Received: 15 February 2022 | Revised: 12 September 2022 | Accepted: 13 September 2022

DOI: 10.1002/mus.27724

CLINICAL RESEARCH ARTICLE

MUSCLE&NERVE WILEY

Early initiation of riluzole may improve absolute survival in amyotrophic lateral sclerosis

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Abstract

Introduction/Aims: Riluzole improves survival in amyotrophic lateral sclerosis (ALS), but optimal time and duration of treatment are unknown. The aim of this study was to examine if timing of riluzole initiation and duration of treatment modified its effect on survival.

Methods: Patients from the PRO-ACT dataset with information on ALS Functional Rating Scale, time from onset to enrollment (TFOE), and riluzole use were selected for analysis. Survival from enrollment was the outcome. Multivariable Cox proportional hazard models were examined for interactions between riluzole and TFOE. Inverse probability of treatment weighting (IPTW) was used to assess average treatment effect.

Results: Of 4778 patients, 3446 (72.1%) had received riluzole. In unadjusted analyses, riluzole improved median survival significantly (22.6 vs. 20.2 months, log-rank $p < 0.001$). In multivariable analyses, no significant interaction between TFOE and riluzole was found. Riluzole effect was uniform during follow-up. By IPTW, estimated

Abbreviations: AIC, Akaike Information Criterion; ALS, amyotrophic lateral sclerosis; ALSFRS, ALS Functional Rating Scale; ALSFRS-R, Revised ALS Functional Rating Scale; BIC, Bayesian Information Criterion; BMI, body mass index; CI, confidence interval; df, degrees of freedom; FVC, forced vital capacity; FVC%, forced vital capacity expressed as percent of predicted normal (FVC%; HR, hazard ratio; IPTW, inverse probability of treatment weighting/weighted; PRO-ACT, Pooled Resource Open-Access ALS Clinical TrialsSS, subscore; TFOE, time from onset to enrollment.

Authors N.J.T., B.R.L., and H.M. confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Data used in the preparation of this article were obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database. As such, the following organizations and individuals within the PRO-ACT Consortium contributed to the design and implementation of the PRO-ACT Database and/or provided data, but did not participate in the analysis of the data or the writing of this report:

- ALS Therapy Alliance
- Knopp Biosciences
- Neuraltus Pharmaceuticals, Inc.
- Neurological Clinical Research Institute, MGH
- Northeast ALS Consortium
- Novartis
- Prize4Life Israel
- Regeneron Pharmaceuticals, Inc.
- Sanofi
- Teva Pharmaceutical Industries, Ltd.
- The ALS Association

riluzole hazard ratio was 0.798 (95% confidence interval 0.686–0.927). Delaying riluzole initiation by 1 y (6 to 18 months from onset) may translate to reducing median survival from onset by 1.9 months (40.1 to 38.2 months).

Discussion: Riluzole appears to reduce risk of death uniformly, regardless of time from onset to treatment, and duration of treatment. Earlier treatment with riluzole may be associated with greater absolute survival gain from onset. Early diagnosis of ALS will facilitate early treatment and is expected to improve survival.

KEYWORDS
survival, prognosis, therapy, diagnostic delay, Riluzole

1 | INTRODUCTION

Randomized controlled trials[1,2] and subsequent observational data have demonstrated a survival benefit of riluzole in amyotrophic lateral sclerosis (ALS).[3,4] The optimal time for initiation of treatment and duration of treatment are generally uncertain from observational data because of various confounders, notably confounding by indication and the immortal time bias.[5] Biological plausibility and empirical experience associate early treatment with better outcomes in various disorders, notably stroke[6] and cancer.[7]. The benefit of early treatment is also reasonably presumed in the case of ALS.[8] However, some uncertainty surrounds the optimal timing and duration of riluzole treatment. A re-analysis of original trial data implied that riluzole improved survival through prolonging advanced stages of disease (King's stage 4)[9]; the trial cohort, however, did not include early (King's stage 1) patients, precluding estimation of early benefits. Patient database analyses have suggested early-stage as well as late-stage benefits of treatment,[10,11] and greater benefit with shorter time from onset.[12] Population-based observational studies[4,13] have yielded conflicting effects, with some reporting greater survival benefits with higher proportional exposure,[14–16] while others suggesting deleterious effects of prolonged treatment.[17] These conflicting reports raise concerns about the current practice of starting riluzole early and continuing it through the course of disease.[18]

