UT Southwestern
O'Donnell Brain Institute

Experience with Edaravone at UT Southwestern

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Disclosures

I got married in this hotel on March 17, 2018.

Outline

- Background
  - Edaravone trials
  - Access issues
- Patient introduction
- Retrospective study of UTSW patients

Edaravone (Radicut or Radicava)

- Free radical scavenger (antioxidant)
- Developed in 1980's
- Used in Japan for stroke since 2001
  - 30 mg IV bid x 14 days
- Oral formulation finished phase 1
  - Phase 2 ADORE – ALS Deceleration study with Oral Edaravone

Edaravone Trials in ALS

- Phase 2 study in Japan in 2006
  - Decrease in an oxidative stress biomarker (3-nitrotyrosine)
  - Slowed decline in ALSFRS-R scores after six months

- Phase 3 study in Japan in 2014
  - No improvement in ALSFRS-R scores compared to placebo
  - Post-hoc analysis → benefit in “early” ALS
  - Abe et al., 2014

Jaiswal 2018

The Key Inclusion Criteria

	Age	Disease duration	FVC	El Escorial Criteria	Japan Severity Classification	Observation period	ALSFRS-R
The new trial	20-75	≤2 years	≥80%	Definite or probable	Grade 1 or 2	1 to 4 point ALSFRS-R decrease	At least 2 points on all items
The negative trial	20-75	≤3 years	≥70%	Definite or probable	Grade 1 or 2	1 to 4 point ALSFRS-R decrease	No restriction

Lancet Neurology, May 2017

Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial

The Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group†*

Treatment period

- 6 cycles
  - Cycle 1: Edaravone 60 mg IV qd x 2 weeks followed by 2 weeks off
  - Other cycles: Edaravone 60 mg IV qd in 10 of 14 days followed by 2 weeks off

Primary endpoint

- Change in ALSFRS-R score from baseline to the end of cycle 6

Abe et al., 2017

Primary Endpoint

	Least-squares mean change		Least-squares mean difference	p value*
	Edaravone (n)	Placebo (n)		
Primary endpoint				
ALSFRS-R score	-5·01, 0·64 (68)†	-7·50, 0·66 (66)†	2·49, 0·76 (0·99 to 3·98)	0·0013

Least squares mean difference in mean ALSFRS-R score was in favor of edaravone.

Roughly 2.5 ALSFRS-R points over 6 months.

FDA approval on May 5, 2017

Abe et al., 2017

Access Concerns

- Insurance coverage is the main barrier to patient access to edaravone.
- Sometimes, coverage is restricted to patients that meet the inclusion criteria for the positive study.
- Payers want to know how a scale relates to human experience.
- Is a 2.5 point difference in ALFRS-R over 6 months clinically meaningful?

Brooks et al., 2018

Quality of Life Concerns

- Healthcare providers have a fiduciary responsibility to their patients.

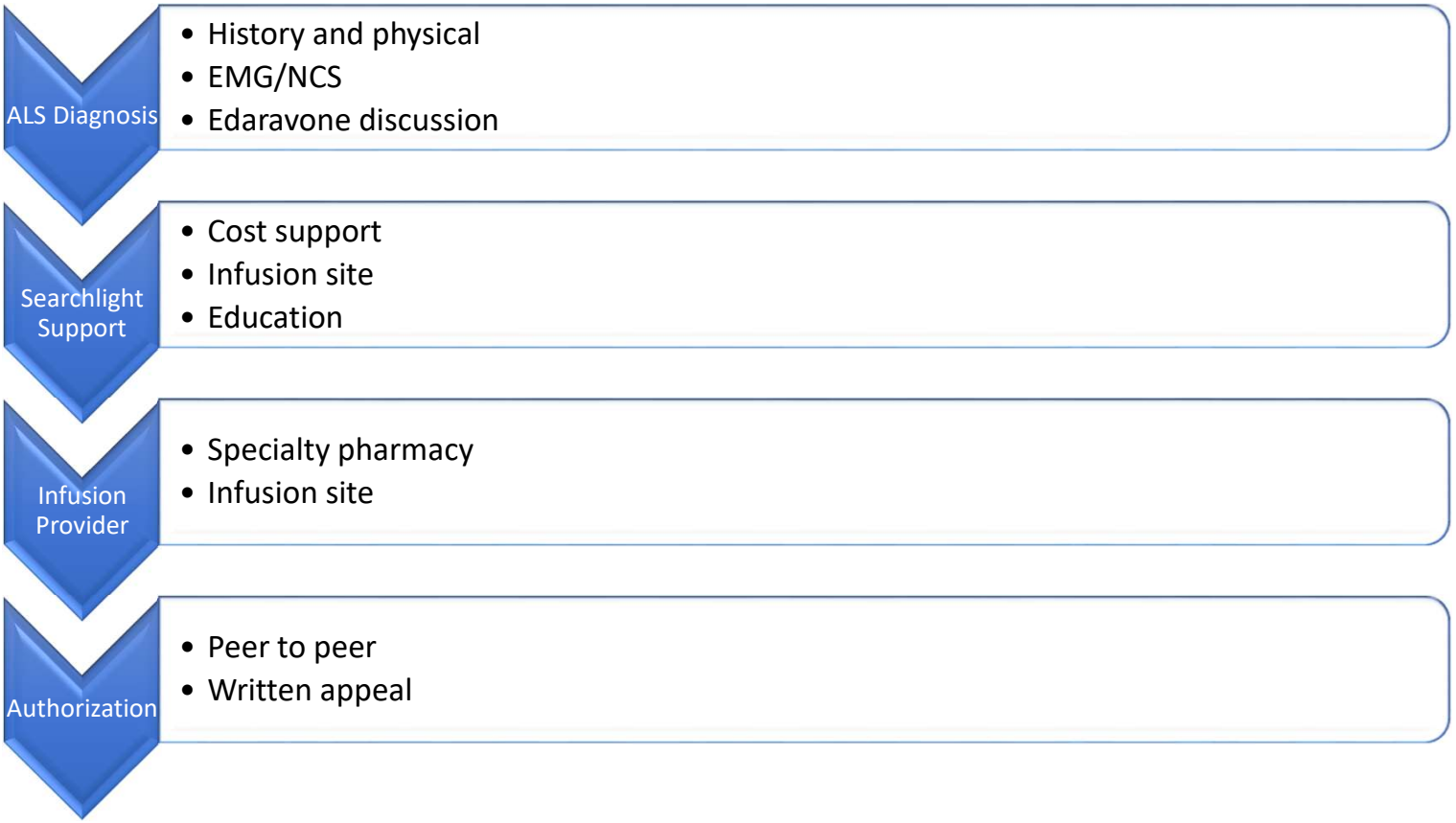
- Treatment with edaravone is intensive.
  - Indwelling line
  - Travel to an infusion center
  - Nearly half of a patient's days involve a one hour infusion

Yeo & Simmons, 2018

Case

- A 68 year old man presents to clinic with progressive right hand weakness and generalized twitching for the last five years.
- Exam
  - Asymmetric distal > proximal extremity weakness
  - Diffuse fasciculations and hyperreflexia
  - Normal sensation
- MR cervical spine: right C5 nerve root compression
- EMG: active denervation in cervical and thoracic myotomes, chronic denervation in lumbar myotomes. Fasciculations seen throughout.

