

# Overview of Current and Emerging Therapies for Amyotrophic Lateral Sclerosis

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## Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by the loss of cortical and spinal motor neurons, leading to weakness, muscle atrophy, and, in a substantial number of patients, cognitive impairment.<sup>1,2</sup> A strong association between frontotemporal dementia (FTD) and ALS is now recognized, with between 20% and 50% of those with the disease developing FTD.<sup>3</sup> Most patients die of respiratory failure within 2 to 5 years of onset. There is no cure and just 2 drugs are approved for the disease, each of which can slow progression somewhat in selected patients.<sup>2</sup>

The majority of patients are diagnosed with sporadic ALS, whereas about 10% are diagnosed with the familial form of the disease. In both familial and sporadic forms of ALS, the symptoms are the same. In the United States, men are almost twice as likely as women to develop the sporadic form. Sporadic ALS is diagnosed at an average age of 55 years, but the familial form of the disease may manifest much earlier.<sup>4</sup> More than 5000 patients in the United States receive a diagnosis of ALS each year, and an estimated 20,000 are living with the disease. The overall prevalence in the United States is approximately 5 per 100,000 individuals.<sup>4,5</sup>

## Etiology and Presentation

The greatest risk factors for ALS are age and family history, with numerous genetic aberrations now identified. Since the first ALS genetic mutation was identified in 1993, more than 120 are now known to contribute to the disease.<sup>4</sup> Several other potential risk factors have been investigated, including exposure to pesticides, chemicals, and heavy metals; military service; athleticism; smoking; and viruses.<sup>6</sup>

The disease has a heterogenous presentation and is a diagnosis of exclusion, which can lead to diagnostic delays of up to 1 year (Table 1).<sup>7</sup> This, in turn, delays initiation of therapies that may improve symptoms and slow disease progression. Diagnosis combines clinical examination, nerve conduction studies and electromyography, and laboratory tests, and is typically made using the revised El Escorial criteria (Table 2).<sup>7,8</sup>

Patients with older age, bulbar-onset, early respiratory dysfunction, and a lower score on the Revised Amyotrophic Lateral Sclerosis

## ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a devastating, fatal neuromuscular disease. Most patients die within 2 to 5 years of diagnosis. The disease stems from death of upper and lower motor neurons leading to degeneration of motor pathways and the paralytic effects of the disease. The economic cost of the disease is not clear, with estimates ranging from about \$64,000 per year to \$200,000. Two drugs, riluzole and edaravone, are currently FDA approved for the treatment of ALS, and each provides modest benefits in mortality and/or function. Recent developments in the understanding of the underlying pathophysiologic processes that contribute to ALS have led to the development of numerous investigational therapies, with several now in phase 3 trials. This article highlights the oral tyrosine kinase inhibitor masitinib; the antisense drug tofersen; the humanized monoclonal antibody C5 complement inhibitor ravulizumab-cwvz; and mesenchymal stem cell (MSC)-neurotrophic factor (NTF) cells, a proprietary platform that induces autologous bone marrow-derived MSCs to secrete high levels of NTFs.

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For author information and disclosures, see end of text.

**TABLE 1.** Phenotypes of ALS<sup>7</sup>

Limb-onset ALS	About 70% of patients present with this form, which involves both upper and lower motor neuron dysfunction.
Bulbar-onset ALS	About 25% of patients present with this form, which manifests with swallowing and speech difficulties, with limb involvement occurring later in the disease.
Primary lateral sclerosis	This type is marked by slower progression, less weight loss, and only lower motor neuron signs in the first few years of the disease, although patients eventually develop upper motor neuron involvement. At that point, this type is called upper motor neuron-dominant ALS. Patients do, however, have a better prognosis than those with the more typical presentation of ALS.
Progressive muscular atrophy (PMA)	There is some debate as to whether this form is ALS. It initially involves lower motor neuron impairment, but eventually progresses to clinical signs of upper motor neuron involvement, at which point it is called lower motor neuron ALS. Autopsies find that 50%-66% of patients with PMA have corticospinal tract involvement.
ALS-plus syndrome	This type is diagnosed in patients with additional symptoms beyond upper and lower motor neuron involvement, including dementia, extrapyramidal manifestations, autonomic dysfunction, ocular motility disturbance, and/or sensory loss.

ALS, amyotrophic lateral sclerosis.