The aim of this study is to address two questions: (a) does time from onset to treatment initiation modify the beneficial effect of riluzole, adjusted for other prognostic variables; and (b) is the beneficial effect of riluzole maintained during treatment, through the period of observation.

2 | METHODS

Data used in the preparation of this article were obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database.[19] We selected patients with information on: (a) ALS Functional Rating Scale (ALSFRS), or ALSFRS-R (the revised ALSFRS),[20] herein we use the term "ALSFRS" to refer to both; (b) time from onset to enrollment (TFOE); and (c) riluzole use. The outcome of interest was survival after enrollment. Unadjusted Kaplan–Meier survival was estimated for the full cohort. Accurate information on riluzole initiation time was lacking in the dataset. Assuming from clinical experience that diagnosis, riluzole initiation, and trial enrollment often occurred in that order in relatively close temporal proximity, we used TFOE as a surrogate for time from onset to riluzole initiation. TFOE had a skewed distribution that was corrected by log transformation; therefore, logTFOE was employed for analyses. In addition to riluzole use and logTFOE, prognostic variables of interest were age, sex, site of onset (bulbar or non-bulbar), initial ALSFRS score, initial forced vital capacity expressed as percent of predicted normal (FVC%), and initial body mass index (BMI). In cases in whom FVC% and BMI were not explicitly recorded in the database, values were calculated from other available information (age, height, weight, sex). NHANES III equations were employed to calculate normative FVC values.[21] Multiple imputation ($m = 10$) was employed to address covariate missingness[22] (noted for age, FVC% and BMI). Multivariable Cox proportional hazard models with interactions were constructed to examine modification of riluzole effect by logTFOE, adjusted for ALSFRS, age, sex, onset site, FVC% and BMI. Models examined included (A) base model (no riluzole*logTFOE interaction), (B) riluzole*logTFOE interaction, (C) riluzole*spline(logTFOE) interaction to allow for curvilinear effects, and (D) riluzole*logTFOE*ALSFRS three-way interaction. Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), log-likelihood, and concordance were examined to compare models constructed from stacked data frames.[23] Graphical displays of riluzole*TFOE interactions from pooled model estimates were also inspected. The proportional hazards assumption (that the effect of riluzole was uniform over the period of observation) was tested graphically using scaled Schoenfeld residuals for riluzole, offset by the parameter estimate, plotted against time from enrollment to event.[24] Interactions of riluzole with other variables was also explored. Average treatment effect of riluzole was then estimated by inverse probability of treatment weighting (IPTW), a propensity-based method that balances measured confounders.[25] Logistic regression models with riluzole use as the outcome were fitted on each imputed data frame to estimate individual probability (propensity) of receiving riluzole. Propensity model goodness of fit was assessed by calibration plots and the Hosmer-Lemeshow test. Stabilized weights were

