

## **Progressive multifocal leukoencephalopathy (PML) – FDA-Requested Listening Session**

July 22, 2020

Objectives of session: To gain a better understanding of PML patient & caregiver perspectives on:

- Disease & symptom impact & burden
- Treatment burden
- Clinical trials – design, risk tolerance, and potentially clinically meaningful endpoints, etc.

*Discussions in FDA Listening Sessions are informal and not meant to replace, but rather complement, existing patient engagement opportunities in the Agency. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report summarizes the input provided by patients and those representing patients with PML at the meeting. To the extent possible, the terms used in this summary to describe specific manifestations of PML, and the health effects and impacts, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire PML patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.*

### **Perspectives on participation in PML clinical trials**

1. At any time after being diagnosed with PML, did you (or the PML patient you cared for) ever think about joining in a clinical trial that was studying an investigational treatment for PML? Why or why not?
  - Half of patients and caregivers indicated they would not or could not join a clinical trial. Patients and caregivers expressed concerns about drug interactions and changes in medication efficacy. Patients and caregivers also cited the following reasons for declining a clinical trial: symptoms from PML were similar to the progression of the underlying condition, condition drastically deteriorated by time diagnosis received, and the desire to get the primary condition under control.
  - Half of patients/caregivers stated they have or would participate in a clinical trial. Two patients/caregivers shared they would participate in a clinical trial since it is the only option, given there are currently no treatments or cures for PML. One patient shared the desire to contribute to the study of PML through participation in a clinical trial.
  - A caregiver added that the patient's participation in a clinical trial was a positive experience; however, it did not yield the results hoped for.
2. What aspects of a clinical trial of an investigational treatment for PML might make you (or the PML patient you cared for) *more or less likely* to want to participate in a PML clinical trial?
  - Half of patients/caregivers indicated that side effects, including potential drug interactions would make them less likely to want to participate in a PML clinical trial. Patients and caregivers added that the duration, severity, and invasiveness of the trial would also be a factor.
  - One patient said he would be anxious about a clinical trial with a placebo. In addition, the patient expressed concerns about cross reaction with existing therapy for underlying condition of Multiple Sclerosis (MS).

- Three patients/caregivers indicated they have or would participate in a PML clinical trial in an effort to advance medical research on the disease. A patient added he was more inclined to participate since researchers (of the clinical trial they participated in) spoke to his impressions and fears in a non-scientific, human manner.
3. Are there any aspects or features of a clinical trial that might *prohibit* you from participating?
- A patient reiterated their decision of nonparticipation in a placebo-based clinical trial. The patient added that PML medications do not work well with medication for underlying condition of MS.
  - Some patients and caregivers mentioned that the side effects of a clinical trial would affect their decision. A caregiver added that she would not participate if the possibility existed for patient's condition to worsen.
  - Patients and caregivers also referenced financial and schedule constraints as it relates to travel and costs related to clinical trials. Patients and caregivers expressed a desire to participate in clinical trials; however, a demanding schedule that takes them away from their children may prohibit participation.
4. Do you have any other thoughts about what scientists and researchers should consider when planning clinical trials that study potential treatments for PML?
- Responses from caregivers and patients varied. Caregivers and patients stated that researchers should consider drug interactions, as all PML patients possess underlying issues that may require drug treatment.
  - Multiple caregivers and patients spoke about the importance of effective communication between researchers and patients. Caregivers and patients indicated that medical professionals and researchers should communicate effectively with family members and patients, even if the patient has diminished ability to communicate. Caregivers and patients would like health care professionals to be transparent and communicate on a human level. They added that medical staff should be coached on how to care for patients with PML.
  - A caregiver stated that scientists and researchers should keep in mind that patients may be unable to afford studies and costs associated with studies.
  - A patient stated he would like to receive a summary of feedback or findings from research study after participation in trial.

#### Use of placebos in PML clinical trials

5. What are your thoughts about randomized, placebo-controlled trials for PML, in which *all* participants receive the best available care, and *some will receive an additional investigational treatment* while others will receive a placebo?

- More than half of caregivers and patients expressed uneasiness with placebo-controlled trials for PML. Some caregivers and patients believed placebo would waste valuable time and would defeat the purpose of treatment, given that a placebo would not address the goal of saving the patient's life. Some caregivers and patients expressed understanding the necessity for the placebo, but stated they would choose not to participate.
- A few caregivers and patients indicated they would have taken any opportunity to delay, reverse, or stop progression of symptoms, including participating in a trial with a placebo. They shared that this option was better than no option.

