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Patient-reported safety and tolerability of the COVID-19 vaccines in persons with rare neuroimmunological diseases

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ABSTRACT

Background: The COVID-19 vaccines are currently recommended for people with rare neuroimmunological diseases such as neuromyelitis optica spectrum disorder (NMOSD), MOG-antibody disease (MOGAD), and transverse myelitis. However, the safety profile of the vaccines in this population is uncertain.

Objective: To report real-world safety data of the COVID-19 vaccines in persons with rare neuroimmunological diseases.

Methods: An anonymous survey was distributed to patients recruited on social media. Participants answered general demographic and disease-related questions, and specific questions about their experiences with the COVID-19 vaccines.

Results: 438 participants completed the questionnaire. The median age was 51 (range 18–82 years); 366 were female (83.6%); 102 (23.3%) had associated comorbidities, and 354 (80.1%) were treated with immunotherapies. 242 participants (55.3%) reported a diagnosis of NMOSD; 99 (22.6%) had MOGAD; 79 (18%) had transverse myelitis. 239 participants (66.2%) were younger than 55 years of age. 138 participants (31.5%) reported early adverse events. Of these, 93 (67.4%) were <55 years old, and 45 (32.6%) were >55 years old (p=0.0086). The most common adverse events were local reactions, including pain, redness, and swelling at the injection site, reported by 155 participants (35.4%). 73 participants (16.7%) reported new or worsening neurological symptoms following the vaccination. Most symptoms occurred within the first week after vaccination and resolved within three days.

Conclusions: This survey indicates an overall favorable safety and tolerability profile of the COVID-19 vaccines among persons with rare neuroimmunological diseases. Longer-term studies are warranted to confirm these data.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Atzrodt et al., 2020). SARS-CoV-2 is a single-stranded, positive-sense RNA genome-bearing virus that belongs to the Coronaviridae family (Siddell et al., 1983). COVID-19 was first reported to the World Health Organization (WHO) on December 31, 2019. On March 11, 2020, COVID-19 was declared a global pandemic (Cucinotta and Vanelli, 2020). The disease is associated with rapid spread and significant morbidity and mortality (Machhi et al., 2020; Wiersinga et al., 2020).

To control the pandemic, a global effort supported by academic, industrial, and governmental sectors focused on developing effective vaccines. This effort led to the approval of three vaccines by the Food and Drug Administration (FDA), while another vaccine has been authorized in the European Union (EU), and others are approaching the final stages of clinical trials and are expected to be approved in the near future (Li et al., 2021; Rawat et al., 2021).

Two of the currently FDA-approved vaccines include two types of mRNA encoding for the full-length spike protein (mRNA-1273, Moderna TX, Inc) or its receptor-binding domain (BNT162b2, BioNTech-Pfizer). The third vaccine, developed by Janssen Pharmaceutical Companies of Johnson & Johnson, is a viral-vector vaccine that uses a replication-defective adenovirus that expresses the full-length spike glycoprotein (Ad26.COV2.S vaccine). The EU – approved vaccine, developed by researchers at Oxford University and AstraZeneca, is a viral-vector vaccine. Other vaccines currently in use include the viral-vector vaccine developed by the Gamaleya National Research Centre for Epidemiology and Microbiology (Russian Federation) and an inactivated whole SARS-CoV-2 virus vaccine developed by the Wuhan Institute of Biological Products.
and Sinopharm (Kaur and Gupta, 2020; Li et al., 2021; Poland et al., 2020; Rawat et al., 2021).

While the incidence of COVID-19 infection among people with neuroimmunological diseases seems similar to the general population (Fan et al., 2020), a recent study reports a higher risk of hospitalization, including hospitalization in intensive care units, among NMOSD patients who are older and more severely disabled (Alonso et al., 2021). Therefore, developing effective measures to prevent the infection is of paramount importance.

The approved vaccines have been tested in large-scale phase 3 trials, which recruited both healthy individuals and people with some chronic medical conditions (Polack et al., 2020). Although the COVID-19 vaccine trials excluded most people with neurological and autoimmune diseases, many expert committees recommend their use among patients with various neurological disorders, including multiple sclerosis (MS, 2021a; MS, 2021b; MS, 2021c; MS, 2021e). Given that the Centers for Disease Control and Prevention (CDC) recommends that people with autoimmune and inflammatory disorders receive the COVID-19 vaccines (2021d), they are being administered to people with MS and other immune-mediated diseases of the central nervous system (CNS), including neuromyelitis optica spectrum disorder (NMOSD), MOG-antibody disease (MOGAD) and transverse myelitis (TM). However, the lack of information regarding the safety and efficacy of the vaccines in this specific population is a cause of uncertainty for both patients and physicians.