TABLE 1 Population summary

	Not on riluzole n = 1332		On riluzole n = 3446		
	Means or counts	SD or %	Means or counts	SD or %	p[a]
Age (y)	55.95	11.74	55.73	11.24	ns
Missing age	*213*	*16.0%*	*565*	*16.4%*	*ns*
Male	818	61.4%	2179	63.2%	ns
Female	514	38.6%	1267	36.8%	
Non-bulbar	1027	77.1%	2731	79.3%	0.11
Bulbar	305	22.9%	715	20.7%	
Time from onset to enrollment (TFOE) (days)	609.1	386.5	632.4	365.0	0.58
Time from diagnosis to enrollment (days)	229.8	240.5	232.8	213.3	ns
Missing time from diagnosis to enrollment	*848*	*63.7%*	*1417*	*41.1%*	*<0.0001*
Initial ALSFRS total score	30.66	5.34	30.01	5.40	<0.001
Bulbar SS	10.16	2.28	10.27	2.19	0.14
Fine motor SS	8.74	2.72	8.23	2.92	<0.0001
Gross motor SS	8.10	2.92	7.83	2.95	<0.01
Respiratory (Question 10)	3.66	0.61	3.67	0.61	ns
ALSFRS pre-slope (points/month)	−0.62	0.51	−0.60	0.46	ns
Initial FVC%	84.10	16.40	85.52	16.95	<0.05
Missing FVC%	*17*	*1.3%*	*562*	*16.8%*	*<0.0001*
Initial BMI (kg/m^2)	26.27	5.03	26.08	4.53	ns
Missing BMI	*151*	*11.3%*	*657*	*19.1%*	*<0.0001*

[a]Continuous and categorical variables compared using t-test and Pearson's chi-squared test respectively.
Abbreviation: Pre-slope = (initial ALSFRS − 40)/TFOE (in months).

employed without trimming. Covariate balance was established by examining weighted empirical cumulative distributions and standardized mean differences between patients by treatment. IPTW was combined with multiple imputation using the "within" method.[26] Herein, 10 IPTW "pseudo-cohorts" were generated from the imputed data frames, and Cox proportional hazard models were fitted with each with riluzole as the only predictor. Estimates from 10 models were pooled using Rubin's rule to calculate a final estimate of riluzole effect. Robust standard errors were used to account for clustering of observations because of IPTW weights.[25]

Projected survival was calculated for different riluzole start times using the baseline survival estimate from an IPTW cohort (assuming no treatment) and applying the IPTW hazard ratio (HR) point estimate uniformly beyond those start times.

In addition to the primary analyses, the following parallel analyses were conducted for sensitivity analyses: (a) Examination of TFOE*riluzole interactions in IPTW data frames ("double-adjusted" models). (b) Analyses employing the ALSFRS pre-slope [(initial ALSFRS − 40)/TFOE (in months)] as a covariate instead of initial ALSFRS. (c) Analyses wherein all patients' outcomes after 18 months (548 days) or after 24 months (730 days) of observation were trimmed (censored) to eliminate potential selection bias. Significance threshold was set at $p < 0.05$. R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria) with additional packages (survival, mice, splines, cobalt, predtools, rspiro) was used for analysis.

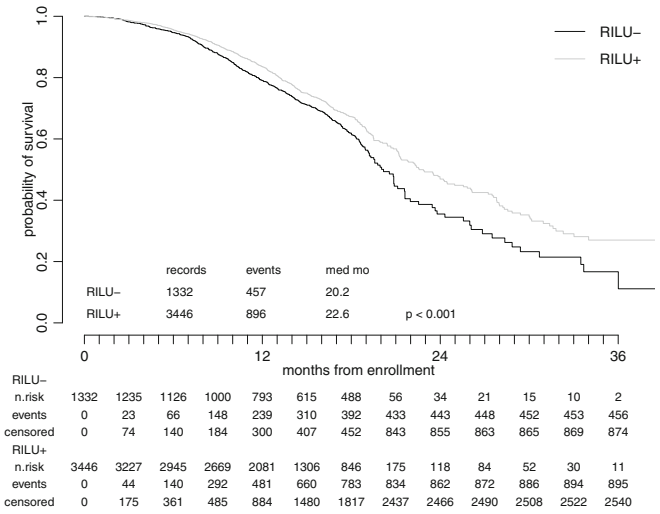

FIGURE 1 Kaplan–Meier survival estimate by treatment. Number at risk and cumulative event and censoring counts are displayed at 3-months intervals.