The Edaravone Process

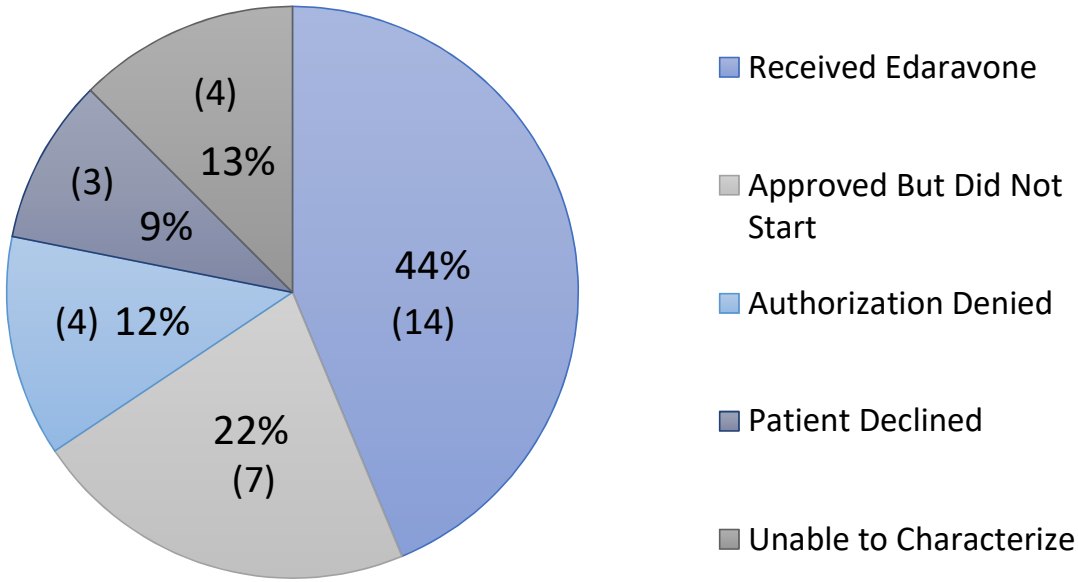


Questions

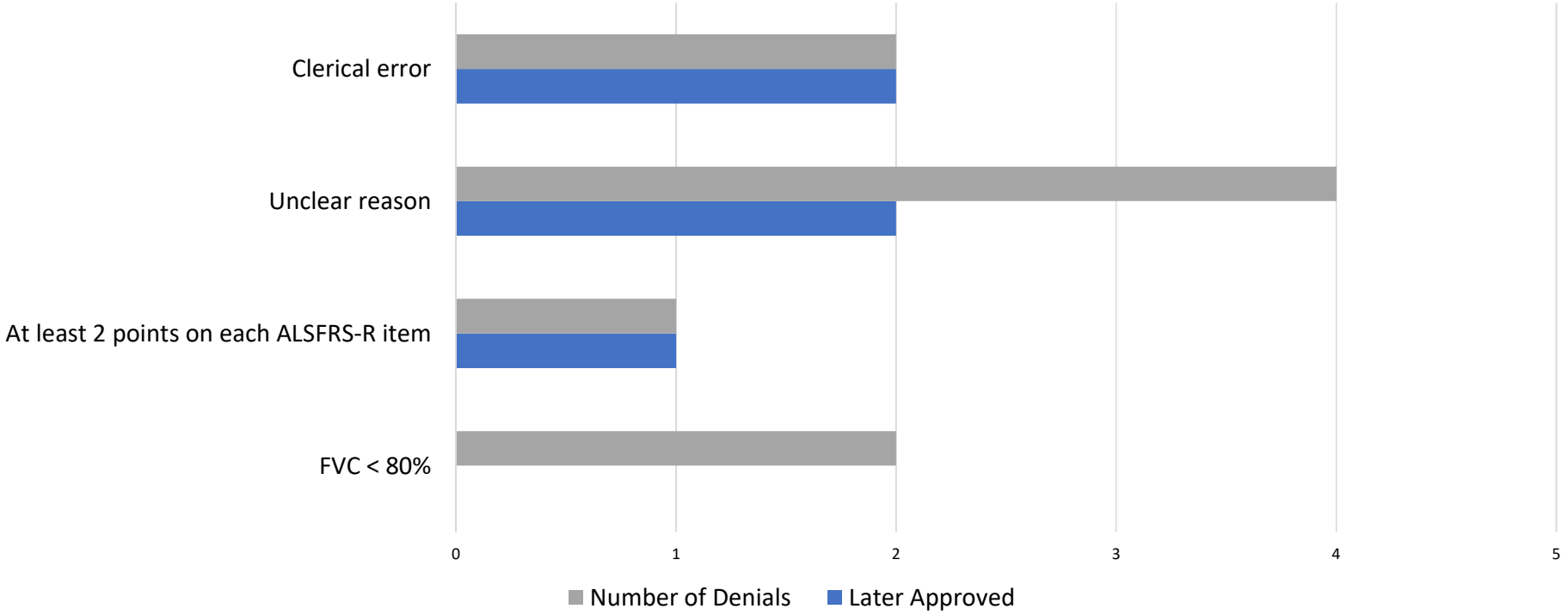
- How long does it take to start edaravone?
- What are the reasons for delay?
- What are the routes of infusion?
- Where does infusion take place?
- What are the reasons for denial?
- Are appeals successful?
- How long do patients stay on edaravone?

The Study Population

32 patients from UT Southwestern referred for edaravone.

