Multidisciplinary Care for the Patient with Amyotrophic Lateral Sclerosis

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Lora L. Clawson discloses no actual or potential conflict of interest related to this program

Objectives

- Meeting the unique needs of the ALS patient and their family
  - Demographic information
  - Criteria for diagnosis
  - How ALS affects individuals
  - Theories, trials and future directions
  - Expectations of Edaravone/Radicava® & Riluzole/Rilutek®
  - Clinical management, ongoing monitoring & research
  - Role of ALS Multidisciplinary Clinical Team including Home Infusion & Home Care Companies in Clinical Care
  - Community Resources/Non-Profit Organizations

ALS – A NEW ERA

- 1874: JM Charcot discusses the features of ALS
- 1990s: rapid increase in understanding of the pathophysiology
- 1995: Riluzole (Rilutek®) is the first drug approved by the FDA
  - Double-blind, placebo-controlled clinical trial
  - Inhibits glutamate release
- 2017: Edaravone (Radicava®) is the second drug approved by the FDA
  - Double-blind, placebo-controlled clinical trial
  - Anti-oxidant

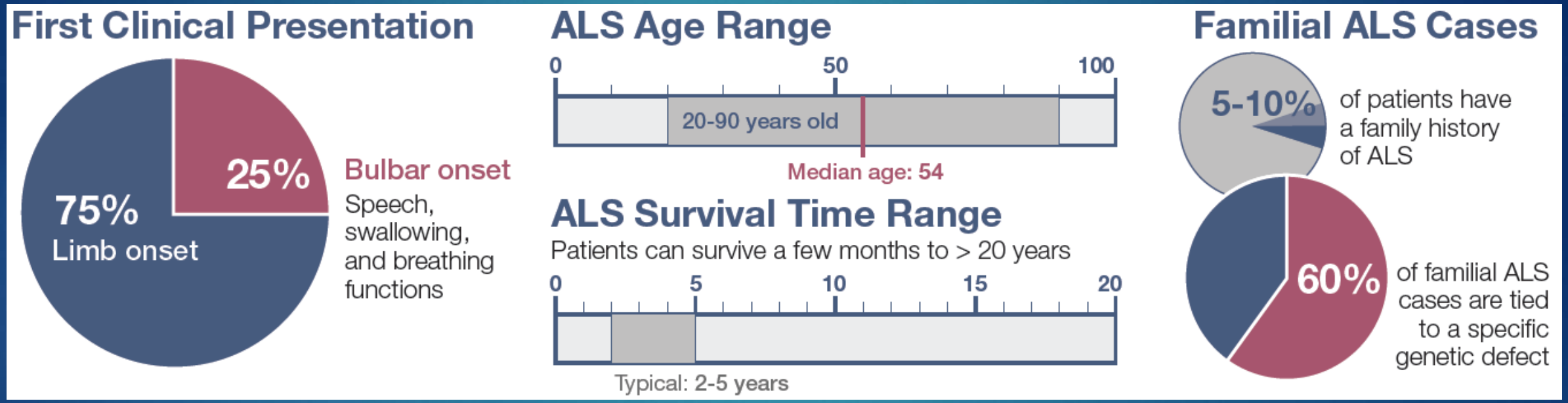
ALS DEFINITION

- World Federation of Neurology El Escorial Criteria for the Diagnosis of Amyotrophic Lateral Sclerosis
  - Upper motor neuron loss
  - Lower motor neuron loss
  - Progression
  - Absence of other disease processes
  - Levels of diagnostic certainty:
    - Definite, Probable, Possible

ALS DEMOGRAPHICS

- Age at onset of symptoms
  - Full adult age range
  - Mean age: 55 years
- Gender
  - 1.5 : 1 males : females
- Incidence
  - 1-2 per 100,000
- Prevalence
  - 6 per 100,000

ALS PATIENT POPULATION



Source: *Cell*, 2017; Volume 171: p. 725

TYPES OF MOTOR NEURON DISEASE

- Progressive Muscular Atrophy (PMA)

Spinal Muscular Atrophy (SMA)

  - Lower Motor Neuron
- Primary Lateral Sclerosis (PLS)
  - Upper Motor Neuron
- Amyotrophic Lateral Sclerosis (ALS)
  - Upper and Lower Motor Neuron
- Progressive Bulbar Palsy (PBP)
  - Bulbar onset of ALS

TYPES OF ALS

- Sporadic (SALS)
  - No family history
- Familial (FALS)
  - SOD 1 gene mutation – autosomal dominant
  - C9orf72 gene mutation – ALS/FTD