### **PML symptoms & disease burden**

6. As you think about the different PML symptoms you (or the patient you cared for) experience, which symptom(s) would you say is the most problematic, or impacts you (or them) the most?
  - Nearly all patients and caregivers cited short term memory as the most problematic symptom of PML. Patients stated that they experience difficulty recalling words and are unable to remember what was said hours or even moments ago. A patient shared memory loss resulted in the loss of one level of education and early retirement.
  - Some caregivers shared the difficulty and emotional struggle associated with observing patients deteriorate from the condition prior to their death. Caregivers shared that it is hard watching patients be reduced to a catatonic state.
  - Patients and caregivers also identify impulse control, tremors, extreme pain and emotion, as well as aphasia as impactful symptoms.
7. What do you feel is the biggest burden of living with PML?
  - Responses to this question varied. Two caregivers believed it was difficult for patients to observe the world around them with the inability to react. Caregivers shared that patients struggled to come to terms with losing their independence. Caregivers also noted that they and family members experience PTSD from observing patients' condition rapidly decline.
  - A patient identified the feeling of vulnerability associated with memory loss as the biggest burden of living with PML, adding that it never goes away.
  - Some patients and caregivers identified the lack of understanding surrounding PML as a major burden. Patients expressed having to go through life explaining why they do things differently or have difficulty remembering information.
  - Patients and caregivers also referenced short term memory loss, confusion, weakness, and loss of mobility in limbs as significant burdens of PML.

### **Partner organizations**

The National Organization for Rare Disorders (NORD) helped identify and prepare patient community participants.

The Reagan-Udall Foundation for the FDA assisted with producing the summary of this meeting. NORD and the Foundation were present during the listening session.

#### **FDA divisions represented**

- **Office of the Commissioner**
  - Patient Affairs Staff (*organizer*)
  - Attendees: Office of Orphan Products Development; Office of Combination Products
- **Center for Biologics Evaluation and Research (CBER)**
  - Requestors: Office of Tissues and Advanced Therapies, Division of Clinical Evaluation and Pharmacology/Toxicology, Clinical Hematology Branch; Office of Tissues and Advanced Therapies, Division of Clinical Evaluation and Pharmacology/Toxicology, General Medicine Branch I
  - Attendees: Office of Tissues and Advanced Therapies, Division of Clinical Evaluation and Pharmacology/Toxicology, General Medicine Branch II, Office of Vaccines Research and Review, Division of Vaccines and Related Products Applications, Clinical Review Branch 1, Office of Blood Research and Review, Division of Blood Components and Devices, Clinical Review Staff, Office of Compliance and Biologics Quality, Division of Inspection and Surveillance, Program Surveillance Branch, Office of the Director, Office of Vaccines Research and Review, Division of Vaccines and Related Products Applications, Clinical Review Branch 1
- **Center for Drug Evaluation and Research (CDER)**
  - Requestors: Office of Infectious Diseases, Division of Antivirals; Office of Neurology, Division of Neurology II; Office of Regulatory Operations, Division of Regulatory Operations for Neuroscience; Office of Medical Policy Initiatives, Division of Clinical Trial Quality
  - Attendees: Office of Neurology, Division of Psychiatry; Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine, Division of Rare Diseases and Medical Genetics; Patient Focused Drug Development Staff
- **Center for Devices and Radiological Health (CDRH)**
  - Office of Strategic Partnerships & Technology

#### **NIH Centers represented**

- Requestor: National Institute of Neurological Disorders and Stroke (NINDS)

#### **Patients and caregivers represented**

4 patients and 5 caregivers participated in the listening session representing a total of 8 PML patients.

- Patient ages ranged from 40 to 64 years old.
- Age of diagnosis varied. Patients' time of diagnosis ranged from less than a year ago to 10 years ago.

#### **Prior to the Listening Session, patients and caregivers shared:**

- PML symptoms: ambulation challenges, inability to speak or function, aphasia, confusion, tremors, loss of motor skills, complete loss of control of body and mind, weakness, loss of speech and vision, aggression, memory loss, aspiration, numbness, anxiety, and lack of strength, coordination
- Management of PML: Immunomodulatory treatments, Keytruda, Prednisone for inflammation, sleep medication, physical, cognitive, and occupational therapies, blood pressure medications, and Cymbalta for anxiety.

### **Financial Interest**

Caregivers/Patients did not identify any conflict of interest relevant to this listening session and are not receiving compensation.