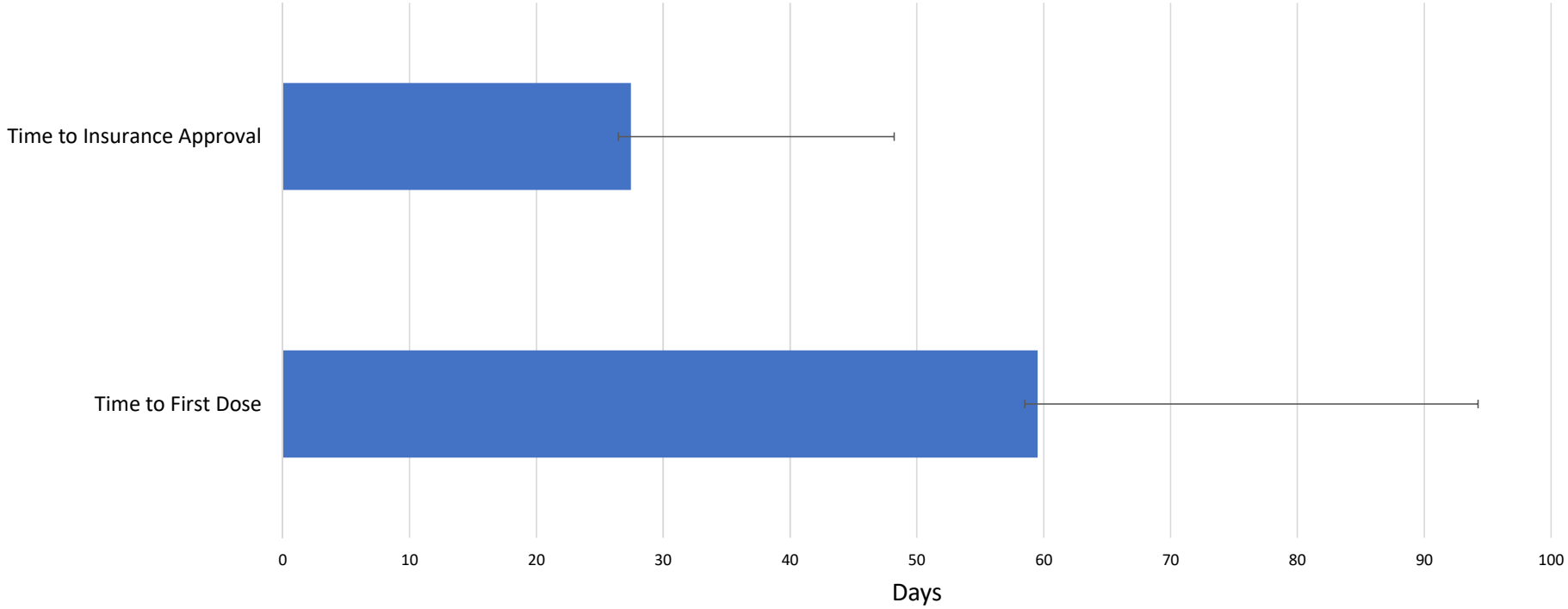


Authorization Denied (n = 9)



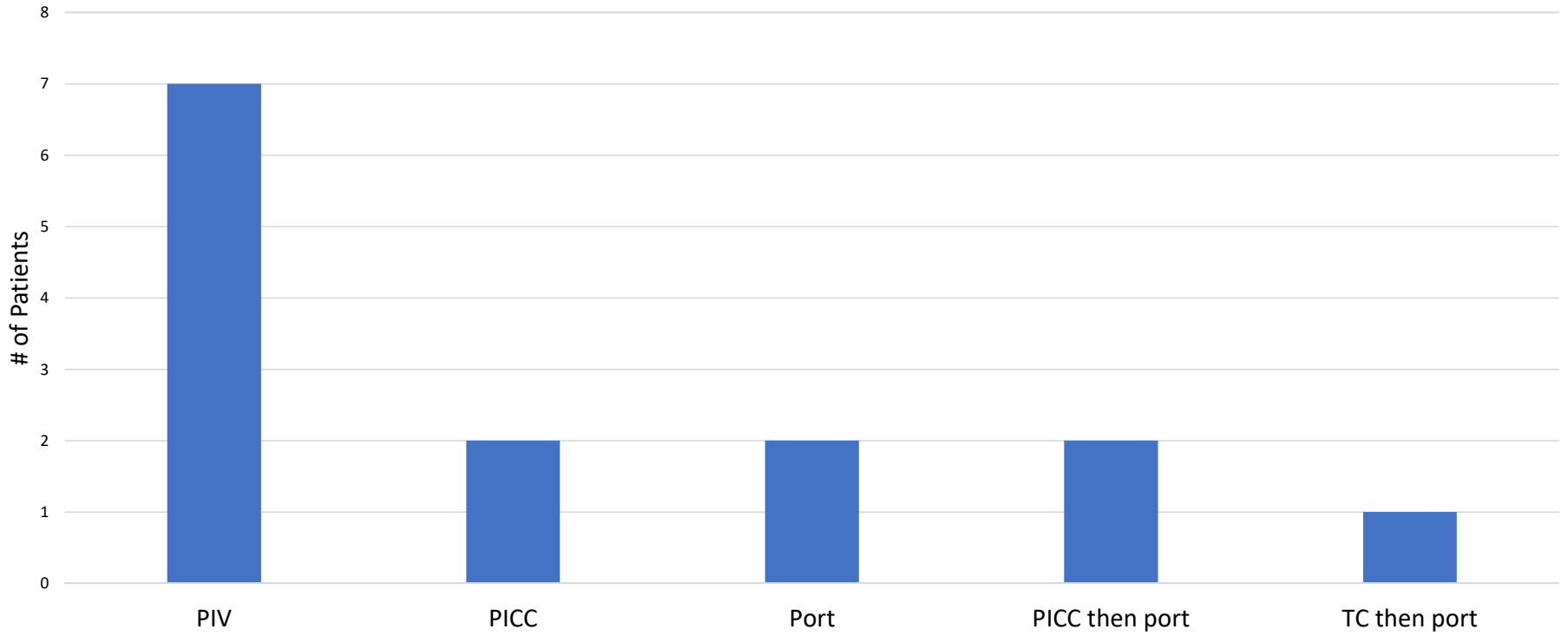
Of the 21 patients approved for edaravone, 8 had FVC < 80%.

Starting Edaravone

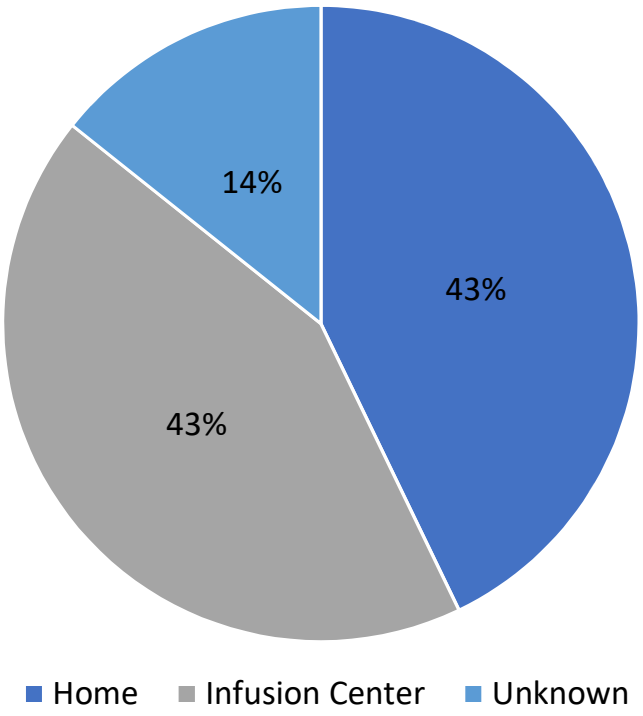


On average, 46% of the time to first dose is accounted for by time to insurance approval.

