COVID-19 Vaccine Responsiveness in Patients with Multiple Myeloma and Waldenstrom’s Macroglobulinemia

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Disclosures:

Consultant: Adaptive Biotechnologies, BeiGene, CSL Behring, Karyopharm Therapeutics, Pharmacyclics, Sanofi-Genzyme.
Plasma cell dyscrasias such as multiple myeloma (MM) and Waldenstrom’s macroglobulinemia (WM) are associated with immunoparesis due to both hypogammaglobulinemia and various alterations of cellular immunity.

Immunodeficiency is manifested by an increased risk for infections and diminished response to routine vaccinations.

Approved and emergency use authorization COVID-19 vaccines are designed to elicit SARS-CoV-2 spike protein (S) Abs in healthy individuals. There are no established titers to determine clinical protection.

Cancer patients particularly hematologic malignancies have higher risk of severe COVID-19 infections. Specific immune responses and degree of clinical protection following COVID-19 vaccines are unknown for MM and WM patients.
COVID-19 Vaccine Response Trial

Study of COVID-19 Vaccine Responsiveness in Patients with Multiple Myeloma and Waldenstrom’s Macroglobulia

• Prospective clinical trial open and Enrolling at Massachusetts General Hospital (MGH) and Dana-Farber Cancer Institute (DFCI)

• Clinicaltrials.gov (NCT04830046)
• PI: Andrew Branagan, MD, PhD (MGH)
• DFCI Site-PIs: Shayna Sarosiek, MD (WM) and Clifton Mo, MD (MM)
• Corollary Immune Studies: Galit Alter MD and Boris Juleg, MD, PhD (Ragon Institute)
Clinical Trial Schema

- **Myeloma Patients**
  - **Cohort 1: Myeloma**
  - **COVID-19 Vaccine**
    - 1 month post vaccine labs
    - 2nd COVID-19 vaccine (if a 2-dose series)
  - Surveillance visits and labs: 6, 9*, 12 mo.
- **WM Patients**
  - **Cohort 2A: WM Treatment Naïve**
  - **Cohort 2B: Active BTK Inhibitor**
  - **Cohort 2C: Current or previous WM treatment**
  - 2nd COVID-19 vaccine (if a 2-dose series)
  - 1 month post 2nd vaccine labs
  - Surveillance visits and labs: 6, 9*, 12 mo.
- *Month 9 visit and labs are recommended
Primary objective:

- To investigate the rate of anti-spike protein SARS-CoV-2 antibodies 28 days following complete COVID 19 vaccination

Secondary objectives:

- To investigate the durability of immune responses

- To investigate clinical correlates of immune response

- To investigate rates of COVID-19 infections within the study period.

- To evaluate functional antibody and cell-mediated immune responses to COVID-19 vaccination; including gene expression profiling, comprehensive systems serology, and SARS-CoV-2-specific T-cell subsets.
SARS-CoV-2 Spike Protein (S) Antibody Detection:

• Roche Elecsys anti-SARS-CoV-2 S Ab assay used to assess primary endpoint Ab responses. Range 0.08 to 2,500 U/mL.

