Exploratory Post Hoc Analysis of Neutrophil-to-Lymphocyte Ratio as a Novel Responsiveness Biomarker for Edaravone Oral Suspension–Treated Patients With Amyotrophic Lateral Sclerosis vs Untreated Propensity Score–Matched PRO-ACT Historical Placebo Controls

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Background

- The United States Food and Drug Administration (FDA) approved an on/off dosing regimen of Radicava ORS® (edaravone) oral suspension for patients with amyotrophic lateral sclerosis (ALS) in May 2022[1]
- This approval was based, in part, on a global, multicenter, open-label, phase 3 study (MT-1186-A01) that investigated the safety and tolerability of on/off dosing of edaravone oral suspension in adults with ALS through 48 weeks and found that edaravone oral suspension was well tolerated with no new safety concerns identified[2]
- Previously, edaravone oral suspension–treated patients with ALS from Studies MT-1186-A01/A02/A03/A04 showed a 7.3-month statistically significantly prolonged mean survival vs propensity score matched Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) controls (P<0.001) over 34 months[3]
- In patients with ALS, neutrophil-to-lymphocyte ratio (NLR) is a potential prognostic biomarker, with elevated levels of NLR correlating with ALS disease progression and clinical deterioration[4]
- Edaravone treatment in some non-ALS oxidative stress disease models has shown effects on neutrophil function[5-12]

Objective

- Define NLR response to edaravone treatment and determine whether baseline NLR may affect NLR response in edaravone oral suspension–treated patients with ALS vs propensity score–matched non-edaravone–treated PRO-ACT control patients with ALS

Methods: Studies MT-1186-A01/A02/A03/A04

- Study MT-1186-A01 (NCT04165824) was a phase 3, open-label, 48-week study that evaluated the long-term safety and tolerability of FDA-approved on/off edaravone oral suspension in patients with ALS,[2] and Study MT-1186-A03 (NCT04577404) was its 96-week extension[13]
- Study MT-1186-A02 (NCT04569084) was a phase 3b, double-blind, parallel-group, study that randomized patients with ALS to evaluate whether investigational once daily edaravone oral suspension dosing was superior to the FDA-approved on/off edaravone oral suspension regimen based on the Combined Assessment of Function and Survival, and assessed safety and tolerability, over 48 weeks,[14] and Study MT-1186-A04 (NCT05151471) was its 48-week extension

Methods: PRO-ACT Database

- Data for the historical, external control patients with ALS who were not treated with edaravone were obtained from the PRO-ACT database, which contains >10 million longitudinally collected data points from phase 2/3 clinical trials[15]
- Trial data are de-identified and provided for research purposes only[16]

Methods: Propensity Score Matching

- Patients from Studies MT-1186-A01/A02/A03/A04 were propensity score matched 1:1 on 11 baseline variables with historical, external PRO-ACT controls (patients with ALS who were not administered investigational treatment [edaravone] but may have received riluzole in their respective trials)
    - Propensity score matched variables included: NLR at baseline, age, sex, body weight, El Escorial revised Airlie House diagnostic criteria, disease duration between ALS symptom onset date and screening visit, baseline ALSFRS-R total score, baseline %vital capacity (VC, either % forced VC [FVC] or % slow VC [SVC]), initial symptom, concomitant use of riluzole, and pre–ALSFRS-R slope per month

Results: Baseline Demographics, Clinical Characteristics, and ALS History

- Baseline demographics, clinical characteristics, and ALS history are reported for the MT-1186-A01/A02/A03/A04 On/Off and Once Daily group vs the PRO-ACT non-edaravone–treated control group (**Table 1**)