ALS ANATOMY

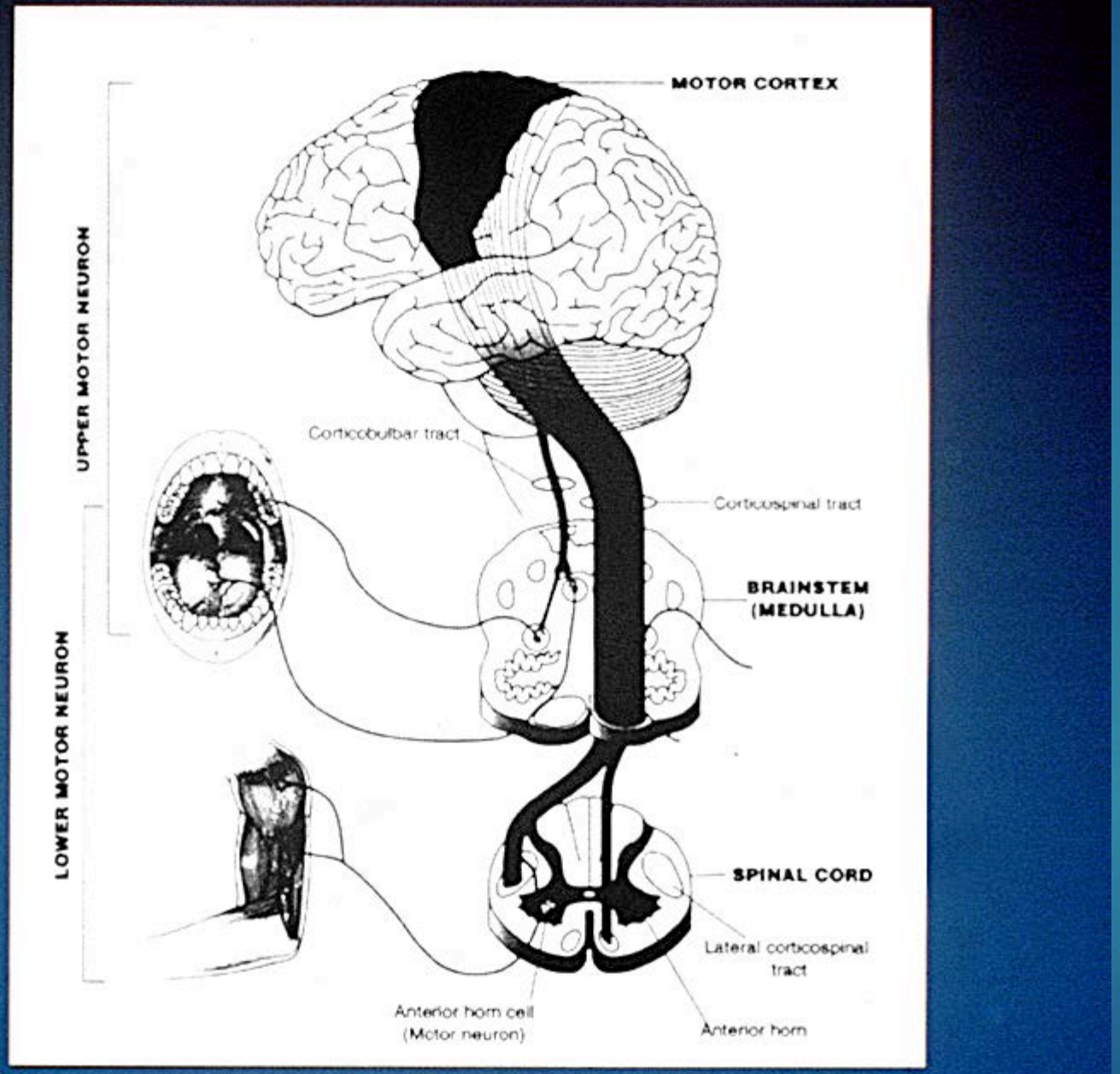
- Overview of Motor System
  - Central – cerebral cortex, basal ganglia, thalamus, cerebellum, brain stem, spinal cord
  - Peripheral – alpha motor neurons, neuromuscular junction, muscles

ALS ANATOMY AND PHYSIOLOGY

- How movements are performed
  - The thought
  - The motor program
  - Target identification, planning of action
  - Activation of appropriate UMN
  - Activation of appropriate LMN
  - Desired movement executed
  - (Feedback and coordination functions normal)

ALS PHYSIOLOGY

- Motor program
  - Strategy for desired movement
- Activation of Motor Cortex (UMN)
  - Corticobulbar neurons
  - Corticospinal neurons
- Motor Unit Recruitment (LMN)
  - Generation of sufficient strength
  - Desired movement accomplished



Source: *Amyotrophic Lateral Sclerosis: Diagnosis and Management for the Clinician*. Belsh JM, Schiffman PL, eds. New York: Futura Publishing Company, Inc; 1996.