**TABLE 2.** Revised El Escorial Criteria<sup>7,8</sup>

The diagnosis of ALS requires:

- Clinical, electrophysical, or neuropathologic evidence of lower motor neuron degeneration
- Clinical, electrophysical, or neuropathologic evidence of upper motor neuron degeneration
- Evidence of progressive spread of symptoms or signs within a region or to other regions

Combined with the absence of:

- Electrophysiologic or pathologic evidence of other disease processes that might explain the patient's motor neuron degeneration
- Neuroimaging evidence of other diseases that might explain the observed clinical and electrophysiologic signs

ALS, amyotrophic lateral sclerosis.

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Functional Rating Scale (ALSFRS-R) have a poorer prognosis. Younger patients and patients with limb-onset or delayed diagnosis typically have a longer survival.<sup>3</sup> No matter the presentation, patients with ALS will need assistance with activities of daily living shortly after diagnosis and require more acute medical interventions and hospitalizations as the disease progresses. A person with ALS may regain motor function but these ALS reversals are rare and fewer than 1% retain improvement for 12 months or longer.<sup>9,10</sup>

## Pathophysiology of ALS

The pathologic hallmark of ALS is the death of upper and lower motor neurons, leading to degeneration of motor pathways. Although the pathogenic mechanism underlying motor neuron death in ALS remains unclear, protein aggregates in the affected neurons proliferate as the disease progresses, contributing to further damage, with the protein TDP43 found in the cytoplasm of affected neurons in 97% of cases.<sup>11</sup> Each ALS subtype is marked, however, by varied protein deposits.<sup>4</sup> The motor neurons that control ocular, bowel, and bladder function are initially spared until the later stages of the disease.<sup>12</sup>

Since 1980, more than 80 randomized controlled trials (RCTs) on ALS have been published and just 2 drugs, riluzole and edaravone, have emerged as FDA-approved therapies for the disease. Reasons for the negative results of RCTs include an incomplete understanding of ALS pathogenic mechanisms, clinical heterogeneity of ALS progression, shortcomings of study design, and pharmacogenetic interactions. In terms of pathogenic mechanisms, it is generally accepted that several damaging processes trigger motor neuron degeneration. These include protein misfolding and aggregation, oxidative stress, mitochondrial dysfunction, RNA processing impairment, neurofilament aggregation, loss of axonal transport, disruption of the neuromuscular junction, and axon demyelination.<sup>13,14</sup> Several potentially disease-modifying drugs are currently under investigation and build on past RCT failures with new research insights.<sup>13</sup>

## Burden of ALS

Medical costs for patients newly diagnosed with ALS in the United States are substantial and increase rapidly with each disability milestone.<sup>15</sup> Care of patients with ALS is intensive and requires a team of medical professionals, special equipment, and support for assistance with activities of daily living. The associated costs are significant and include direct medical costs, nonmedical costs, and loss of household income (eg, reduced employment of both the patient and/or family caregivers). Compared with other degenerative neuromuscular diseases (eg, Duchenne muscular dystrophy, myotonic muscular dystrophy, spinal muscular atrophy), ALS is the costliest for medical, nonmedical, and indirect costs.<sup>12</sup> An analysis of the economic costs of ALS in the United States published in 2014 estimated the per patient per year cost at \$63,693 (\$31,121 in direct

medical costs). Of the direct medical costs, outpatient care was the largest cost driver, including hospital outpatient visits, physician visits, and physical and occupational therapy. The mean annual prescription medication cost was \$2473, which, in this author's experience, likely reflects costs for symptomatic medications. The study authors do not provide disaggregated data for medication costs, so it is unknown how much of the \$2473 includes the cost of riluzole.<sup>16</sup>

Ventilator and wheelchair use were the main drivers for family out-of-pocket payments. Overall, this amounted to an annual cost to the healthcare system of between \$256 million and \$433 million.<sup>17</sup> The authors noted that interventions to slow disease progression, reduce care requirements, and keep patients walking for longer could significantly lessen costs. An analysis published in 2012 estimated \$502 million (2010 dollars) in annual direct medical costs (inpatient acute or long-term hospitalization, outpatient costs, durable medical equipment, and prescription medication); \$287 million in nonmedical costs (home or motor vehicle purchase or modifications; professional home care; costs of food, supplements, travel, and training the family or others incurred); and \$236 million in indirect costs (household income loss) using moderate prevalence estimates, making ALS the most expensive among the major neuromuscular diseases.<sup>18</sup>