Table 1. Baseline Demographics, Clinical Characteristics, and ALS History

Demographics, Clinical Characteristics, and ALS History	MT-1186-A01/A02/A03/A04 On/Off and Once Daily Edaravone Oral Suspension			Non-Edaravone–Treated PRO-ACT Controls		
	All (N=221)	NLR <3 (n=149)	NLR ≥3 (n=72)	All (N=221)	NLR <3 (n=149)	NLR ≥3 (n=72)
Sex, n (%)						
Male	130 (58.8)	85 (57.0)	45 (62.5)	132 (59.7)	86 (57.7)	46 (63.9)
Female	91 (41.2)	64 (43.0)	27 (37.5)	89 (40.3)	63 (42.3)	26 (36.1)
Age, years						
Mean (SD)	57.8 (10.5)	57.4 (10.5)	58.6 (10.3)	57.9 (9.6)	57.5 (9.3)	58.6 (10.3)
Median (min, max)	59.0 (29, 75)	59.0 (29, 75)	59.0 (34, 75)	58 (24, 80)	58.0 (33, 78)	60.0 (24, 80)
Body weight, kg						
Mean (SD)	74.4 (16.0)	73.8 (15.7)	75.6 (16.5)	74.6 (15.3)	75.8 (15.9)	72.0 (13.8)
Median (min. max)	75.0 (41.2, 125.9)	73.7 (41.4, 125.9)	79.3 (41.2, 124.2)	73.9 (40.0, 123.8)	76.0 (46.0, 123.8)	69.9 (40.0, 103.9)
El Escorial Criteria, n (%)						
Definite ALS	101 (45.7)	69 (46.3)	32 (44.4)	96 (43.4)	66 (44.3)	30 (41.7)
Probable ALS	100 (45.2)	65 (43.6)	35 (48.6)	81 (36.7)	52 (34.9)	29 (40.3)
Probable laboratory-supported ALS	17 (7.7)	12 (8.1)	5 (6.9)	36 (16.3)	25 (16.8)	11 (15.3)
Possible ALS	3 (1.4)	3 (2.0)	0	8 (3.6)	6 (4.0)	2 (2.8)
Disease duration from symptom onset to screening, years						
Mean (SD)	1.3 (0.6)	1.4 (0.6)	1.2 (0.5)	1.3 (0.7)	1.3 (0.7)	1.3 (0.6)
Median (Min, Max)	1.2 (0.1, 3.0)	1.3 (0.3, 3.0)	1.1 (0.1, 2.7)	1.2 (0.3, 7.3)	1.3 (0.3, 7.3)	1.2 (0.5, 2.6)
Initial symptom onset, n (%)						
Bulbar onset	80 (36.2)	55 (36.9)	25 (34.7)	92 (41.6)	68 (45.6)	24 (33.3)
Limb onset	141 (63.8)	94 (63.1)	47 (65.3)	129 (58.4)	81 (54.4)	48 (66.7)

ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; NLR, neutrophil-to-lymphocyte ratio; PB-TURSO, sodium phenylbutyrate and taurursodiol; PRO-ACT, Pooled Resource Open-Access ALS Clinical Trials; VC, vital capacity.

Results: Baseline Demographics, Clinical Characteristics, and ALS History (continued)

Table 1. Baseline Demographics, Clinical Characteristics, and ALS History (continued)