The aim of this study is to report real-life data on the safety and tolerability of the COVID-19 vaccines in people with rare autoimmune diseases of the CNS.

2. Materials and methods

This study was conducted using an anonymous questionnaire that was distributed online through ‘The NMO Clinic’ Facebook group, a closed group of approximately 3,700 members with international representation.

In the first part of the questionnaire, participants were asked general demographic and disease-related questions, including age, gender, use of disease-modifying therapies, and associated comorbidities.

The second part of the questionnaire was dedicated to the safety profile of the COVID-19 vaccine. In this section, participants were asked if they received the vaccine (one or two doses), date of vaccination, presence and type of early reactions to the vaccine (pain/redness/swelling at the injection site, generalized muscle pain, headache, dizziness, fever, chills, fatigue, or other), as well as presence, type, and timing of new or worsening neurological symptoms following the vaccination. In case of worsening neurological symptoms after the vaccination, additional information regarding the need for specific treatment and the duration of symptoms was inquired.

The study data was collected and managed using REDCap, an electronic data capture tool (Harris et al., 2019; Harris et al., 2009) from December 2020 to May 2021. Data analysis was performed between May 10, 2021, and May 18, 2021.

2.1. Standard protocol approvals, registrations, and patient consents

The study was approved by the Massachusetts General Hospital institutional review board (protocol #2019P003556). An invitation with a link to the survey was posted on ‘The NMO Clinic’ Facebook page on December 31, 2020, and remained open to members to contribute data through May 10. Informed consent was implied upon participation.

2.2. Statistical analysis

Statistical analysis was performed using GraphPad Prism version 9.1.2 (GraphPad Software, San Diego, CA, USA).

Descriptive statistics are presented as total counts and percentages, median and range. Fisher’s exact test was used for comparison of non-parametric variables between groups.

3. Results

3.1. Demographic and disease-related characteristics of the study population

Four hundred and thirty-eight participants completed the questionnaire. The median age was 51 (range 18–82 years); 366 were female (83.6%). Three hundred and sixty-seven participants (83.7%) were residents of the US, and 330 (75.3%) were white. Two hundred and forty-two participants (55.3%) reported a diagnosis of NMOSD; 99 (22.6%) had MOGAD; 79 (18%) had transverse myelitis; 11 (2.5%) had recurrent optic neuritis; 6 (1.4%) had acute demyelinating encephalomyelitis (ADEM); and 1 (0.3%) had isolated optic neuritis. One hundred and twenty participants (27.4%) reported associated comorbidities, including lung disease (49 participants, 11.2%), diabetes mellitus (22 participants, 5.1%), hypertension (19 participants, 4.4%), malignancy (17 participants, 3.9%), and heart disease (13 participants, 3%).

Three hundred and fifty-four participants (80.1%) were treated with immunotherapies. Of these, 172 (48.6%) were on rituximab.

Table 1 summarizes the demographic and disease-related characteristics of the study population.

3.2. Rate of early adverse events following the COVID-19 vaccines

Of the total of 438 participants, 251 participants (57.3%) received the Pfizer (BNT162b2) vaccine; 153 (34.9%) received the Moderna vaccine; 32 (7.3%) received the AstraZeneca vaccine, and 2 participants (0.4%) received the Johnson & Johnson vaccine. Of those participants who received the Pfizer vaccine, 110 (43.8%) responded to the survey after one dose, and 141 (56.2%) responded after having received two doses; from those who received the Moderna vaccine, 72 (47%) responded after one dose, and 81 (53%) responded after two doses. Of those who received the AstraZeneca vaccine, 28 (87.5%) responded after one dose, and 4 (12.5%) responded after two doses. The Johnson & Johnson vaccine is given in a single dose only. For those who responded after receiving one dose of the vaccine, the mean time between vaccination and data analysis was 77.5 ± 95.5 days (median 74 days, range 5–145 days); for those who responded after receiving two doses, the mean time between the second dose to data analysis was 58.74 ± 29.62 days (median 56 days, range 4–124 days).