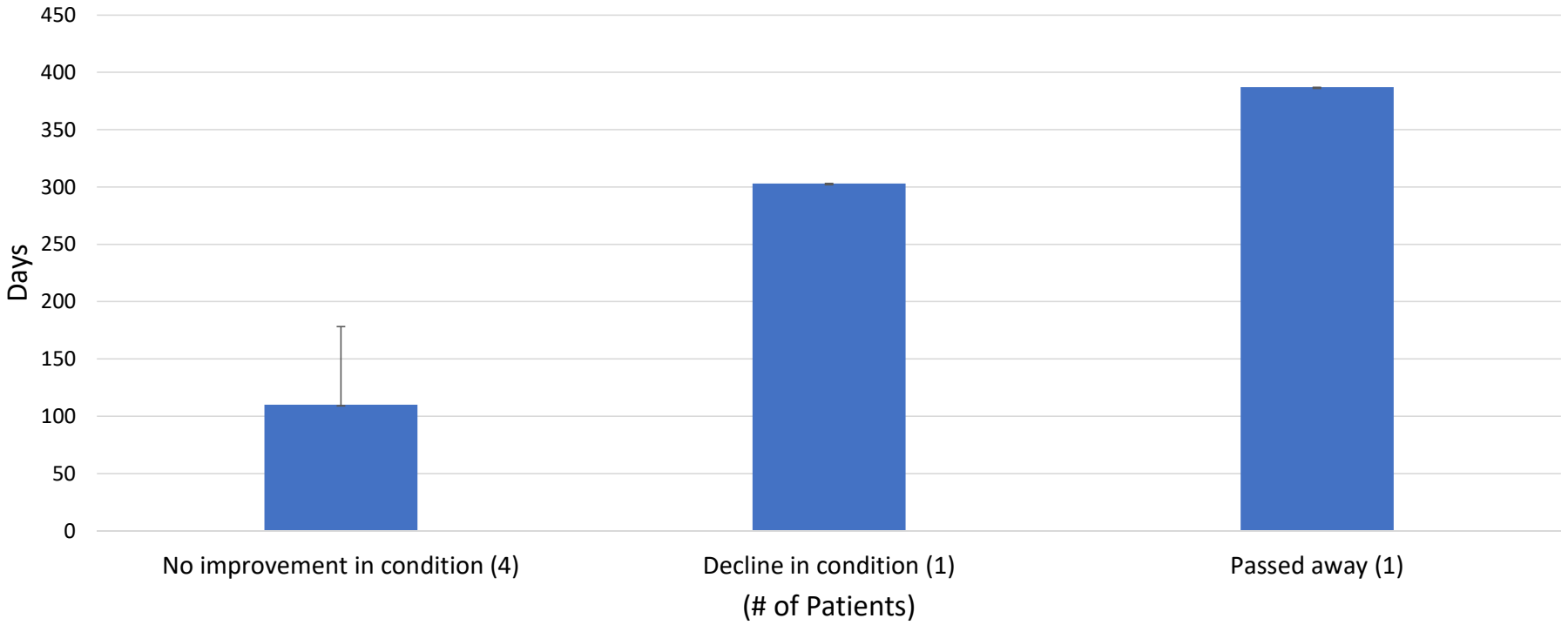
Routes of Infusion



Location of Infusion



First Dose To Stop Date



Average number of days on edaravone is 188 days (roughly 6 cycles).

Summary

- How long does it take to start edaravone? **60 days on average**
- What are the reasons for delay? **Insurance approval accounts for 27 days.**
- What are the routes of infusion? **Port > PICC**
- Where does infusion take place? **Home and away are equally common.**
- What are the reasons for denial? **Often the reason is unclear but sometimes clerical and sometimes trial based.**
- Are appeals successful? **Often unless FVC is the reason for denial**
- How long do patients stay on edaravone? **188 days on average**

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What is a Free Radical Scavenger?

- It is an antioxidant.
- A free radical is any atom or molecule that has an unpaired electron.
- Famous antioxidants
  - Glutathione
  - Superoxide dismutase
  - Ascorbic acid
- And now edaravone
  - Hydrophobic crossing BBB
  - ~$1,000 per infusion
  - ~$145,000 per year

Edaravone (Radicut or Radicava)

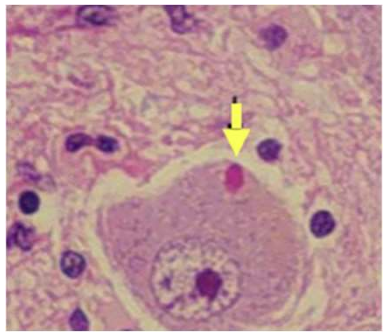
- Developed by *Mitsubishi Tanabe Pharma* in 1980's
- Alias is MCI-186
- Used in Japan for stroke since 2001
  - 30 mg IV bid x 14 days
  - Multiple small trials have shown mRS benefit
- Oral formulation by *Treeway* is in phase I trials

Amyotrophic Lateral Sclerosis

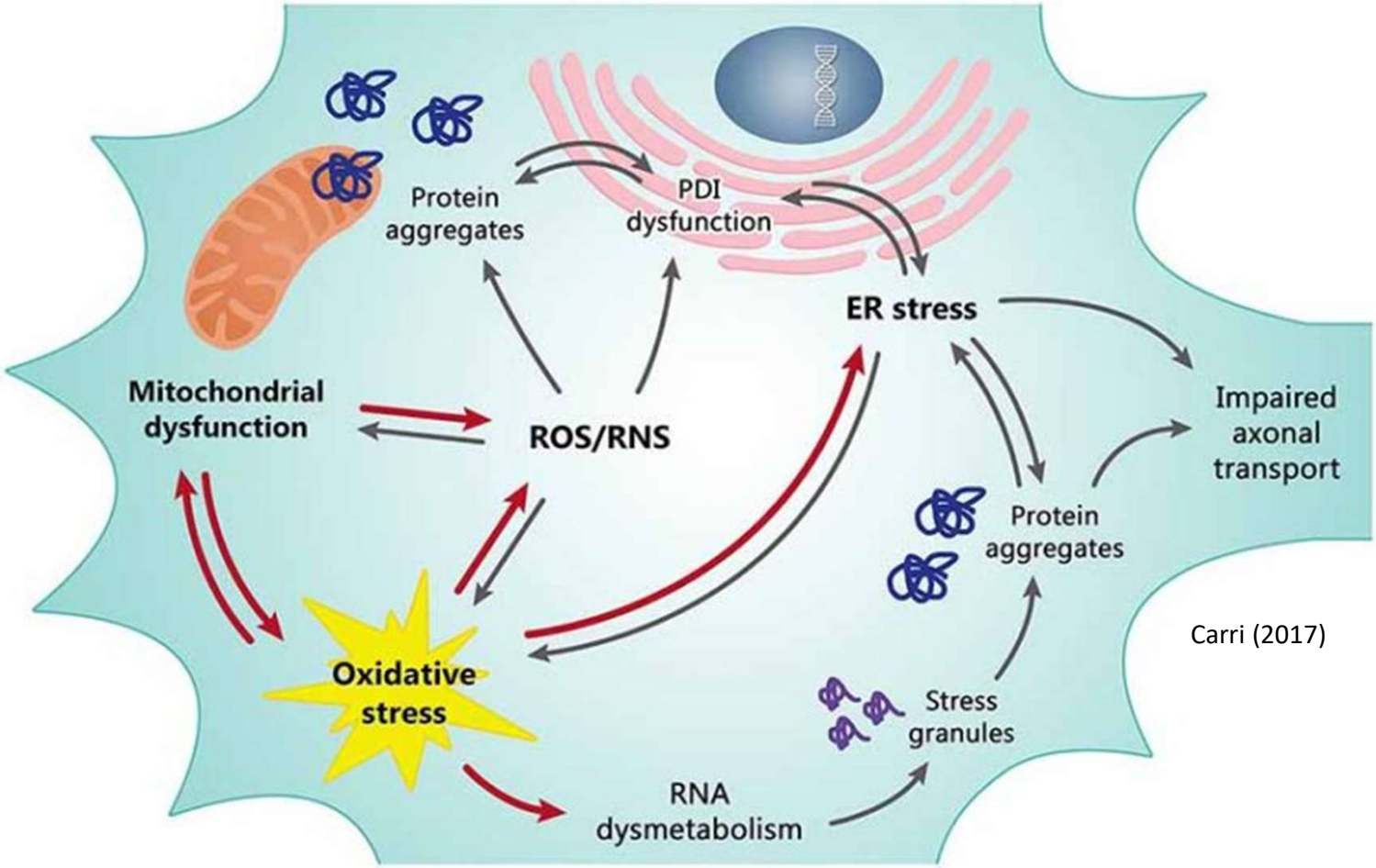
A Clinical Lesson at the Salpêtrière (1887)

Free Radicals in ALS?