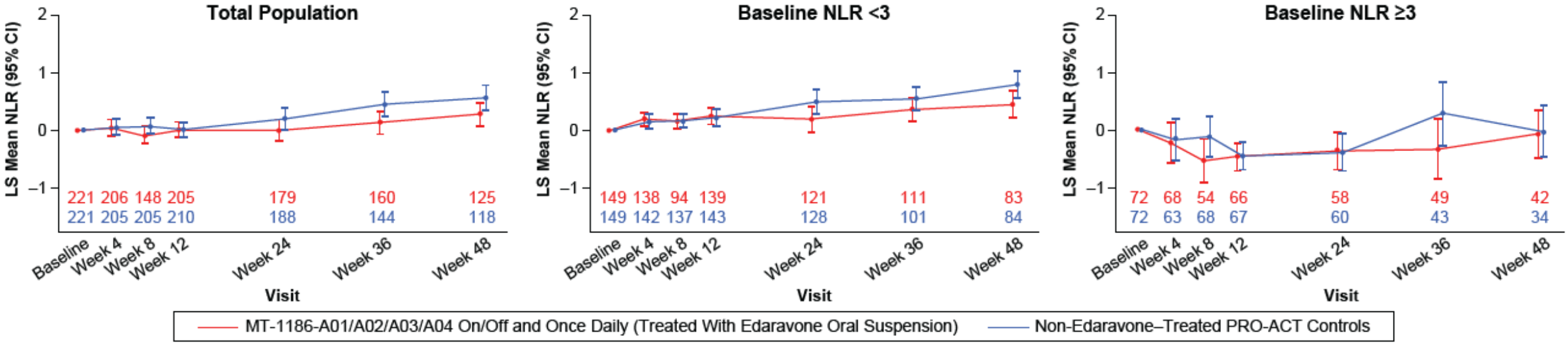
Demographics, Clinical Characteristics, and ALS History	MT-1186-A01/A02/A03/A04 On/Off and Once Daily Edaravone Oral Suspension			Non-Edaravone–Treated PRO-ACT Controls		
	All (N=221)	NLR <3 (n=149)	NLR ≥3 (n=72)	All (N=221)	NLR <3 (n=149)	NLR ≥3 (n=72)
Baseline ALSFRS-R total score						
Mean (SD)	39 (4)	38.6 (4.1)	39.8 (3.9)	38.9 (4.5)	39.6 (4.4)	37.5 (4.5)
Median (Min, Max)	39 (22, 47)	39.0 (25, 46)	40.0 (22, 47)	40.0 (20, 47)	40.0 (26, 47)	38.0 (20, 45)
Pre-ALSFRS-R slope (for comparison with PRO-ACT control group), points/month						
Mean (SD)	−0.7 (0.5)	−0.7 (0.5)	−0.7 (0.5)	−0.6 (0.4)	−0.6 (0.4)	−0.8 (0.5)
Median (Min, Max)	−0.6 (−4.3, −0.1)	−0.6 (−4.3, −0.1)	−0.6 (−3.9, −0.1)	−0.6 (−3.1, −0.03)	−0.5 (−3.1, −0.03)	−0.6 (−2.7, −0.2)
Baseline VC, %						
Mean (SD)	89.9 (13.8)	89.7 (13.7)	90.3 (14.1)	88.6 (15.5)	89.0 (15.8)	87.8 (15.1)
Median (Min, Max)	88.0 (62, 125)	88.0 (62, 121)	87.0 (70, 125)	87.0 (59, 146)	87.0 (59, 146)	85.8 (60, 125)
Concomitant riluzole use, n (%)						
Present	177 (80.1)	114 (76.5)	63 (87.5)	171 (77.4)	114 (76.5)	57 (79.2)
Absent	44 (19.9)	35 (23.5)	9 (12.5)	16 (7.2)	10 (6.7)	6 (8.3)
Missing	0 (0)	0 (0)	0 (0)	34 (15.4)	25 (16.8)	9 (12.5)
Concomitant use of PB-TURSO, n (%)						
Present	18 (8.1)	11 (7.4)	7 (9.7)	0 (0)	0 (0)	0 (0)
Absent	133 (60.2)	83 (55.7)	50 (69.4)	0 (0)	0 (0)	0 (0)
Missing	70 (31.7)	55 (36.9)	15 (20.8)	221 (100)	149 (100)	72 (100)
Baseline NLR, neutrophils/lymphocytes						
Mean (SD)	2.7 (1.1)	2.1 (0.5)	4 (0.9)	2.7 (1.2)	2.1 (0.5)	4.0 (1.1)
Median (Min, Max)	2.5 (0.7, 7.9)	2.1 (0.7, 3.0)	3.7 (3.0, 7.9)	2.5 (0.9, 9.9)	2.2 (0.9, 3.0)	3.6 (3.0, 9.9)

ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; NLR, neutrophil-to-lymphocyte ratio; PB-TURSO, sodium phenylbutyrate and taurursodiol; PRO-ACT, Pooled Resource Open-Access ALS Clinical Trials; VC, vital capacity.

Results: Descriptive Analysis for NLR

- After propensity score matching, 221 patients were assigned to each group in the overall population. This population was subsequently divided into subgroups according to baseline NLR <3 (n=149 per group) or baseline NLR ≥3 (n=72 per group)
- Edaravone oral suspension-treated patients tended to have a lower mean change from baseline in NLR vs matched PRO-ACT controls over 48 weeks, primarily for the total population and baseline NLR <3 group (**Figure 1, Table 2**)

Figure 1. Mean Change From Baseline NLR Over 48 Weeks For Edaravone Oral Suspension-Treated Patients From Studies MT-1186-A01/A02/A03/A04 and Propensity Score Matched Non-Edaravone–Treated PRO-ACT Controls (Total Population, Baseline NLR <3, and Baseline NLR ≥3)



CI, confidence interval; LS, least squares; NLR, neutrophil-to-lymphocyte ratio; PRO-ACT, Pooled Resource Open-Access Amyotrophic Lateral Sclerosis Clinical Trials.