ALS PATHOLOGY

- Death of Upper Motor Neurons
  - Loss of Betz cells from motor cortex
  - Degeneration of lateral corticospinal tract – "lateral sclerosis"
- Death of Lower Motor Neurons
  - Loss of anterior horn cells
  - Fiber type grouping in muscle – "amyotrophy"

ALS PATHOPHYSIOLOGY

- Compensatory collateral reinnervation in muscle
  - Surviving motor neurons sprout new branches to reinnervate widowed muscle fibers
  - Preserves muscle strength in early phase
  - Reinnervation fails to continue to compensate when >50% of LMN's die
  - Clinical weakness appears at this point

ALS DIAGNOSIS

- Patient History
  - Diffuse asymmetric weakness and atrophy of voluntary muscles
  - Steady progression
  - Fatigue, cramps, fasciculations, weight loss
  - Ease of laughing, crying or yawning
  - Occasional sensory symptoms

ALS DIAGNOSIS

- Examination: Lower Motor Neurons
  - Asymmetric atrophy and weakness in a diffuse pattern
    - Diffuse fasciculations and cramps
  - EMG findings: ongoing diffuse acute & chronic denervation
- Examination: Upper Motor Neurons
  - Pathologic tendon reflexes (spread) ; Clonus
  - Spasticity to passive manipulation
  - Extensor plantar (Babinski) response (in 50% - presents late)
  - Associated signs – ease of laughing, crying or yawning

ALS DIAGNOSIS

- Uninvolved
  - Bowel and bladder function (incontinence)
  - Special senses
  - Ocular function
  - Organ function
- Occasionally Involved
  - Pain
  - Mental status
  - Sensory system

ALS DIAGNOSIS

- Electromyographic (EMG) Findings
  - Ongoing denervation and reinnervation in a diffuse pattern
  - Normal motor and sensory nerve conduction velocities
- Muscle biopsy (r/o myopathies)
- Magnetic Resonance Imaging (MRI) (r/o lesions)
- Cerebrospinal Fluids (r/o MS, malignancies)
- Routine laboratory testing

ALS CLINICAL FEATURES

- Bulbar
  - Impaired ability to: handle saliva, chew/swallow, speak, nutrition
- Neck Weakness
  - Impaired ability to hold head erect, saliva, chew/swallow, walk
- Upper Extremity Weakness
  - Distal, proximal, Impaired ability to perform activities of daily living
- Trunk Weakness
  - impaired ability to turn in bed, stand erect, walk, breath
- Lower Extremity Weakness
  - Distal, proximal, impaired ability to rise from chair, falls, walk, transfer, dress
- Respiratory Muscle Weakness
  - Impaired ability to cough, breath, speak, walk

ALS CLINICAL FEATURES

- General
  - Fatigue
  - Cramps
  - Fasciculations
  - Spasticity
  - Ease of laughing, crying or yawning
  - Musculoskeletal aches and pains

ALS CLINICAL FEATURES

- Functions Rarely Affect
  - Cognitive
  - Sensory
  - Ocular
  - Bowel and Bladder
- Functions Not Affected
  - Smooth and cardiac muscle
  - Internal organ (function)
  - Sexual

ALS CLINICAL FEATURES

- Prognosis
  - 50% die within 2-5 years of symptom onset
  - 10-25% of patients are alive at 10-15 years after symptom onset
  - Late onset associated with rapid progression
  - Rate of progression generally constant within an individual
  - Rate of progression may plateau in late stages

PATHOGENESIS OF ALS: CURRENT RESEARCH THEORIES

- Excitotoxic Hypothesis
  - Excess glutamate, transporter defect
- Oxidative Stress/Free Radical Damage
  - Cu/Zn (SOD1 gene mutation) on chromosome 21
- Autoimmune Hypothesis
  - Calcium channels (L-type) antibodies
- Cytoskeletal Abnormalities
  - Neurofilament accumulations

POSSIBLE THERAPIES & FUTURE DIRECTION FOR RESEARCH

- Antiexcitotoxic agents
- Antioxidants
- Immunosuppressants
- Neurotrophic Factors
- Stem Cell Therapy
- Gene Transfer Therapy
- Combination therapy

PHILOSOPHY OF CLINICAL TRIAL PARTICIPATION **www.clinicaltrials.gov**

- "A valid, controlled clinical trial is a real expression of hope."
  - Clawson, Rothstein & Kuncl (1993)

PHILOSOPHY OF MEDICAL TREATMENT

- "There is a great deal that can be done to treat the symptoms of ALS, to improve the quality of life of a patient, and to help caregivers and the family cope with the disease."
  - Mitsumoto & Norris (1994)