One hundred and thirty-eight participants (31.5%) reported early adverse events following the COVID-19 vaccine. Of those who responded after one dose of the vaccine, 57 participants (26.9%) experienced adverse events. Of those who received two doses of the vaccine, 87 participants (38.5%) reported early adverse events (Table 2). Local reactions, including pain, redness, and swelling at the injection site, were the most common adverse events, reported by 155 participants (35.4%), followed by headache, muscle pain, fatigue, fever, chills, and dizziness (Table 3).

Of those who reported early adverse events, 93 participants (67.4%) were < 55 years old, and 45 (32.6%) were ≥ 55 years old (p = 0.0086). Three hundred and fifty-four participants (80.1%) were treated with immunotherapies. Of these, 125 participants (35.3%) reported adverse events. Among the 84 participants who were not treated with immunotherapies, 27 (32.1%) reported adverse events (p = 0.6124).

Two hundred and forty-three participants treated with immunotherapies were younger than 55 years of age (68.6%), and 111 (31.4%) were older than 55. Ninety-eight participants in the young-age group (40.3%) and 35 participants in the old-age group (31.5%) reported adverse events (p = 0.1249).

Of the participants treated with immunotherapies, 182 (51.4%) were treated with B-cell depleting agents (172 participants were treated with rituximab, 10 with ocrelizumab, and 2 with inebilizumab). Of these, 61
Table 1
Demographic and disease-related characteristics of survey participants.

| Demographic or disease-related characteristic | Number of participants |
|----------------------------------------------|------------------------|
| Total                                        | 438                    |
| Female (%)                                   | 366 (83.6%)            |
| Age (median; range)                          | 51; range 18-82        |
| Age < 55 years old                          | 239 (66.2%)            |
| Diagnosis                                    |                        |
| MOGAD                                        | 242 (55.3%)            |
| Transverse myelitis                          | 79 (18%)               |
| Recurrent optic neuritis                     | 11 (2.5%)              |
| Isolated optic neuritis                      | 1 (0.3%)               |
| ADEM                                         | 6 (1.4%)               |
| Country of residency                         |                        |
| USA                                          | 367 (83.8%)            |
| United Kingdom                               | 37 (8.5%)              |
| Canada                                       | 10 (2.3%)              |
| Australia                                    | 6 (1.4%)               |
| France                                       | 3 (0.6%)               |
| Ireland                                      | 2 (0.4%)               |
| Israel                                       | 2 (0.4%)               |
| Austria                                      | 1 (0.2%)               |
| Egypt                                        | 1 (0.2%)               |
| Finland                                      | 1 (0.2%)               |
| Honduras                                     | 1 (0.2%)               |
| New Zealand                                  | 1 (0.2%)               |
| Germany                                      | 1 (0.2%)               |
| Denmark                                      | 1 (0.2%)               |
| Poland                                       | 1 (0.2%)               |
| Switzerland                                  | 1 (0.2%)               |
| United Arab Emirates                         | 1 (0.2%)               |
| Race/ethnicity *                             |                        |
| White                                        | 330 (75.3%)            |
| Hispanic/Latino                              | 28 (6.4%)              |
| Black/African American                       | 16 (3.6%)              |
| Asian                                        | 9 (2%)                 |
| First/Native/Indigenous people               | 3 (0.6%)               |
| Hawaiian/Pacific islander                    | 2 (0.4%)               |
| Other                                        | 7 (1.6%)               |
| Associated comorbidities                     | 120 (27.4%)            |
| Lung disease                                 | 49 (11.2%)             |
| Diabetes mellitus                            | 22 (5.1%)              |
| Hypertension                                 | 19 (4.4%)              |
| Malignancy                                   | 17 (3.9%)              |
| Heart disease                                | 13 (3%)                |
| Treated with immunotherapy                   | 354 (80.1%)            |
| Rituximab                                    | 172 (48.6%)            |
| Mycophenolate mofetil                        | 41 (11.5%)             |
| Oral corticosteroids                         | 33 (9.3%)              |
| IVIG                                         | 27 (7.6%)              |
| Azathioprine                                 | 21 (5.9%)              |
| Eculizumab                                   | 17 (4.8%)              |
| Tocilizumab                                  | 7 (1.9%)               |
| Hydralazinechloroquine                      | 7 (1.9%)               |
| Satalizumab                                  | 6 (1.6%)               |
| Methotrexate                                 | 4 (1.2%)               |
| PLEX                                         | 4 (1.2%)               |
| Inebulizumab                                 | 2 (0.6%)               |
| Other                                        | 15 (4.3%)              |
| Ocrelizumab                                  | 10 (2.8%)              |
| SCIG                                         | 2 (0.6%)               |
| Ravalibilumab                                | 1 (0.03%)              |
| IVMP 1 g every 4 weeks                       | 1 (0.03%)              |
| Tofacitinab                                  | 1 (0.03%)              |

