiving:
  - B cell malignancy therapies (notably Multiple Myeloma)
  - Breast cancer receiving: doxorubicin, cyclophosphamide and paclitaxel

Conclusion

- Vaccination with COVID-19 vaccines do not appear to provide protection against common coronavirus strains in this population

- Adequate titers do no correlate to adequate neutralization
  - 37.7% of patients able to adequately neutralize at 1 month
  - 11.8% adequate neutralization by month 6

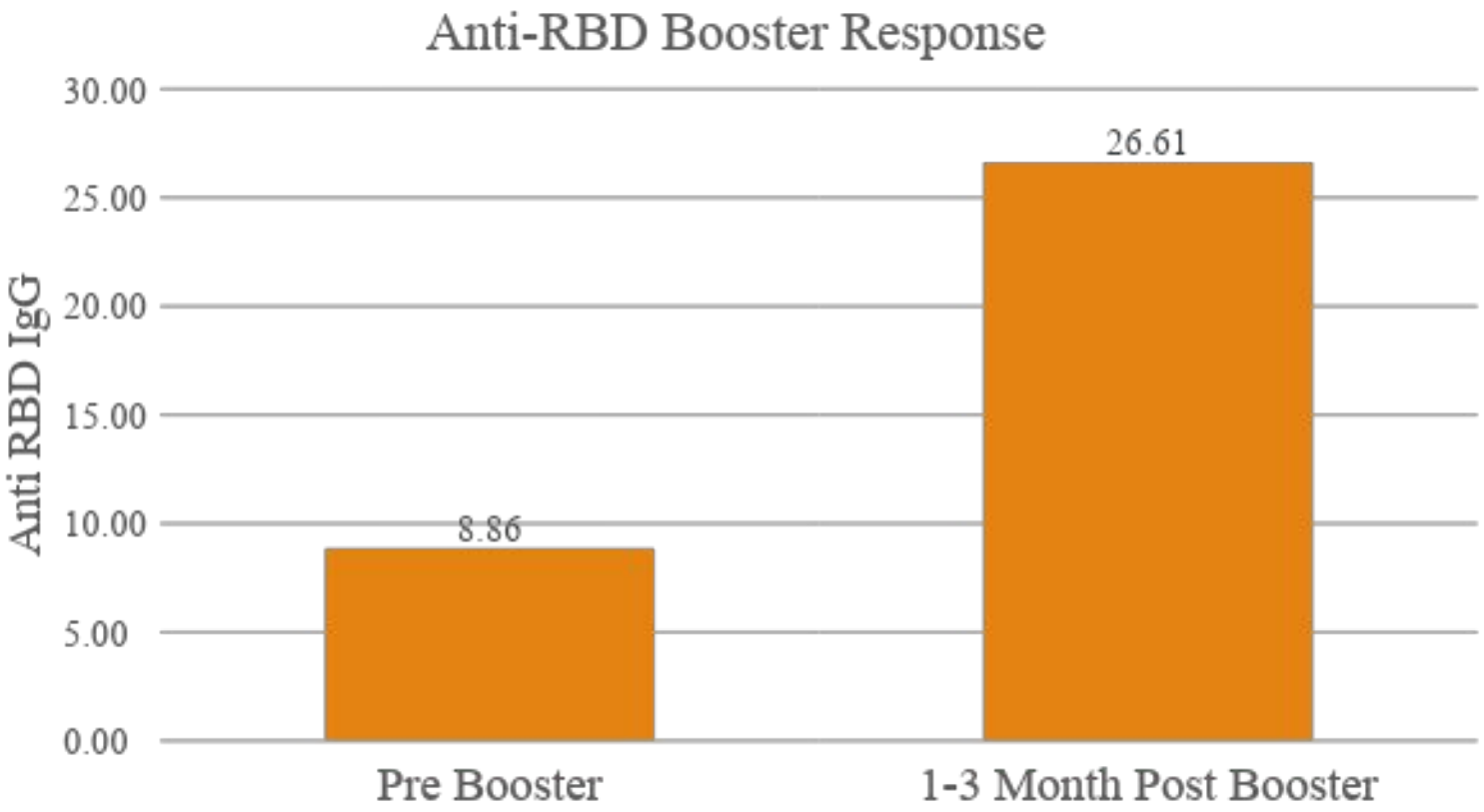
- Breakthrough infections observed in hematologic malignancies:
  - Multiple myeloma, Waldenstrom macroglobulinemia, primary myelofibrosis
  - Two patients died from COVID-19 between 5-6 months after vaccination

Research Team

Dr. Chung-Ting Kou, Manuel Caballero, Dr. Tom Gibbons, Dr. Jason Okulicz, Dr. James Aden, Patricia Blas, Peggy Smith, Dr. Joshua Fenderson

Questions

Boosters


Anti-RBD Booster Response
Anti RBD IgG
30.00
25.00
20.00
15.00
10.00
5.00
0.00
8.86
26.61
Pre Booster
1-3 Month Post Booster