• There are no FDA approved or established spike Ab titers to determine clinical protection. Elecsys assay titers 100-500 U/mL are most associated with neutralization of SARS-CoV-2 virus.
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All (n=134)</th>
<th>MM (n=89)</th>
<th>WM (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>66 (59-71)</td>
<td>65 (59-71)</td>
<td>66.5 (60-71)</td>
</tr>
<tr>
<td>Age greater than 75, n (%)</td>
<td>15 (11.2)</td>
<td>10 (11.2)</td>
<td>5 (11.1)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>74 (55.2)</td>
<td>48 (53.9)</td>
<td>26 (57.8)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>122 (91)</td>
<td>79 (88.9)</td>
<td>43 (95.6)</td>
</tr>
<tr>
<td>Non-white</td>
<td>12 (9)</td>
<td>10 (11.2)</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>COVID-19 vaccine, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNT162b2</td>
<td>72 (53.7)</td>
<td>45 (50.6)</td>
<td>27 (60)</td>
</tr>
<tr>
<td>mRNA-1273</td>
<td>49 (36.6)</td>
<td>34 (38.2)</td>
<td>15 (33.3)</td>
</tr>
<tr>
<td>JNJ-78436735</td>
<td>13 (9.7)</td>
<td>10 (11.2)</td>
<td>3 (6.7)</td>
</tr>
<tr>
<td>Involved heavy chain and/or light chain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>-</td>
<td>42 (47.2)</td>
<td>-</td>
</tr>
<tr>
<td>IgA</td>
<td>-</td>
<td>16 (18)</td>
<td>-</td>
</tr>
<tr>
<td>Kappa FLC</td>
<td>53 (60)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lambda FLC</td>
<td>22 (24.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MYD88 mutational status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYD88 mutant</td>
<td>-</td>
<td>-</td>
<td>34 (79)</td>
</tr>
<tr>
<td>MYD88 wild-type</td>
<td>-</td>
<td>-</td>
<td>7 (15.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>-</td>
<td>-</td>
<td>3 (6.7)</td>
</tr>
<tr>
<td>CXCR4 mutational status, n (%)</td>
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<td></td>
</tr>
<tr>
<td>CXCR4 mutant</td>
<td>-</td>
<td>-</td>
<td>12 (26.1)</td>
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<tr>
<td>CXCR4 wild-type</td>
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<td>11 (24.4)</td>
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<tr>
<td>Unknown</td>
<td>-</td>
<td>-</td>
<td>21 (46.7)</td>
</tr>
<tr>
<td>Prior ASCT, n (%)</td>
<td>27 (20.1)</td>
<td>27 (30.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>History IVIG use within 90 days, n (%)</td>
<td>18 (12.7)</td>
<td>14 (15.7)</td>
<td>3 (6.7)</td>
</tr>
<tr>
<td>Treatment status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously treated</td>
<td>115 (85.8)</td>
<td>83 (93.3)</td>
<td>32 (71.1)</td>
</tr>
<tr>
<td>Treatment naive</td>
<td>19 (14.2)</td>
<td>6 (6.7)</td>
<td>13 (28.9)</td>
</tr>
<tr>
<td>Current line of therapy, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First line</td>
<td>60 (44.8)</td>
<td>43 (48.3)</td>
<td>17 (37.8)</td>
</tr>
<tr>
<td>Second line</td>
<td>32 (23.9)</td>
<td>25 (28.1)</td>
<td>7 (15.6)</td>
</tr>
<tr>
<td>Third line or greater</td>
<td>23 (17.2)</td>
<td>15 (16.9)</td>
<td>8 (17.8)</td>
</tr>
<tr>
<td>Hypogammaglobulinemia, n (%)*</td>
<td>31/129 (24)</td>
<td>20/87 (23)</td>
<td>11/42 (26.2)</td>
</tr>
<tr>
<td>IgG, median (IQR)</td>
<td>541 (403.5-780.5)</td>
<td>549.0 (406-876)</td>
<td>483 (348.5-741)</td>
</tr>
</tbody>
</table>

*IgG <400 mg/dL
Median SARS-CoV-2 Spike Ab Titers After Complete Vaccination

<table>
<thead>
<tr>
<th>Patients</th>
<th>COVID-19 spike antibody test – titer (U/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25th Percentile</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>14.05</td>
</tr>
<tr>
<td>Waldenstrom’s macroglobulinemia</td>
<td>0</td>
</tr>
</tbody>
</table>
SARS-CoV-2 Spike Ab Responses Myeloma vs. Waldenstrom’s macroglobulinemia

% of Patients with Detectable SARS-CoV-2 Spike Ab

- 91% (Multiple Myeloma)
- 57.80% (Multiple Myeloma)
- 46.10% (Waldenstrom’s macroglobulinemia)
- 24.40% (Waldenstrom’s macroglobulinemia)

- Any positive spike Ab
- Positive Spike Ab >250 U/mL
SARS-CoV-2 Spike Ab Responses in Pts Stratified Age

- Age <75 years:
  - Spike Ab Titer ≤250 U/mL: 57.98%
  - Spike Ab Titer >250 U/mL: 42%