3 | RESULTS

Inclusion criteria were satisfied by 4778 patients, of whom 3446 (72.1%) had received riluzole (characteristics of the cohort are summarized in Table 1). Relative to excluded patients in the dataset, patients

who met inclusion criteria were younger and less likely to be female. They also had shorter TFOE, higher ALSFRS, less steep pre-slope, higher FVC%, and higher BMI (Supplementary Data Table S1). Kaplan–Meier survival estimates by treatment arm are presented in Figure 1. Death was recorded in 896 patients receiving riluzole, and in 457 patients not receiving riluzole, with median survival 22.6 and 20.2 months respectively (log rank $p < 0.001$, unadjusted HR 0.794, 95% confidence interval [CI] 0.709–0.889). Survival at 6, 12, 18, and 24 months from enrollment for those on riluzole was 95.6%, 83.6%, 67.3%, and 46.9%, and for those not on riluzole was 94.7%, 79.0%, 61.9%, and 35.5%, respectively. Examination of crude unadjusted survival in subgroups divided by quantiles of TFOE and initial ALSFRS did not disclose any consistent TFOE-dependent pattern (Supplementary Data Figure S1).

3.1 | Multivariable models

Fit indices of multivariable models without and with interactions are presented in Supplementary Data Table S2, and interaction estimates are graphically presented in Figure 2. In multivariable Cox proportional hazard models that included age, sex, and onset site (bulbar or non-bulbar), ALSFRS, TFOE and riluzole, riluzole*TFOE interactions did not reach statistical significance, and did not offer better concordance (c-statistic) compared to the base model (model A) without such interaction. Model A parameter estimates are presented in Table 2. Other prognostic variables of note were age, ALSFRS, logTFOE, and FVC%. We tested the proportional hazard assumption and found that it was satisfied for riluzole, implying that the reduced hazard from riluzole is invariant throughout the period of observation (Supplementary Data Figure S2). This finding is in keeping with continuing separation of Kaplan–Meier survival plots (Figure 1) and parallel plots of cumulative hazard against time on a logarithmic scale (not presented). Interactions between riluzole and other covariates (age, sex, site of onset, ALSFRS total score, ALSFRS subscores, FVC%, and BMI) also did not reach statistical significance.

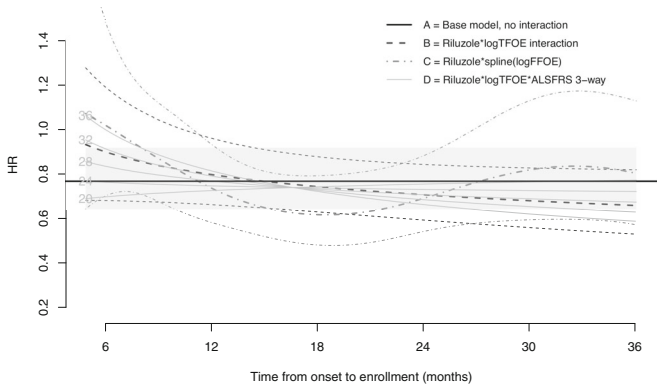

FIGURE 2 Riluzole*TFOEinteractions graphically depicted for the four models (A-D) defined in Methods and presented in Supplementary Data Table S2. TFOE and riluzole HR are indicated on the x and y axes respectively. The solid horizontal line and the gray band depict the base model (Model A – no interaction) point estimate and confidence band respectively. For the three-way riluzole*TFOE*ALSFRS interaction (Model D), point estimates for ALSFRS scores of 20, 24, 28, 32, and 36 are plotted.

3.2 | IPTW model

Propensity score-estimating logistic regression models that included the following variables were fitted with each imputed data frame: age, sex, onset site, logTFOE, initial ALSFRS bulbar, fine motor, and gross motor subscores and response to question 10 (respiratory), FVC%, and BMI. Goodness-of-fit was acceptable in 9 of 10 imputed datasets, but discrimination was low ($c \sim 0.59$ for each, see Supplementary Data Figure S3). Pooled parameter estimates from these models are presented in Supplementary Data Table S3. In the multivariable logistic model, the only significant predictors of riluzole use were higher logTFOE and lower ALSFRS fine motor subscale. Stabilized weights were well-conditioned and satisfied the positivity assumption, although with narrower spread for riluzole-treated than non-treated patients (range 0.81–1.52 treated versus 0.55–2.51 non-treated, Supplementary Data Figure S4). Excellent covariate balance was accomplished with all standardized mean differences less than 0.1 (Supplementary Data Figure S5). The IPTW treatment model estimated a riluzole HR of 0.798 (95% CI 0.686–0.927, $p = 0.004$).