The disease also takes a tremendous toll on the patient's family, who provide the bulk of caregiving, sometimes up to 15 hours a day for an average of 47 hours a week.<sup>19</sup> Most are female and most are caring for their partner. The physical, emotional, and financial effects of caregiving can lead to significant declines in the caregiver's own health.<sup>20</sup>

## Management of ALS

The American Academy of Neurology (AAN) 2009 practice parameters for the management of ALS were reaffirmed in January 2020. They noted that multidisciplinary clinics improve patient outcomes and, where available, encourage referral. Such teams should include a physician, physical therapist, occupational therapist, speech pathologist, dietitian, social worker, respiratory therapist, and nurse case manager.<sup>21</sup>

Study results find that patients treated in ALS clinics are more likely to use percutaneous endoscopic gastrostomy (PEG) and noninvasive ventilation (NIV). Patients receive more aids and appliances and have a higher quality of life, with even a single visit to a multidisciplinary clinic providing benefits. Patients also have fewer hospital admissions and longer mean survival.<sup>2</sup> One 5-year study concluded the use of multidisciplinary clinics reduced overall mortality by 47% and 1-year mortality by 29.7%.<sup>22</sup> However, results of studies show that patients in these clinics tend to be younger and have longer symptom duration than the general population, suggesting some referral bias.<sup>21</sup>

Although beyond the scope of this article, a mainstay of treatment is to manage symptoms as the disease progresses and provide palliative care.<sup>7</sup> This includes medical management for painful muscle spasms, hypersalivation, pseudobulbar affect (which can affect up to half of patients with ALS), cognitive impairment, and depression; as well as the use of adaptive aid devices and medical interventions, such as ventilation (invasive or noninvasive) and PEG. Guidelines also recommend that clinicians talk with patients and their families about palliative care and end-of-life decisions. However, the AAN 2009 guidelines also highlight the underutilization of many therapies, particularly PEG and NIV.<sup>2,21</sup>

## FDA-Approved Treatments for ALS

### Riluzole

The FDA approved the glutamate antagonist riluzole in 1995 as the first treatment for ALS. The approval was based on 2 studies demonstrating a modest survival benefit of about 2 to 3 months.<sup>23</sup> Subsequent analyses and modeling suggest a slightly longer benefit of 6 to 7 months, while a *Cochrane* review of 4 randomized clinical trials suggests it increases the likelihood of an additional year of survival by 9%.<sup>24,25</sup> Real-world evidence from patient databases suggests an even greater improvement, with survival benefits ranging from 6 to 21 months.<sup>2,25</sup>

Riluzole exerts an inhibitory action on glutamate release, inactivating sodium channels and interfering with downstream events resulting from transmitter binding at excitatory amino acid receptors.<sup>23</sup> Guidelines from the AAN recommend its use upon diagnosis.<sup>2</sup> It is available in oral and liquid forms.<sup>26,27</sup>

The effect of riluzole on mortality was first evaluated in a study of 155 patients randomized to 100 mg/day of riluzole or placebo. The riluzole group demonstrated a significantly higher 12-month survival compared with placebo (74% vs 58%;  $P = .014$ ), with an even greater benefit for patients with bulbar-onset disease (73% vs 35%;  $P = .014$ ). One-year survival in patients with limb-onset disease was 74% compared with 64% in patients receiving placebo ( $P = .17$ ).<sup>28</sup>

The riluzole group also demonstrated less muscle strength deterioration. However, the therapeutic effect decreased between 12 and 21 months (the end of the placebo-controlled period). Adverse effects (AEs) included asthenia, spasticity, and mild aminotransferase level increases. A significantly higher drug-related withdrawal rate among the study group was also observed.<sup>28</sup>

A larger follow-up trial of 959 patients with fewer than 5 years of probable or clinically diagnosed ALS used tracheostomy-free status or death as end points. Patients received 50, 100, or 200 mg/day of riluzole or placebo and were followed for 1 year. An analysis conducted at a median 18 months follow-up found that 57% of patients in the riluzole group versus 50% of those in the placebo group demonstrated survival without tracheostomy (adjusted relative risk [RR], 0.65; 95% CI, 0.50-0.85), but there was no significant difference in functional measures or mortality.<sup>29</sup>