- Primary degeneration of gray matter
  - Spinal cord motor neurons
  - Cortical motor neurons (pyramidal cells) → retrograde loss of the corticospinal tract
- Intracellular inclusions
  - Superoxide dismutase (SOD1)
  - TDP-43
  - FUS
  - Cystatin C or transferrin (Bunina bodies)
  - Ubiquitinated inclusions

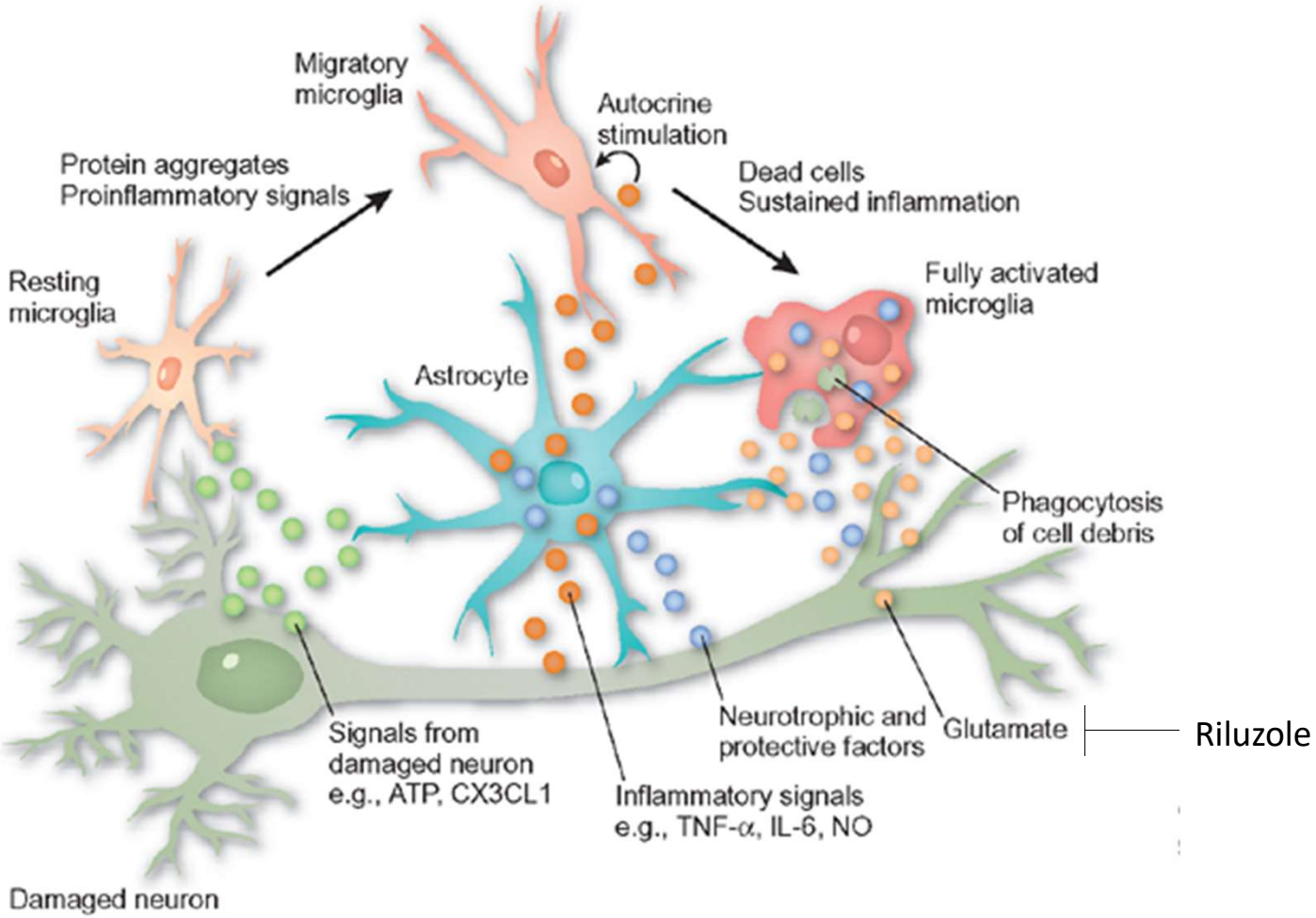


- SOD1 gain of function mutation → *increased* free radicals



Carri (2017)

Mutated motor neurons are not enough. Mutated glial cells are needed too.


Migratory microglia
Autocrine stimulation
Protein aggregates
Proinflammatory signals
Dead cells
Sustained inflammation
Resting microglia
Fully activated microglia
Astrocyte
Phagocytosis of cell debris
Signals from damaged neuron e.g., ATP, CX3CL1
Inflammatory signals e.g., TNF-α, IL-6, NO
Neurotrophic and protective factors
Glutamate
Riluzole
Damaged neuron

Monk (2006)

Edaravone Trials in ALS

- Phase II study in Japan in 2006
  - Decrease in an oxidative stress biomarker (3-nitrotyrosine)
  - Slowed decline in ALSFRS-R scores after six months

- Phase III study in Japan in 2014
  - No improvement in ALSFRS-R scores compared to placebo
  - Post-hoc analysis → benefit in “early” ALS

Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial

The Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group†*

Lancet Neurology, May 2017

PICO Question

P:
"Early" ALS

I: Edaravone

C:
Placebo

O:
ALSFRS-R

Revised ALS Functional Rating Scale (ALSFRS-R), 1999

12 Point Scale

1. **SPEECH** No change value = 4 Noticeable speech disturbance value = 3 Asked often to repeat words or phrases value = 2 Alternative communication methods value = 1 Unable to communicate verbally value = 0 Q1. Score =	7. **TURNING IN BED AND ADJUSTING BEDCLOTHES** No change value = 4 Slower or more clumsy, without assistance value = 3 Can turn alone or adjust bed clothes value = 2 Can initiate but requires assistance value = 1 Helpless in bed value = 0 Q7. Score =
2. **SALIVATION** No change value = 4 Slight excess saliva, nighttime drooling value = 3 Moderately excessive saliva, minimal drooling value = 2 Marked excess of saliva, some drooling value = 1 Marked drooling, requires constant tissue value = 0 Q2. Score =	8. **WALKING** No change value = 4 Change in walking, no assistance or devices value = 3 Requires assistance to walk value = 2 Can move legs or stand up, unable to walk from room to room value = 1 Cannot walk or move legs value = 0 Q8. Score =

3. **SWALLOWING** No change value = 4 Occasional choking episodes value = 3 Modified the consistency of foods value = 2 Supplemental tube feedings value = 1 NPO (do not eat anything by mouth) value = 0 Q3. Score =	9. **CLIMBING STAIRS** No change value = 4 Slower value = 3 Unsteady and/or more fatigued value = 2 Requires assistance value = 1 Cannot climb stairs value = 0 Q9. Score =
4. **HANDWRITING** No change value = 4 Slow or sloppy, all words legible value = 3 Not all words legible value = 2 Able to hold pen, unable to write value = 1 Unable to hold pen value = 0 Q4. Score =	10. **DYSPNEA** No change value = 4 Occurs only with walking value = 3 Occurs with minimal exertion value = 2 Occurs at rest, either sitting or lying value = 1 Significant shortness of breath considering mechanical support value = 0 Q10. Score =