TABLE 2 Model A: Multivariable Cox proportional hazard model, no interactions

Parameters	Point estimates of hazard ratios (HRs)	95% CIs of HRs	Pooled t	Pooled df	*p* value
Riluzole	0.768	0.642–0.919	−3.007	28.34	<0.0001
Time from onset (TFOE) (doubling)	0.609	0.566–0.656	−13.280	254.05	<0.0001
ALSFRS (per point)	0.929	0.914–0.944	−9.330	24.84	<0.0001
Age (per decade)	1.477	1.353–1.612	9.247	22.27	<0.0001
Female sex	0.912	0.804–1.034	−1.444	193.15	ns
Bulbar onset	1.015	0.880–1.172	0.210	150.16	ns
Initial FVC (%)	0.979	0.967–0.991	−3.735	10.48	<0.01
Initial BMI (kg/m^2)	0.976	0.945–1.008	−1.630	10.96	ns

Note: Pooled parameter estimates from m = 10 imputed data frames.

3.3 | Projected survival from IPTW model estimates

Assuming non-variability of riluzole HR regardless of TFOE, and uniform HR regardless of treatment duration, we applied treatment at different time points after onset. For the baseline survival function, we used an IPTW Cox model baseline hazard estimate (without treatment), counting time from onset of symptoms. Projected survival estimates without treatment and with treatment applied at 6, 12, 18, 24, and 30 months after onset are presented in Figure 3 and in Table 3. Early treatment is projected to return modest gains in median survival from onset and in surviving fraction at different time points from onset relative to delayed treatment. As an example, delaying riluzole initiation from 6 to 18 months from onset would reduce median survival from onset by 1.9 months (from 40.1 to 38.2 months).

3.4 | Sensitivity analyses

Examination of logTFOE*riluzole interactions in models using IPTW data frames yielded similar lack of significant interaction (data not presented). Reparameterization using log(pre-slope) instead of ALSFRS score as a covariate also found no strong evidence of logTFOE*riluzole interaction (Supplementary Data, Table S4 and Figure S6). Analyses using data trimmed at 24 months (48 events excluded) yielded qualitatively similar results, whereas analyses using data trimmed at 18 months (178 events excluded) found (a) a weaker and non-significant benefit of riluzole assuming no interaction (IPTW HR 0.840, 95% CI 0.696–1.014, $p = .07$), and (b) significant TFOE*riluzole interaction (no benefit with short TFOE, greater benefit with longer TFOE). Model fits from trimmed data are presented in Supplementary Data (Table S5 and Figures S7-8).

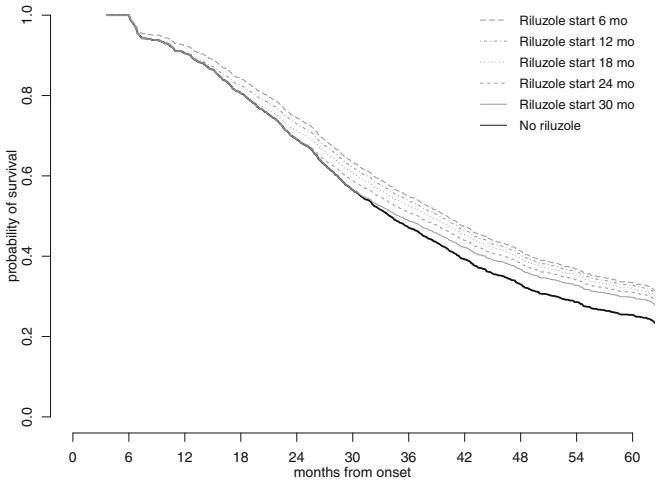

FIGURE 3 Projected survival for different riluzole start times. Setting the riluzole HR at the IPTW point estimate (0.798), projected survival from onset can be calculated for different riluzole start times. Corresponding median survival and surviving fraction at specific time points from onset for different treatment start times are presented in Table 3.