## Edaravone

Edaravone is an antioxidant and free radical scavenger that has been shown to reduce excess oxidative stress and cell death.<sup>7,12</sup> However, its exact mechanism of action in ALS remains unknown.<sup>23,30</sup> It is administered as 60 mg intravenously (IV) over a 1-hour infusion daily for 14 days followed by a 14-day drug-free period initially. Subsequent dosing is done in cycles of daily dosing for 10 days of 14-day periods, again followed by 14-day drug-free periods.<sup>31</sup>

The phase 3 trials for edaravone used change in ALSFRS-R score as the primary outcome. An initial 24-week trial randomized 206 participants with ALS with a disease duration of 3 years who lived independently and had forced vital capacity (FVC) of at least 70%.<sup>32</sup> There was no significant change on ALSFRS-R in the edaravone versus placebo groups in the overall population, although a post hoc analysis showed a significant improvement in function based on the ALSFRS-R in those who scored 2 or more on all items of the instrument, had an FVC of at least 80% at baseline, and a disease duration of at most 2 years.<sup>33</sup> However, the authors wrote, “there is no indication that edaravone might be effective in a wider population of patients with ALS who do not meet the criteria.”<sup>33</sup>

A second trial enrolled individuals who met the criteria of those demonstrating a benefit in the first study. A clinically significant smaller decline in function at 24 weeks occurred in the intervention group (−5.01 vs −7.50, difference 2.49; 95% CI, 0.99–3.98;  $P = .0013$ ) versus the placebo group, with a 33% slower decline in function and improvement based on the ALS assessment questionnaire (ALSAQ-40).<sup>31</sup>

A post hoc analysis of an open-label follow-up of 65 edaravone-treated patients and 58 placebo-treated patients who then received edaravone for 24 weeks showed continued benefit out to 48 weeks in the 93 patients who completed the follow-up. Patients who switched from placebo to edaravone demonstrated a 34% lower functional decline than projected for those who would have remained on placebo through week 48 (−10.9 vs −13.0;  $P < .0001$ ) based on the ALSFRS-R. There was also a 38% difference in disease progression in those who received the drug for 48 consecutive weeks compared with the projected decline in the placebo group (−8.0 vs −13.0;  $P < .0001$ ). The most frequent AEs were injection-site contusion, gait disturbance, and headache.<sup>34</sup>

The results of edaravone in a real-world setting are mixed. A retrospective study of 22 patients treated with edaravone and 71 untreated patients with similar baseline demographic and clinical characteristics—albeit shorter disease duration in the treated patients—found similar ALSFRS-R, muscle strength, and respiratory function between the groups 6 months after the baseline visit.<sup>35</sup>

An Italian retrospective study of 243 patients who received a median treatment period of 6.4 months (median 3 cycles) with edaravone found good adherence and a good safety profile, but no significant difference in ALSFRS-R or FVC percentage scores

at 6 months.<sup>36</sup> Another retrospective analysis of 167 patients with ALS who had been using edaravone for at least 3 months (median 332 days per patient) found an average improvement in ALSFRS-R score of −0.62 units per month. However, no information about the baseline characteristics of these patients was provided.<sup>37</sup>

Perhaps the longest-term data comes out of Japan, where edaravone was approved in 2015. A retrospective, single-center study analysis of 27 patients treated with edaravone and 30 not treated between 2010 and 2016 found significant reductions in ALSFRS-R score from baseline to 6 months in the treated group, with significantly improved levels of serum creatinine, a possible marker for ALS severity, and improved survival.<sup>38</sup>

As stated previously, the FDA has approved 2 drugs for treatment of ALS to date, regardless of whether patients have sporadic or familial ALS. Overall, treatment with riluzole can be expected to delay time to death or time to tracheostomy for patients with ALS by about 3 months.<sup>25</sup> Treatment with edaravone preserves function and delays motor deterioration, specifically when initiated in patients with early disease (ie, those with functionality retained in most activities of daily living). To circumvent IV administration challenges and to provide an alternative route of administration, a novel oral suspension formulation of edaravone is undergoing phase 3 investigation (ClinicalTrials.gov Identifier: NCT04165824) for safety and efficacy in ALS.<sup>39</sup>

## Investigational Treatments

Clinical research into new treatments for ALS is plagued by difficulties in study design and questions over the appropriateness of primary and secondary interactions. Research and clinical trial guidelines published in 2019 may rectify some of those challenges.<sup>11,40</sup> One hundred forty key members of the ALS community, including researchers, clinicians, patient representatives, and regulatory agencies, revised the Airlie House guidelines to provide consensus on design and implementation of clinical trials in 9 areas<sup>40</sup>:

1. Preclinical studies
2. Biological and phenotypic heterogeneity
3. Outcome measures
4. Therapeutic and symptomatic interventions
5. Recruitment and retention
6. Biomarkers
7. Clinical trial phases
8. Beyond traditional trial designs
9. Statistical considerations

Additionally, the FDA has issued guidance to assist industry sponsors in the clinical development of drugs and biological products for the treatment of ALS. Specifically, the guidance addresses the FDA’s current thinking regarding the clinical development

program and clinical trial designs for drugs to support an indication for the treatment of ALS.<sup>41</sup>

Pharmacogenetic interactions with investigational compounds create another issue, as not taking genetic information into account may mask evidence of response to treatment or be an unrecognized source of bias, and it is suggested to account for genetic polymorphisms in clinical studies.<sup>41</sup> For example, genetic variants, such as the expanded hexanucleotide repeats in *C9orf72* and mutations in superoxide dismutase 1 (*SOD1*), are more prevalent in familial ALS cases. Carriers of the *C9orf72* repeat expansion have been associated with greater functional decline, and thus they may have an altered response to investigational compounds.<sup>42</sup>

Nonetheless, the greater understanding of the pathophysiology and genetic underpinnings of ALS has led to the development of numerous compounds targeting various pathways, including oxidative stress, excitotoxicity, mitochondrial dysfunction, neuroinflammation, apoptosis, nucleocytoplasmic transport, DNA damage, and RNA splicing/metabolism, among others. Additionally, clinical studies are underway to investigate the impact of treatments on an array of molecular biomarkers (REFINE ALS study, ClinicalTrials.gov Identifier: NCT04259255); however, it is beyond the scope of this article to discuss all investigational compounds. Four compounds ready for phase 3 clinical trial investigation are highlighted in the following paragraphs.

### Masitinib

The oral tyrosine kinase inhibitor masitinib targets microglia, macrophage, and mast cell activity in the central and peripheral nervous systems to provide a neuroprotective effect. It was investigated in a phase 2/3 study evaluating its use in combination with riluzole in 394 patients. Participants were randomized to riluzole plus placebo or riluzole plus masitinib (4.5 or 3.0 mg/kg/day) over a 48-week treatment period. Enrolled patients must have had disease duration fewer than 3 years from their first ALS symptom, an FVC of at least 60%, and received a stable dose of riluzole 100 mg/day for at least 30 days prior to baseline. The primary efficacy population (ie, "normal progressors" receiving riluzole and masitinib 4.5 mg/kg/day vs riluzole and placebo) comprised 105 and 113 patients, respectively, of which 99 and 102 were assessable at study end.<sup>43</sup>

The combination treatment demonstrated a statistically and clinically meaningful 27% slowing of ALSFRS-R deterioration over the 48 weeks (between group difference in ALSFRS-R of 3.39;  $P = .016$ ). Patients on the combination therapy also demonstrated a 29% lower decline in quality of life (ALSAQ-40 score,  $P = .008$ ) and 22% less respiratory deterioration ( $-26.45$  FVC vs  $-33.99$  FVC;  $P = .03$ ). A time-to-event analysis showed that patients on masitinib had a 25% delay in disease progression (20 vs 16 months,  $P = .016$ ). The greatest treatment-related benefits occurred in patients with lower baseline disease severity.<sup>43</sup>

Rates of AEs in patients receiving the lower dose of masitinib were similar to those on placebo (22% vs 17%, respectively). However, serious AEs occurred in 29% of those in the 4.5-mg dose group. In the 4.5-mg and 3.0-mg group, 16.3% and 16.0% of patients, respectively, discontinued the study drug compared with 9% in the placebo arm. The most common AEs in the masitinib group (>5%) versus placebo were maculopapular rash and peripheral edema.<sup>43</sup> A phase 3 randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov Identifier: NCT03127267) with a planned enrollment of 495 patients is underway and will compare the efficacy and safety of combination treatment with masitinib and riluzole to that of riluzole monotherapy.<sup>44</sup>

### Tofersen

Tofersen is an antisense oligonucleotide being investigated for treatment of ALS caused by mutations in the *SOD1* gene, which occurs in up to 2% of ALS cases. The mechanisms by which mutations in the *SOD1* gene cause degeneration of motor neurons is not fully understood, but an overproduction of toxic *SOD1* protein is a leading mechanism. Tofersen is designed to reduce the synthesis of *SOD1* protein.<sup>45,46</sup>