5a. **CUTTING FOOD AND HANDLING UTENSILS**
(patients without gastrostomy)

No change	value = 4
Somewhat slow and clumsy, needs no help	value = 3
Sometimes needs help	value = 2
Foods cut by someone else	value = 1
Needs to be fed	value = 0

Q5a. Score =

5b. **CUTTING FOOD AND HANDLING UTENSILS**
(patients with gastrostomy)

Uses PEG without assistance or difficulty	value = 4
Somewhat slow and clumsy, needs no help	value = 3
Requires assistance with closures and fasteners	value = 2
Provides minimal assistance to caregiver	value = 1
Unable to perform any manipulations	value = 0

Q5b. Score =

6. **DRESSING AND HYGIENE**

No change	value = 4
Performs without assistance with increased effort or decreased efficiency	value = 3
Intermittent assistance or different methods	value = 2
Requires daily assistance	value = 1
Completely dependent	value = 0

Q6. Score =

11. **ORTHOPNEA**

No change	value = 4
Occasional shortness of breath, does not routinely use more than two pillows	value = 3
Require more than 2 pillows to sleep	value = 2
Can only sleep sitting up	value = 1
Require the use of respiratory support (BiPAP®) to sleep	value = 0

Q11. Score =

12. **RESPIRATORY INSUFFICIENCY**

No respiratory support	value = 4
Intermittent use of BiPAP®	value = 3
Continuous use of BiPAP® at night	value = 2
Continuous use of BiPAP day and night	value = 1
Invasive mechanical ventilation	value = 0

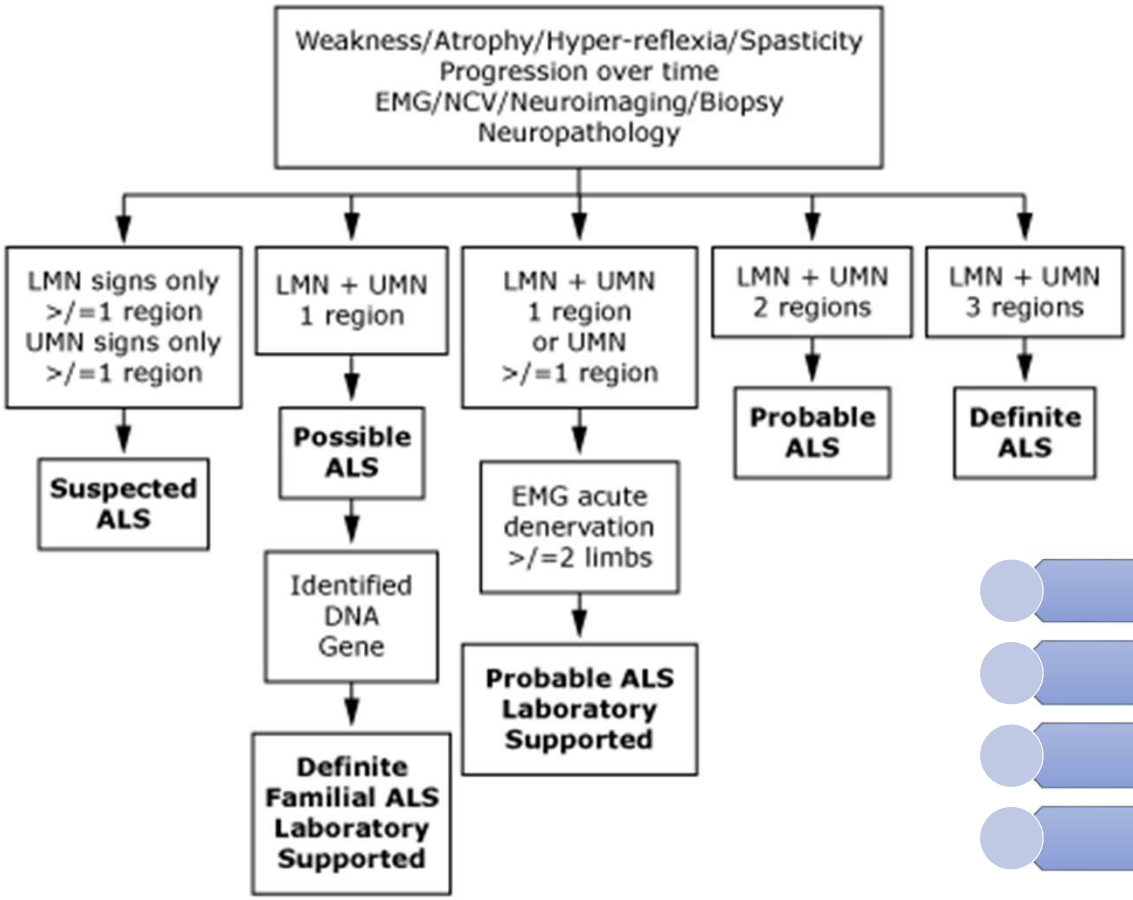
Q12. Score =

Total Score = ***/ 48***

Japan ALS Severity Classification

1. Able to work or perform housework
2. Independent living but unable to work
3. Requiring assistance for eating, excretion or ambulation
4. Presence of respiratory insufficiency, difficulty in coughing out sputum or dysphagia
5. Using a tracheostomy tube, tube feeding or tracheostomy positive pressure ventilation.

El Escorial Criteria, 2000



- Cranial
- Cervical
- Thoracic
- Lumbosacral

“Early” ALS

- Inclusion criteria
  - Age 20-75
  - Disease duration of ≤ 2 years
  - Forced vital capacity ≥ 80%
  - Grade 1 or 2 on *Japan ALS Severity Classification*
  - At least 2 points on all items of *ALSFRS-R*
  - Definite or probable ALS by *El Escorial criteria*
  - Observation period
    - Must have a 1 to 4 point decrease in the ALSFRS-R in a 12 week period