MOGAD = MOG-antibody disease
ADEM = Acute demyelinating encephalomyelitis
IVIG = Intravenous immunoglobulins
SCIG = Subcutaneous immunoglobulins
PLEX = Plasma exchange
IVMP = Intravenous methylprednisolone

* Some participants did not report their race/ethnicity
** Some participants reported more than one associated comorbidity

3.3. New or worsening of neurological symptoms following the COVID-19 vaccines

Seventy-three participants (16.7%) reported new or worsening neurological symptoms following the vaccination. Of these, 39 (53.4%) received the Pfizer vaccine, 25 (34.2%) received the Moderna vaccine, and 9 (12.3%) received the AstraZeneca vaccine. The median age was 50 years (range 22–75 years; mean age 49.67 ± 13.3 years). Fifty-nine were women (80.8%), and 53 (72.6%) were treated with immunotherapies. Eighteen participants (24.6%) had associated comorbidities (seven lung disease, four - DM, five - hypertension, and two - heart disease).

The most common new or worsening neurological symptoms included sensory disturbances (i.e., numbness, tingling, and itching sensations, n = 48), increased pain (n = 31), muscle weakness (n = 30), gait instability (n = 17), visual symptoms (n = 13), and sphincteric problems (n = 13) (Table 4).

Twenty participants reported that the onset of new or worsening neurological symptoms occurred within the first 24 h after vaccination (27.4%); 40 participants (54.8%) reported the occurrence of new or worsening neurological symptoms within 2–7 days after vaccination; 6 participants (8.3%) reported the onset of new or worsening neurological symptoms between 8–14 days after vaccination; and 7 participants (9.6%) reported the onset of symptoms > 14 days after vaccination.

Sixty participants who reported new or worsening neurological symptoms (82.2%) did not require any additional treatment. Nine participants (12.4%) received corticosteroids (1 in conjunction with IVIG), 3 (4.2%) were treated with additional analgesics and 1 (1.4%) with antiemetic medications.

Thirty-eight participants (52.1%) reported that new or worsening neurological symptoms resolved within 1–3 days; in 11 participants (11.1%), the symptoms resolved within one week; in 7 participants (9.6%), the duration of symptoms was between 1–2 weeks; the remaining 17 participants (23.3%) reported that new or worsening neurological symptoms were still present when completing the survey. For these, the median time of symptoms was 3.5 days (range 1–32 days).

4. Discussion

Prior to this study, there have been no clinical data available on the safety (as well as the efficacy) of the COVID-19 vaccines in this specific autoimmune population, which created hesitation and uncertainty for both patients and their treating neurologists.

Vaccines are intended to provide protection against specific antigens, but in ramping up an immune response, rogue autoimmune elements may also become activated and potentially trigger an unwanted attack. Vaccine-associated attacks have been linked to neuroimmunological disorders including TM, optic neuritis, ADEM, and NMOSD (Agmon-Levin et al., 2009; Huynh et al., 2008; Karussis and Petrou, 2014; Mealy et al., 2018; Zanoni et al., 2002). Injuries are also potent triggers of attack; more than 40 cases of TM following COVID have been reported (Mondal et al., 2021; Schulte et al., 2021). In trying to balance the risks of vaccination vs. infection-triggered autoimmune attacks, vaccinations are generally favored as the lesser risk, especially in patients on immunosuppressive therapies. Immunosuppressive therapies may blunt the efficacy of a vaccine, but they may also blunt a potential vaccine-triggered event.