Results: Mixed Model for Repeated Measures Analysis for NLR

- Relative to baseline NLR, edaravone oral suspension-treated patients from Studies MT-1186-A01/02/03/04 showed a statistically significantly suppressed NLR vs matched PRO-ACT controls at 36 weeks (LS mean difference=−0.323, *P*=0.033) and a numerical trend in suppressing NLR vs matched PRO-ACT controls at 48 weeks (LS mean difference=−0.285, *P*=0.065) (**Figure 1, Table 2**)
- Edaravone-treated patients with baseline NLR <3 showed statistically significant suppressed NLR at 48 weeks vs PRO-ACT controls (LS mean difference=−0.351, *P*=0.038)

Table 2. Change From Baseline NLR for Edaravone Oral Suspension-Treated Patients From Studies MT-1186-A01/A02/A03/A04 vs Matched Non-Edaravone–Treated PRO-ACT Controls at Weeks 36 and 48

NLR (Change From Baseline)		Total (N=221)	Baseline NLR <3 (n=149)	Baseline NLR ≥3 (n=72)
At 36 weeks				
MT-1186-A01/A02/A03/A04 On/Off and Once Daily Edaravone Oral Suspension	LS mean (SE)	0.130 (0.104)	0.351 (0.094)	−0.331 (0.263)
PRO-ACT Controls (Non-Edaravone–Treated)	LS mean (SE)	0.454 (0.109)	0.539 (0.098)	0.288 (0.277)
	LS mean difference (SE) *P* value	−0.323 (0.151) 0.033	−0.188 (0.136) 0.167	−0.619 (0.382) 0.108
At 48 weeks				
MT-1186-A01/A02/A03/A04 On/Off and Once Daily Edaravone Oral Suspension	LS mean (SE)	0.279 (0.107)	0.439 (0.119)	−0.070 (0.212)
PRO-ACT Controls (Non-Edaravone–Treated)	LS mean (SE)	0.564 (0.110)	0.790 (0.119)	−0.028 (0.227)
	LS mean difference (SE) *P* value	−0.285 (0.154) 0.065	−0.351 (0.168) 0.038	−0.041 (0.311) 0.895

Statistics are from Mixed Model for Repeated Measures including treatment group, visit and treatment-by-visit interaction, propensity score as a fixed factor in the model. An unstructured covariance structure is assumed, and the denominator degrees of freedom is computed using Kenward-Roger method.
LS, least squares; NLR, neutrophil-to-lymphocyte ratio; PRO-ACT, Pooled Resource Open-Access Amyotrophic Lateral Sclerosis Clinical Trials.

Results: Survival Analyses

- Survival analyses demonstrated improved survival over 36 months in patients treated on/off and once daily with edaravone oral suspension compared with matched PRO-ACT controls for the total population, and baseline NLR <3 and NLR ≥3 subgroups (**Table 3, Figure 3**)

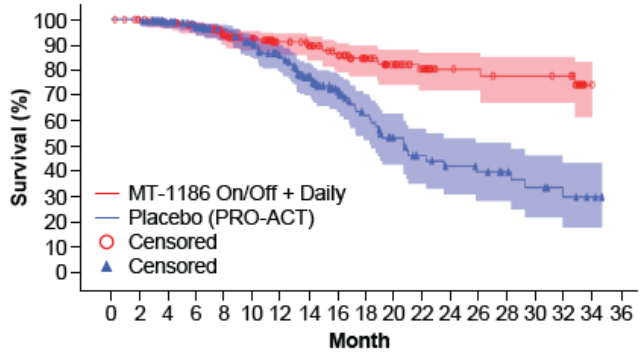
Table 3. Survival Outcomes Over 36 Months For Edaravone Oral Suspension-Treated Patients vs Matched Non-Edaravone–Treated PRO-ACT Controls (Total Population, Baseline NLR <3, Baseline NLR ≥3)

	Edaravone Oral Suspension On/Off and Once Daily (MT-1186-A01/A02/A03/A04)			PRO-ACT Controls (Non-Edaravone–Treated)		
	Total	Baseline NLR <3	Baseline NLR ≥3	Total	Baseline NLR <3	Baseline NLR ≥3
n	221	149	72	221	149	72
Number of events (%)	29 (13.1)	17 (11.4)	12 (16.7)	66 (29.9)	40 (26.8)	26 (36.1)
Median, months	-	-	-	20.70	20.93	20.70
Min, Max	2.5, 32.9	2.5, 26.2	3.5, 32.9	2.1, 32.0	4.9, 28.4	2.1, 32.0
***P* value log-rank[a]**	*P*<0.001	*P*<0.001	*P*=0.004			
Hazard ratio (SE)[b]	0.348 (0.225)	0.318 (0.293)	0.382 (0.351)			
***P* value Cox[b]**	*P*<0.001	*P*<0.001	*P*=0.006			