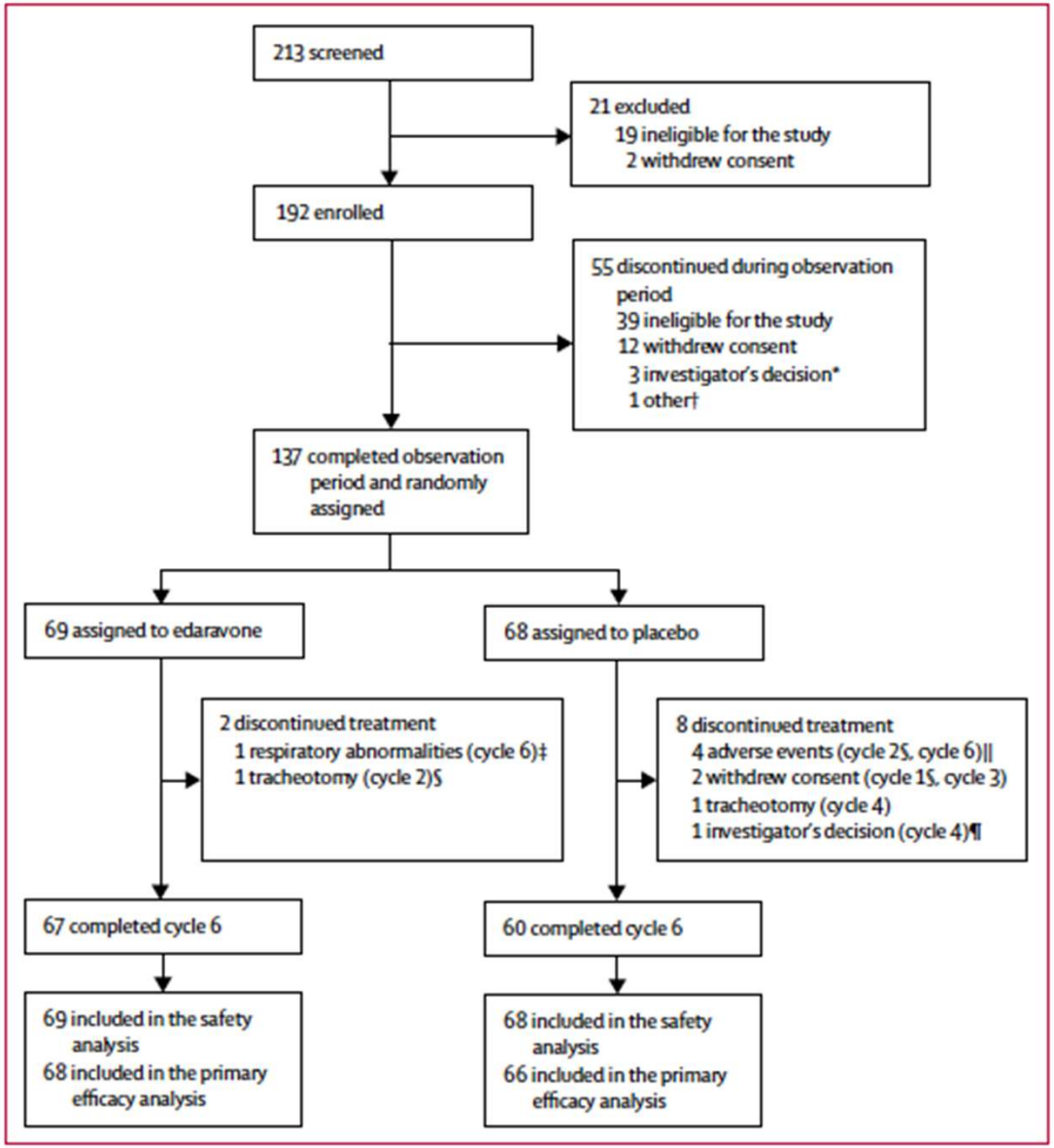
Further details

- Exclusion criteria
  - Spinal surgery after onset of ALS
  - Creatinine clearance ≤ 50 mL/min
- Riluzole
  - OK to continue without changing dose
  - Cannot start
- Patient population
  - 31 hospitals in Japan
  - 2011 to 2014

Do you dare?

- After the observation period, an independent registration center randomized patients.
- Identical ampules
  - Edaravone 60 mg in 100 mL
  - Saline only placebo

- Treatment period
  - 24 weeks
  - 6 cycles
    - Cycle 1: Edaravone 60 mg IV qd x 2 weeks followed by 2 weeks off
    - Other cycles: Edaravone 60 mg IV qd in 10 of 14 days followed by 2 weeks off
  - Extended to 12 cycles (unpublished)


213 screened
21 excluded
19 ineligible for the study
2 withdrew consent
192 enrolled
55 discontinued during observation period
39 ineligible for the study
12 withdrew consent
3 investigator's decision*
1 other†
137 completed observation period and randomly assigned
69 assigned to edaravone
68 assigned to placebo
2 discontinued treatment
1 respiratory abnormalities (cycle 6)‡
1 tracheotomy (cycle 2)§
8 discontinued treatment
4 adverse events (cycle 2§, cycle 6)||
2 withdrew consent (cycle 1§, cycle 3)
1 tracheotomy (cycle 4)
1 investigator's decision (cycle 4)¶
67 completed cycle 6
60 completed cycle 6
69 included in the safety analysis
68 included in the primary efficacy analysis
68 included in the safety analysis
66 included in the primary efficacy analysis

	Edaravone group (n=69)	Placebo group (n=68)
Sex		
Men	38 (55%)	41 (60%)
Women	31 (45%)	27 (40%)
Age, years	60·5 (10)	60·1 (10)
Younger than 65 years*	46 (67%)	46 (68%)
65 years or older*	23 (33%)	22 (32%)
Bodyweight, kg	57·9 (12·9)	57·8 (9·3)
Height, cm	161·8 (9·5)	162·5 (8·4)
BMI, kg/m²†	21·9 (3·6)	21·8 (2·7)
ALS diagnosis		
Sporadic	68 (99%)	66 (97%)
Familial	1 (1%)	2 (3%)
ALS diagnostic criteria‡		
Definite*	28 (41%)	27 (40%)
Probable*	41 (59%)	41 (60%)
ALS severity§		
Grade 1	22 (32%)	16 (24%)
Grade 2	47 (68%)	52 (76%)
Duration of disease, years	1·13 (0·5)	1·06 (0·5)
Initial symptom		
Bulbar onset	16 (23%)	14 (21%)
Limb onset	53 (77%)	54 (79%)

ALSFRS-R score		
Before observation period	43·6 (2·2)	43·5 (2·2)
At baseline (at the end of 12 week observation period)	41·9 (2·4)	41·8 (2·2)
Change about observation period		
–4 or –3*	12 (17%)	11 (16%)
–2 or –1*	57 (83%)	57 (84%)
Riluzole use		
Yes	63 (91%)	62 (91%)
No	6 (9%)	6 (9%)

Data are n (%) or mean (SD). ALS=amyotrophic lateral sclerosis. ALSFRS-R=Revised ALS Functional Rating Scale. *Factor used in dynamic allocation. †Post-hoc assessment. ‡According to revised El Escorial criteria. §According to Japan ALS severity classification (grade 1–5, grade 5 most severe).

Table 1: **Demographics and baseline clinical characteristics**

Outcomes

- Primary endpoint
  - Change in ALSFRS-R score from baseline to the end of cycle 6
- Secondary endpoints
  - Change in FVC
  - Modified Norris Scale (limb, bulbar, total)
  - ALS Assessment Questionnaire (ALSAQ-40) → subjective well being
  - Japanese ALS Severity Classification
  - Grip strength
  - Pinch strength
  - Time to death or time to “specified state of disease”

Statistical analysis

- ALSFRS-R change was judged by least squares mean difference
- Anyone who reached cycle 3 was included
  - For missing values at the end of cycle 6, data was imputed by the last observation carried forward (LOCF) method
    - Affects type 1 error (false positive) rate for the treatment effect
    - Post-hoc analysis with a mixed effects model for repeated measures (MMRM)

Results

- Primary endpoint
  - Least squares mean difference in mean ALSFRS-R scores was in favor of edaravone.
    - **2.49 (95% CI 0.99 – 3.98, p = 0.0013)**
- Secondary endpoints
  - Modified Norris Scale (total) favored edaravone
  - ALSAQ-40 favored edaravone
  - No difference in:
    - FVC
    - Grip, pinch strength
    - Time to death or time to “specified state of disease”
    - Japanese ALS severity classification