4 | DISCUSSION

From this large prospective cohort, we estimated a survival benefit of riluzole (HR 0.798) that is almost identical to estimates from seminal trial data.[1–3] Importantly, we did not find evidence of significant variation in riluzole effect for different TFOE, nor did hazard reduction from riluzole change with duration of treatment. In other words, a uniform riluzole hazard ratio regardless of TFOE and duration of observation is a reasonable approximation of reality. This does not imply that timing and duration of treatment do not matter. Because overall survival is a function of the *cumulative* hazard, the earlier the treatment is applied and the longer the exposure to treatment, the greater the time enjoyed with a lower hazard (rate of death), and thereby the more improved the overall survival.

What does this mean for the clinician? These data and analyses provide empirical support for starting early treatment and adhering to treatment. Calculations assuming a uniform riluzole protective benefit indicate an improved median survival from onset by almost 2 months, with about 4% more patients surviving at 2 y from onset, if treatment is started at 6 months from onset rather than at 18 months from onset. Although these incremental gains from early treatment are rather small in absolute terms, they are relatively large compared to the modest overall benefit seen with any ALS treatment to date. In addition to other factors, it is possible that early timing of treatment may explain some of the survival gain difference noted between original randomized controlled trials of riluzole (median survival gain 2–3 months, with mean disease duration about 2 y at enrollment)[1,2] and subsequent clinical experience from retrospective cohorts (median survival exceeding 6 months in some).[4]

TABLE 3 Projected survival according to riluzole start times, calculated using IPTW model point estimate of riluzole hazard ratio

Riluzole start time after onset (months)	Median survival from onset (months)	Surviving fraction 24 months from onset, %	Surviving fraction 36 months from onset, %	Surviving fraction 48 months from onset, %
6	40.1	74.4	54.8	41.3
12	39.3	72.9	53.7	40.5
18	38.2	71.2	52.5	39.6
24	37.1	69.1	50.9	38.3
30	35.0	69.1	48.8	36.8
No riluzole	34.0	69.1	47.1	33.1

Is it possible to reconcile our findings with those of a retrospective re-analysis of trial data[2,9] that showed benefits predominantly in advanced stages of disease? One possible explanation is the heterogeneity of disease progression rate. Even with a short time from onset to start of treatment, some rapidly progressing patients may already be in more advanced stages of disease and begin accruing survival benefits, accounting for an early separation of survival plots. Additionally, riluzole may have beneficial effects also in early stages.[10,11] Simulation studies using Markov models will be required to examine if stage-specific treatment effects are compatible with a uniform treatment effect (HR) regardless of time from onset to start of treatment. Our analysis finds an enduring benefit of continued riluzole treatment, which is congruent with greater benefit with longer treatment duration[14] and in late stages of disease. However, our study differs from population-based studies from Austria[17] and Italy[14] that found "crossing" Kaplan–Meier plots (violation of the proportional hazards assumption), with riluzole-treated patients having worsening survival beyond 1.5–2 y of observation. This discrepancy will need further exploration, noting that our findings may have been confounded by increased censoring beyond that time point, as discussed below.