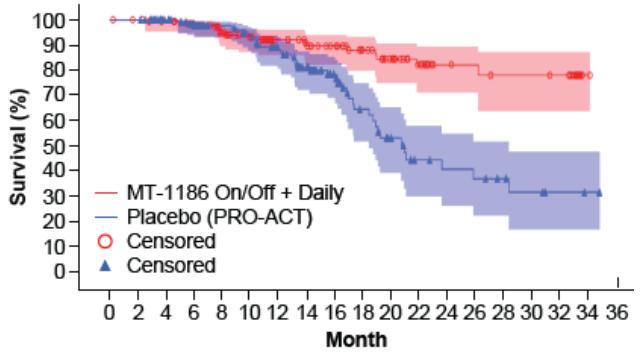
[a]Statistics are from the log-rank test.
bStatistics are from the Cox proportional hazard regression model with treatment and propensity scores as explanatory variables.
NLR, neutrophil-to-lymphocyte ratio; PRO-ACT, Pooled Resource Open-Access Amyotrophic Lateral Sclerosis Clinical Trials; SE, standard error.

Figure 2. Kaplan-Meier Survival Curves Over 36 Months For Edaravone Oral Suspension-Treated Patients vs Matched PRO-ACT Controls for a) Total Population b) Baseline NLR <3 and c) Baseline NLR ≥3

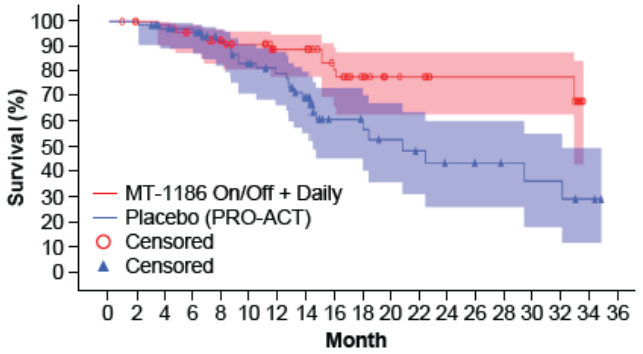
a) Total Population



b) Baseline NLR <3



c) Baseline NLR ≥3



Conclusions

- This exploratory post hoc analysis of propensity score–matched, edaravone oral suspension–treated patients with ALS from Studies MT-1186-A01/A02/A03/A04 vs non-edaravone–treated PRO-ACT controls expands existing evidence regarding the possible role of NLR as a novel ALS biomarker that might allow for assessment of ALS prognosis with edaravone treatment
- Edaravone oral suspension–treated patients tended to have a lower mean change from baseline in NLR vs matched non-edaravone–treated PRO-ACT controls over 48 weeks, primarily for the total population and baseline NLR <3 group. Notably, edaravone–treated patients with baseline NLR <3 showed statistically significant suppression of NLR at 48 weeks vs PRO-ACT controls
- Patients treated with edaravone oral suspension showed improved survival outcomes over 36 months vs matched non-edaravone–treated PRO-ACT controls for the total population, and baseline NLR <3 and NLR ≥3 subgroups
- This was a retrospective, external control analysis comparing patients from RADICAVA ORS® clinical trials with historical placebo patients from the PRO-ACT database. Although propensity score matching was used to reduce bias, the analysis remains subject to limitations inherent to non-randomized comparisons, including potential residual confounding due to unmeasured or inadequately balanced variables. Differences in trial protocols, data collection methods, and supportive care over time may also limit comparability
- These data are considered exploratory. No adjustments were made for multiplicity, and the findings should be interpreted with caution given the retrospective nature of the analysis and use of external controls. Thus, no definitive conclusions can be drawn
- Further studies are needed to validate NLR as a prognostic biomarker across different ALS populations

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Disclosures

- **BRB** is a consultant for Tanabe Pharma, Inc.
- **AG** has served as a consultant for Tanabe Pharma, Inc.
- **FTanaka** has served as an investigator and received research funding from Tanabe Pharma, Inc.
- **YK, FTakahashi** and **YU** are employees of Tanabe Pharma Corporation.
- **MH** is an employees of Tanabe Pharma America, Inc.
- **SA** is an employee of Shionogi Inc.
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