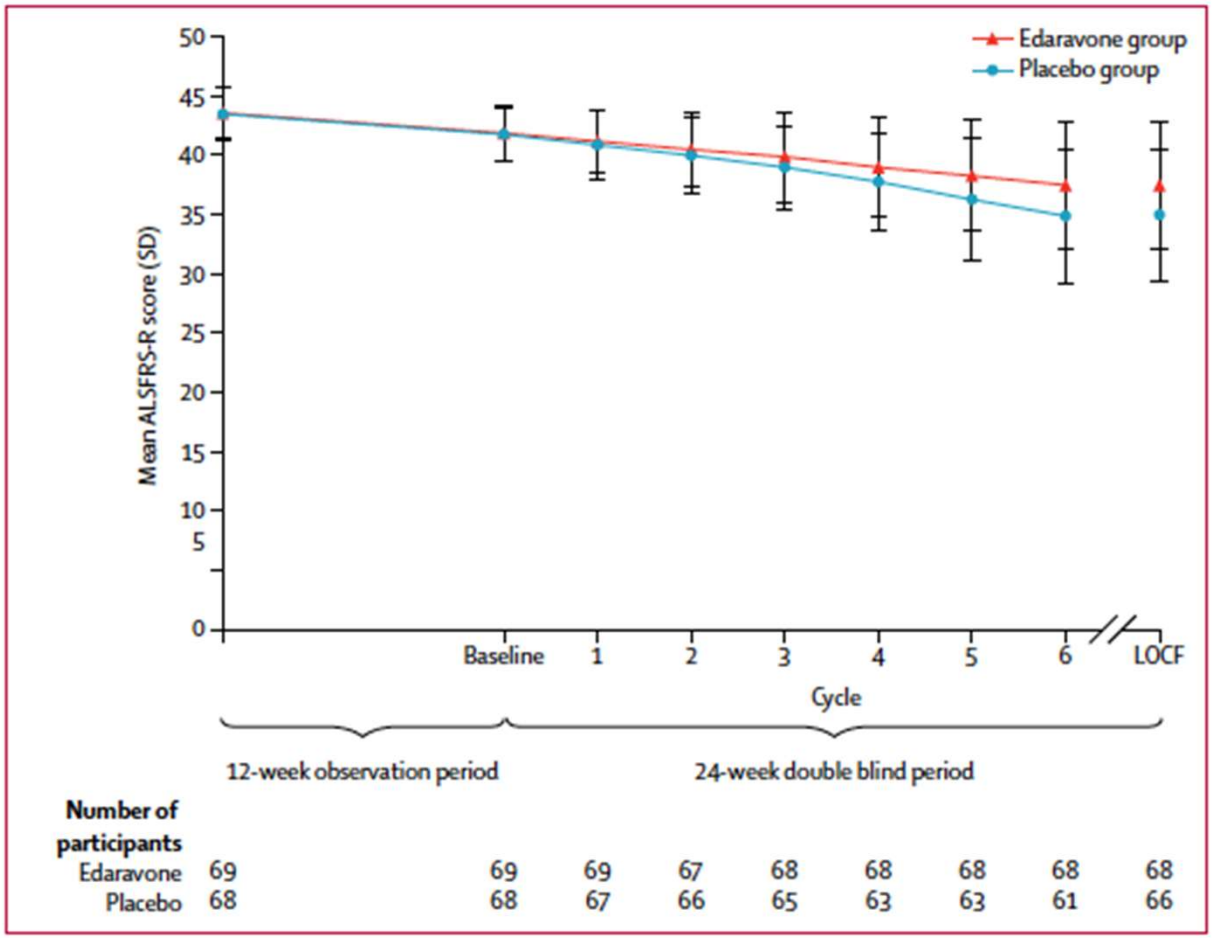


***Figure 2*: Mean ALSFRS-R scores during treatment**

For patients with missing values at the end of cycle 6, data were imputed by the LOCF method, provided that they had completed at least cycle 3. ALS=amyotrophic lateral sclerosis. ALSFRS-R=Revised ALS Functional Rating Scale. LOCF=last observation carried forward. One patient's evaluation at the end of cycle 2 was excluded from analysis as the clinician assessing ALSFRS-R score did not have adequate training.

	Adverse events		Serious adverse events	
	Edaravone group (n=69)	Placebo group (n=68)	Edaravone group (n=69)	Placebo group (n=68)
Any	58 (84%)	57 (84%)	11 (16%)	16 (24%)
Contusion	13 (19%)	9 (13%)	0	1 (2%)
Constipation	8 (12%)	8 (12%)	0	0
Dermatitis contact	8 (12%)	3 (4%)	0	0
Dysphagia	8 (12%)	10 (15%)	8 (12%)	8 (12%)
Eczema	5 (7%)	2 (3%)	0	0
Insomnia	5 (7%)	4 (6%)	0	0
Upper respiratory tract inflammation	5 (7%)	2 (3%)	0	0
Back pain	4 (6%)	1 (2%)	0	0
Headache	4 (6%)	5 (7%)	0	0
Myalgia	4 (6%)	1 (2%)	0	0
Nasopharyngitis	3 (4%)	5 (7%)	0	0
Respiratory disorder	3 (4%)	2 (3%)	2 (3%)	2 (3%)
Diarrhoea	2 (3%)	4 (6%)	0	0
Speech disorder	1 (1%)	2 (3%)	1 (1%)	2 (3%)
Pneumonia aspiration	0	2 (3%)	0	2 (3%)

Data are n (%). Includes all adverse events that had occurred in at least 5% of patients or were rated as serious adverse events in more than two patients in either treatment group during the specified study period. Adverse events were defined using the Medical Dictionary for Regulatory Activities, Japanese Version 17.0. Serious adverse events were defined as fatal, life-threatening, causing or potentially causing disability, or causing or prolonging hospitalisation.

Table 3: **Adverse events**

Conclusion

- Progression of early ALS is slowed by edaravone.
  - Roughly 2.5 ALSFRS-R points over 6 months

FDA Approval

- May 5, 2017
- Orphan Drug Status
- “The efficacy of edaravone for the treatment of ALS was demonstrated in a six-month clinical trial conducted in Japan. In the trial, 137 participants were randomized to receive edaravone or placebo. At Week 24, individuals receiving edaravone declined less on a clinical assessment of daily functioning compared to those receiving a placebo.” – *FDA* press release

Is this a high quality trial?

- Is 137 patients an adequate amount of test subjects?
  - The failed phase III trial had 206 patients.
- Bias is inherent in a trial run by the pharmaceutical company.
- However, the trial appears well run with a focused conclusion.

Is this a clinically meaningful population?

	Age	Disease duration	FVC	Diagnosis	Japan Severity	Observation period	ALSFRS-R
This trial	20-75	≤2 years	≥80%	Definite or probable	Grade 1 or 2	1 to 4 point ALSFRS-R decrease	At least 2 points on all items
The failed trial	20-75	≤3 years	≥70%	Definite or probable	Grade 1 or 2	1 to 4 point ALSFRS-R decrease	No restriction

Is the result clinically meaningful?

	Least-squares mean change		Least-squares mean difference	p value*
	Edaravone (n)	Placebo (n)		
Primary endpoint				
ALSFRS-R score	-5·01, 0·64 (68)†	-7·50, 0·66 (66)†	2·49, 0·76 (0·99 to 3·98)	0·0013