- Age ≥75 years:
  - Spike Ab Titer ≤250 U/mL: 13%
  - Spike Ab Titer >250 U/mL: 86.67%

P<0.05
SARS-CoV-2 Spike Ab Response Based on Specific COVID-19 Vaccine

Response in All Patients Based on Vaccine

- **Comirnaty (Pfizer/BioNTech) (BNT162b2)**: 72.22%
- **Moderna COVID-19 Vaccine (mRNA-1273)**: 61%
- **Johnson and Johnson (JNJ-78436735 (formerly Ad26.COV2.S))**: 84.62%

* *p<0.001

Specific COVID-19 Vaccine Received
SARS-CoV-2 Spike Ab Responses in WM Pts Stratified by Study Cohort

**Cohort 2A**
- Treatment naïve WM patients
- 36.36%

**Cohort 2B**
- WM patients receiving BTK inhibitor
- 10%
- 90.00%

**Cohort 2C**
- Currently or previously treated WM patients
- 14%

* p<0.05
SARS-CoV-2 Spike Ab Responses in WM Pts
Stratified by BTK and Rituximab Treatment Status

Rituximab Treatment Within 6 months

- **No**: 31%
- **Yes**: 0%

*p<0.05*
SARS-CoV-2 Spike Ab Responses in MM Pts
Stratified by IMiD, CD38 mAb, and PI Treatment Status

Active IMiD
- Spike Ab Titer ≤250 U/mL: 50.00%
- Spike Ab Titer >250 U/mL: 50%

Active CD38 mAb
- Spike Ab Titer ≤250 U/mL: 63.64%
- Spike Ab Titer >250 U/mL: 36%

Active PI
- Spike Ab Titer ≤250 U/mL: 67.65%
- Spike Ab Titer >250 U/mL: 32%
SARS-CoV-2 Spike Ab Responses in Patients with ALC less than 1000 cells/L

MM Patients

- ALC ≥1000 cells/L: 32.43%
- ALC <1000 cells/L: 68%

WM Patients

- ALC ≥1000 cells/L: 73.33%
- ALC <1000 cells/L: 9%

*p=0.001
SARS-CoV-2 Spike Ab Responses Stratified by Previous Lines of Treatment

**#MM Lines of Therapy**
- First Line: 63%
- Second Line or Greater: 72.5%

**#WM Lines of Therapy**
- First Line: 12%
- Second Line or Greater: 13.33%

*p=0.001*
SARS-CoV-2 Spike Ab Responses in MM Patients Stratified by Disease Response Status

**MM Disease Response**

- PD: 70.00%
- VGPR or better: 45.28%, 55%
- Asymptomatic: 50.00%, 50%

**WM Disease Response**

- PD: 66.67%
- VGPR or better: 90.00%
- Asymptomatic: 10.00%, 10%

*p<0.05*
Conclusions

• Preliminary data suggest poor COVID-19 spike Ab responses in patients with MM and WM, WM patients showed more severe impairment of adequate spike Ab response compared to MM, 24% vs. 58%

• MRNA-1273 (Moderna) elicited highest spike Ab response rates followed by BNT162b2 mRNA (Pfizer/BioNTech), followed by JNJ-78436735

• Older age >75 years was associated with significantly lower spike Abs in WM and MM

• Among MM patients, progressive disease, 2+ prior lines of therapy, and ALC count <1K associated with significantly lower spike Abs

• Asymptomatic and most previously untreated WM patients achieved adequate spike Ab responses however the most significant reduction in spike Abs were seen in patients actively treated with BTK inhibitors or rituximab within 6 months

• Longitudinal spike Ab responses, comprehensive functional antibody responses, SARS-CoV-2 specific T cell responses, and COVID-19 strain-specific responses are ongoing

• Further understanding of immune responses to vaccination is needed to clarify patient risks, and need for boosters or alternative protective measures against COVID-19.
Thank you!!

All Our Patients

MGH Center for Multiple Myeloma
Thank you!!

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MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Dana-Farber Cancer Institute

Ragon Institute of MGH, MIT and Harvard