This study has numerous limitations. First, this subgroup of the PRO-ACT dataset was a select population that enrolled in clinical trials, and also met our inclusion criteria. Heterogeneity within the included population also existed because they belonged to different clinical trials with varying inclusion criteria and differing lengths of follow-up. Second, being a non-randomized study (relating to riluzole use), there was potential for confounding/bias from unmeasured covariates that associate with treatment as well as outcome, despite multivariable adjustment and employing propensity methods. For instance, patients declining riluzole could have been less accepting of other beneficial treatments such as non-invasive ventilation.[27] On the other hand, unlike population-based cohorts that could have more confounders, this was a closely followed cohort that received relatively uniform care. Furthermore, it is reassuring that our survival benefit estimate is almost identical to that obtained from original riluzole randomized controlled trials.[3] Third, information on riluzole start times was largely lacking, requiring the use of an imperfect surrogate, namely TFOE. Our assumption that riluzole was initiated a few months prior to enrollment potentially introduces bias. Nor did we have any information on adherence to treatment, which may have been inconsistent, and may have decreased with advancing disease.[28] It should be noted that methodology employed by some investigators to associate ex post facto variables such as duration of treatment and "proportion of days covered" with survival[14,17] is flawed and likely to introduce bias.[29] Fourth, there was significant censoring beyond 18 months of observation, presumably administrative (dictated by trial protocol), which could have biased HR estimates with longer follow-up. A parallel analysis with trimming data beyond 24 months found a qualitatively similar uniform riluzole benefit regardless of TFOE and duration of follow-up. However, another analysis trimming data beyond 18 months failed to identify a significant survival benefit from riluzole, and varying HR by TFOE (no benefit of early treatment), indicating that events beyond 18 months were influential. Kaplan–Meier plots of survival beyond 18 and 24 months are available in Supplementary Data Figure S8. Last, this study may have been underpowered to detect moderate interactions with riluzole effect. Although with >0.85 power to detect a treatment HR of 0.8 with alpha error set at 0.05, a rough calculation shows that this study had less than 0.5 power to detect a treatment*(binary) covariate interaction that had HR 0.8. Therefore, modest heterogeneity of riluzole benefit by time of initiation and by duration of treatment cannot be excluded. Although better data from larger prospective cohorts are desirable, it is unlikely that a prospective study of sufficient size to find optimal timing of riluzole or other ALS treatment will ever be initiated.

It could be suggested that inferences of this analysis are trivial and do not change practice. We argue that they are meaningful. First, our observations provide a useful estimate of the magnitude of survival gain from early treatment. More importantly, a strong argument for early treatment, and therefore, for urgent diagnosis of ALS is made. This argument applies to riluzole, and potentially also to other treatments.

ETHICS APPROVAL

No ethical approval was sought for this analysis of publicly available data.

AUTHOR CONTRIBUTIONS

H.M. and N.J.T. conceptualized the study. N.J.T. conducted the statistical analysis, interpreted the data, and prepared the initial manuscript. H.M. and B.R.L. interpreted the data and critically revised the manuscript for important intellectual content. All authors contributed equally to the approval of the final manuscript. Members of the PRO-ACT Consortium contributed to the design and implementation of the PRO-ACT Database and/or provided data but did not participate in the analysis of the data or the writing of this report.

ACKNOWLEDGMENTS

We are indebted to the PRO-ACT Consortium for providing the data for these analyses. We would also like to thank the Neurological Institute Center for Outcomes, Research and Evaluation (NI-CORE) and Quantitative Health Sciences (QHS) at Cleveland Clinic for supporting this effort.

DATA AVAILABILITY STATEMENT

Research analytic data are not shared. Original data is available publicly (PRO-ACT, available at https://nctu.partners.org/ProACT/)

FUNDING AND DECLARATION OF INTEREST

This study was not supported by any external or internal grant. There are no competing interests. Dr. Thakore reports research grants from Novartis Pharmaceuticals Corporation and consulting fees from Amylyx Pharmaceuticals outside the submitted work. Dr. Lapin has nothing to disclose. Dr. Mitsumoto has received research grants from National Institutes of Health, ALS Association, Spastic Paraplegia Foundation, Muscular Dystrophy Association Wings, Tsumura & Co,

and Mitsubishi-Tanabe Pharma, also has served on advisory boards for Amylyx and PTC Bio outside of the submitted work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Thakore NJ, Lapin BR, Mitsumoto H, Pooled Resource Open-Access ALS Clinical Trials Consortium. Early initiation of riluzole may improve absolute survival in amyotrophic lateral sclerosis. *Muscle & Nerve*. 2022;66(6): 702-708. doi:10.1002/mus.27724