A phase 1/2 trial in 50 patients with ALS and *SOD1* mutations who received varying doses of tofersen or placebo via a lumbar intrathecal injection over 3 months found that those assigned to the highest dose ( $n = 10$ ; 100 mg) demonstrated a 36% reduction from baseline of the protein in their spinal fluid compared with 3% for those who received placebo ( $n = 12$ ). Patients treated with tofersen also scored better on the exploratory outcome of ALSFRS-R (breathing capacity, muscle strength, and function), with an average 1.19-point decline on activity function versus 5.63-point decline on placebo. The most common AEs were mild to moderate headache, procedural pain, post lumbar puncture syndrome, and falls.<sup>47</sup> Cerebrospinal fluid pleocytosis was also observed in tofersen-treated individuals, but the clinical significance remains unknown.<sup>46</sup> The safety and efficacy of tofersen are being evaluated in a phase 3, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov Identifier, NCT02623699) and its long-term extension study (NCT03070119).<sup>45</sup>

### Ravulizumab-cwvz

Ravulizumab-cwvz is a long-acting humanized monoclonal antibody that blocks terminal complement C5 activation and is designed to reduce neuroinflammation. It is FDA approved as a treatment for atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria and is now in a phase 3 randomized clinical trial for ALS.<sup>11</sup>

The CHAMPION-ALS study (ClinicalTrials.gov Identifier: NCT04248465) is enrolling approximately 350 adults with sporadic or familial ALS with disease onset within the prior 3 years, a slow vital capacity of at least 65% predicted, and no respiratory support dependence. Participants will be randomized to receive either

ravulizumab-cwvz or placebo (and may continue receiving their existing standard of care treatment) for 50 weeks, followed by a 2-year, open-label extension phase in which all patients will receive ravulizumab-cwvz. The primary end point is the change in ALSFRS-R score from baseline. Secondary end points include ventilation assistance-free survival and respiratory capacity.<sup>48</sup>

## Mesenchymal stem cell (MSC)-neurotrophic factor (NTF) cells

NurOwn is an autologous bone marrow-derived MSC platform that expands and induces the cells to secrete high levels of NTFs (MSC-NTF) to promote the growth of nerve tissue and improve neuroprotective function. The compound is delivered via intramuscular or intrathecal injection.<sup>49</sup>

A phase 2 safety and efficacy study randomized 48 patients with an ALSFRS-R of at least 30, slow vital capacity at least 65% of the predicted normal value, and symptom duration between 1 and 2 years. The trial met its primary end point of demonstrated safety, with all serious AEs that developed after treatment began related to the disease not the treatment.<sup>50</sup>

There was a significant improvement in the ALSFRS-R slope at 2 and 4 weeks post transplant in the MSC-NTF group (+1.7 and +0.6 points, respectively), but no statistically significant benefit after 4 weeks. The rapid progressors subgroup demonstrated an even greater improvement at 2 and 4 weeks (+3.3 vs -1.3,  $P = .021$ ; and +2.0 vs -0.1,  $P = 0.033$ , respectively) with a continued trend for improvement throughout the remainder of the trial.<sup>50</sup>

Biomarker changes also indicated a positive response to treatment with increases in neuroprotective and anti-inflammatory biomarkers and significant decreases in inflammatory biomarkers, suggesting the treatment successfully moderated neuroinflammation. Response rates slowed towards the end of the follow-up period, signifying a need for repeated treatments in order to maintain a therapeutic benefit.<sup>50</sup>

NurOwn recently completed enrollment ( $N = 261$ ) of a randomized, double-blind, placebo-controlled phase 3 trial (ClinicalTrials.gov Identifier: NCT03280056) assessing the safety and effectiveness of a series of 3 intrathecal injections administered at 2-month intervals. Primary end point is patient score on the ALSFRS-R. Secondary end points are biomarker assessment, including cell-secreted NTFs, inflammatory factors, and changes in blood and cerebrospinal fluid. The study is slated to be complete in late 2020.<sup>51</sup>

## Conclusions

ALS is a motor neuron disease associated with early death due to respiratory failure. Treatment with riluzole or edaravone has demonstrated some prolonged survival and/or function. However, additional pharmacologic therapies are needed and several compounds are in clinical trials to evaluate disease-modifying and/or functional benefits. ■

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