The current safety data of the COVID-19 vaccines are available from the Pfizer’s phase 3 clinical trial (Polack, Fernando P et al., 2020). In this study, the rate of adverse events was similar to that of other viral vaccines. Adverse events were more common among participants younger than 55 years of age compared to those older than 55. The most common (33.5%) reported adverse events, compared to 77 participants (67.5%) receiving other immunotherapies (p < 0.0001).

The rate and type of early adverse events are summarized in tables 2 and 3.
adverse event was pain at the injection site, reported by 83% of those younger than 55 years of age, and by 71% of those older than 55 after the first dose, and by 78% of those younger than 55 years of age and 66% of those older than 55 after the second dose. Systemic adverse events were reported less frequently than the local reactions, and included fatigue, headache, fever, and chills. As seen in the general population, local reactions (i.e., pain, redness, and swelling at the injection site) were the most common adverse events reported by our survey participants. Also in line with what was reported in the general population, adverse events among NMOSD and MOGAD patients were more frequent in the young-age group (<55 years old) compared to older individuals (>55 years old). A possible explanation for this may be the more vigorous immune response mounted by younger people. In fact, the occurrence of adverse events following vaccination is thought to be mediated by immunological responses, therefore reflecting the activity of the immune system (Nakayama, 2019; Zhuang et al., 2021). As the immune system tends to gradually senesce with age (Müller et al., 2019; Sadighi Akha, 2018), older people often experience less pronounced side effects after vaccination (Spila-Alegiani et al., 1999; Tanizaki et al., 2016). However, the overall rate of adverse events among our survey respondents is lower than that reported in the general population (Polack, Fernando P et al., 2020). A possible explanation for this observation may be related to the fact that most of the participants in our survey were treated with immunosuppressants. If the rate of adverse events is indeed related to the activity of the immune system, people who are treated with immunosuppressive medications, as were most of the participants in our survey (in particular, those younger than 55 years old), may develop fewer adverse events following vaccination. Another interesting finding of our survey regards the rate of adverse events among the participants treated with B-cell depleting therapies (i.e., rituximab, ocrelizumab, and inebilizumab). While more than half of the participants (51.4%) were treated with one of these medications, the rate of adverse events reported in this group was significantly lower than that reported in the general population (Polack, Fernando P et al., 2020). A possible explanation for this might be the more vigorous immune response mounted by younger people. In fact, the occurrence of adverse events following vaccination is thought to be mediated by immunological responses, therefore reflecting the activity of the immune system (Nakayama, 2019; Zhuang et al., 2021). As the immune system tends to gradually senesce with age (Müller et al., 2019; Sadighi Akha, 2018), older people often experience less pronounced side effects after vaccination (Spila-Alegiani et al., 1999; Tanizaki et al., 2016). However, the overall rate of adverse events among our survey respondents is lower than that reported in the general population (Polack, Fernando P et al., 2020). A possible explanation for this observation may be related to the fact that most of the participants in our survey were treated with immunosuppressants. If the rate of adverse events is indeed related to the activity of the immune system, people who are treated with immunosuppressive medications, as were most of the participants in our survey (in particular, those younger than 55 years old), may develop fewer adverse events following vaccination. Another interesting finding of our survey regards the rate of adverse events among the participants treated with B-cell depleting therapies (i.e., rituximab, ocrelizumab, and inebilizumab). While more than half of the participants (51.4%) were treated with one of these medications, the rate of adverse events reported in this group was significantly lower than those treated with other immunotherapies. Whether this observation is
related to a specific role of B-cells in mediating the adverse events after vaccination should be evaluated in additional studies.

The occurrence of new or worsening neurological symptoms following the vaccination was reported by 16.7% of the participants in our survey. The most common symptoms were sensory disturbances, and only 17.8% of those who reported new or worsening neurological symptoms required medical treatment. This relatively low rate of new or worsening neurological symptoms following the COVID-19 vaccines, as well as the overall mild severity of those symptoms, is in line with prior data on other (non-live-attenuated) vaccines that were not related to an increased risk of clinical exacerbation of autoimmune diseases (Faraz and Correale, 2011; Glück and Müller-Ladner, 2008; Mailand and Frederiksen, 2017; Rondaan et al., 2019). Although 17 participants had not resolved their new or worsening neurological symptoms post-vaccination at the time they answered the survey, no participant reported having a relapse after getting the COVID-19 vaccines.

Hesitancy to receive the COVID-19 vaccines has been reported in a significant proportion of patients with MS (Diem et al., 2021; Ehde et al., 2021; Xiang et al., 2021), and is likely similar in NMOSD and MOGAD. The data reported here may be helpful in addressing the safety concerns related to the vaccines in this population.

This study has several limitations. First, the data was anonymously collected online, and diagnosis could not be confirmed by reviewing source records beyond patient reports of aquaporin-4 and MOG-antibody serostatus. Second, this study did not include a formal examination of the participants, and we could not evaluate those participants who reported new or worsening neurological symptoms for objective signs of relapse. Last, the patient population may not reflect the NMOSD population as a whole, as socioeconomic status, ethnic background, and physical disability can all affect patient access to social media. This may explain the high proportion of USA residents and white respondents in our sample. On the other hand, other group characteristics such as female predominance, age, and treatments are in line with other NMOSD cohorts reported in the literature (Bukhari et al., 2017; Flanagan et al., 2016; Jonsson et al., 2019; Mealy et al., 2012; Miyamoto et al., 2018).

### 5. Conclusions

The early safety and tolerability profile of the COVID-19 vaccines in people with rare neuroimmunological diseases seems favorable. The overall rate of adverse events may be lower in patients treated with immunotherapies, especially B-cell depleting agents. The rate of new or worsening neurological symptoms is relatively low, with most events being of mild severity, not requiring additional treatment, and resolving within a few days. These data should be validated in additional prospective, large-scale studies.

### Authors disclosures

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### CRediT authorship contribution statement

**Ityat Lotan:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing.

**Gabriela Romanow:** Methodology, Investigation, Writing – original draft.

**Michael Levy:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

### Declaration of competing interest

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### Table 4

| Frequency and type of new or worsening neurological symptoms. | Muscle weakness | Visual symptoms | Gait instability | Increased pain | Sensory disturbances | Sphincteric problems |
|-------------------------------------------------------------|----------------|----------------|-----------------|----------------|---------------------|---------------------|
| Number of responders (%) *                                   | 30 (6.8%)      | 13 (3%)        | 17 (3.9%)       | 31 (7.1%)      | 48 (11%)            | 13 (3%)             |
| Number of responders <55 years old (%) **                   | 19             | 11             | 10 (58.8%)      | 19 (61.3%)     | 29                  | 7                   |
| One dose                                                    | 8 (26.7%)      | 2 (15.4%)      | 6 (35.3%)       | 7 (22.6%)      | 9 (18.8%)           | 5 (38.5%)           |
| Two doses                                                   | 11 (36.7%)     | 9 (69.2%)      | 4 (23.6%)       | 12 (38.8%)     | 20                  | 2                   |
| Number of responders >55 years **                          | 11             | 2              | 7               | 12 (38.8%)     | 19                   | 6                   |
| One dose                                                    | 3 (19%)        | 0              | 3 (17.7%)       | 3 (9.7%)       | 7 (14.6%)           | 6 (41.6%)           |
| Two doses                                                   | 8 (26.7%)      | 2 (15.4%)      | 4 (23.6%)       | 9 (29.1%)      | 12 (25%)            | 6 (41.6%)           |
| Number of responders treated with immunotherapies (%) **    | 22             | 9              | 13 (76.5%)      | 24 (77.4%)     | 32                  | 9                   |
| One dose                                                    | 9              | 2              | 7               | 10 (32.3%)     | 10                   | 4                   |
| Two doses                                                   | 13             | 7              | 6               | 14 (45.2%)     | 22                   | 5                   |
| Number of responders not treated** with immunotherapies (%) | 8 (26.7%)      | 6 (46.2%)      | 4 (23.6%)       | 7 (22.6%)      | 16 (33.3%)          | 4 (30.8%)           |
| One dose                                                    | 5 (16.7%)      | 3 (23.1%)      | 3 (17.7%)       | 2 (6.5%)       | 7 (14.6%)           | 2 (15.4%)           |
| Two doses                                                   | 3 (10%)        | 3 (23.1%)      | 1 (5.9%)        | 5 (16.2%)      | 9 (18.8%)           | 2 (15.4%)           |

* Out of the total number of responders; some participants reported more than one event
** Out of the responders who reported the specific event