CLINICAL CARE OF ALS – OVERVIEW

- Psychosocial Issues
- Functional Disabilities
- Dysarthria
- Dysphagia
- Respiratory Insufficiency & Failure
- Symptom Management
- Terminal Care

ALSFRS-R
Revised ALS Functional Rating Scale

- Validated Questionaire to Evaluate Functional Decline – assessing bulbar, fine motor, gross motor, and respiratory functions
- Assessing physical functioning carrying out activities of daily living
- Each task is rated on a five-point scale for
- 0 = can not perform task to 4 = normal stability
- Individual item scores are summed to produce a reported score of between 0=worst to 48=best

PSYCHOSOCIAL ISSUES

- Assess coping mechanisms and problem solving skills
- Promote support group participation by patient and family
- Encourage participation in valid clinical trials
- Encourage continued lifestyle – hobbies, social interaction
- Promote use of ALS informational sites on the internet

FUNCTIONAL DISABILITIES

- Assess muscle strength, endurance, gait and balance
- Teach stretching and exercise program
- Teach energy conservation and compensatory techniques
- Discuss barriers to independence
- Encourage communication with other patients to learn about existing solutions
- Familiarize patient with adaptive aids and equipment

DYSARTHRIA

- Assess speech volume, quality, time of day affected
- Discuss relaxation, positioning, compensatory techniques
- Utilize simple communication tools
- Encourage concise phrasing, exaggerated articulation
- Recommend use of augmentative communication device

COMMUNICATION AIDS

- Note pad
- Magic slate – Boogie Board
- Call device (dinner bell, clicker, intercom system, Speak and Spell)
- Letterboards (ETRAN, letter cuff [alphabet list worn on forearm])
- Hand-held computers with print-out device
- IPHONE, IPAD, Laptop computer – Applications - Proloquo2go
- Speech Amplifier Devices
- Speech Generating Devices – Tobii-Dynavox
  - Specific software capabilities adapted to patient needs
  - Voice synthesizer
  - Switches adaptable to head movement, eye blink or suck/blow

DYSPHAGIA

- Assess nutritional state – weight, swallowing study
- Instruct in swallowing techniques – chin tuck, concentrate/minimize distractions
- Eating & drinking with MND Guide – **www.mndassociation.org**
- EMST – expiratory muscle strength training; Heimlich maneuver
- 5-6 small portion meals per day, small bite size pieces, avoid problem textures and consistencies – avoid sweet/sour (increase secretions) avoid milk products (thick stringy secretions)
- Adequate calories, fiber and fluid intake
- Alternative feeding devices – GT, PEG, percutaneous gastrojejunostomy

FEEDING TUBE DECISION

- Educate patient and family regarding ALS and prognosis
- Encourage a thoughtful decision, not an emotional one
- Emphasis on nutrition & hydration support
- Discuss type of feeding tubes – pros and cons
- Discuss advanced directives
- Seek advice from experienced individuals

RESPIRATORY INSUFFICIENCY & FAILURE

- Assessment of respiratory state – FVC, strength of cough and voice
- Vaccinate for flu and pneumovac
- Instruct in energy conservation, breathing exercises
- Instruct in chest PT, assistive cough techniques
- Discuss assistive breathing devices, secretion mobility devices, tracheostomy, long term ventilation, advanced directives, hospice

VENTILATOR DECISION

- Educate patient and family
- Encourage a thoughtful decision – discuss the long-term impact
- Discuss all alternatives – pros and cons
- Assess resource availability
- Discuss advanced directives
- Seek advice from experienced individuals

SYMPTOM MANAGEMENT I

- Sialorrhea: Robinul, Elavil, Levsin, Sal-Tropine, suction machine
- Xerstomia: Humibid, bedside humidification, chin strap at night
- Cramps: Quinine sulfate, Baclofen, Valium, stretching exercises
- Constipation: adequate fluid & fiber intake, laxatives, herbal teas
- Phlegm: adequate hydration, avoidance of milk products, chest PT
- Cough: honey & lemon juice, Robitussin, codeine, Atrovent inhaler, Proventil/saline in nebulizer, chest PT, cough assist device

SYMPTOM MANAGEMENT II

- Depression: Zoloft, Paxil, patient & family counseling
- Emotional lability: Nuedexta, Elavil, patient & family education
- Fatigue: Mestinon, Modafinil, energy conservation techniques
- Dyspnea: Relaxation & breathing exercises, BiPAP, Nebulizer treatments, morphine
- Insomnia: Benadryl, Ambien, Restoril, Ativan, Trazadone, positioning, adequate room ventilation, meditation, relaxation exercises, sleep study evaluation
- Skin Breakdown: keep skin clean & dry, pressure relief, frequent repositioning, Jay cushion for wheelchair, floatation mattress for hospital bed

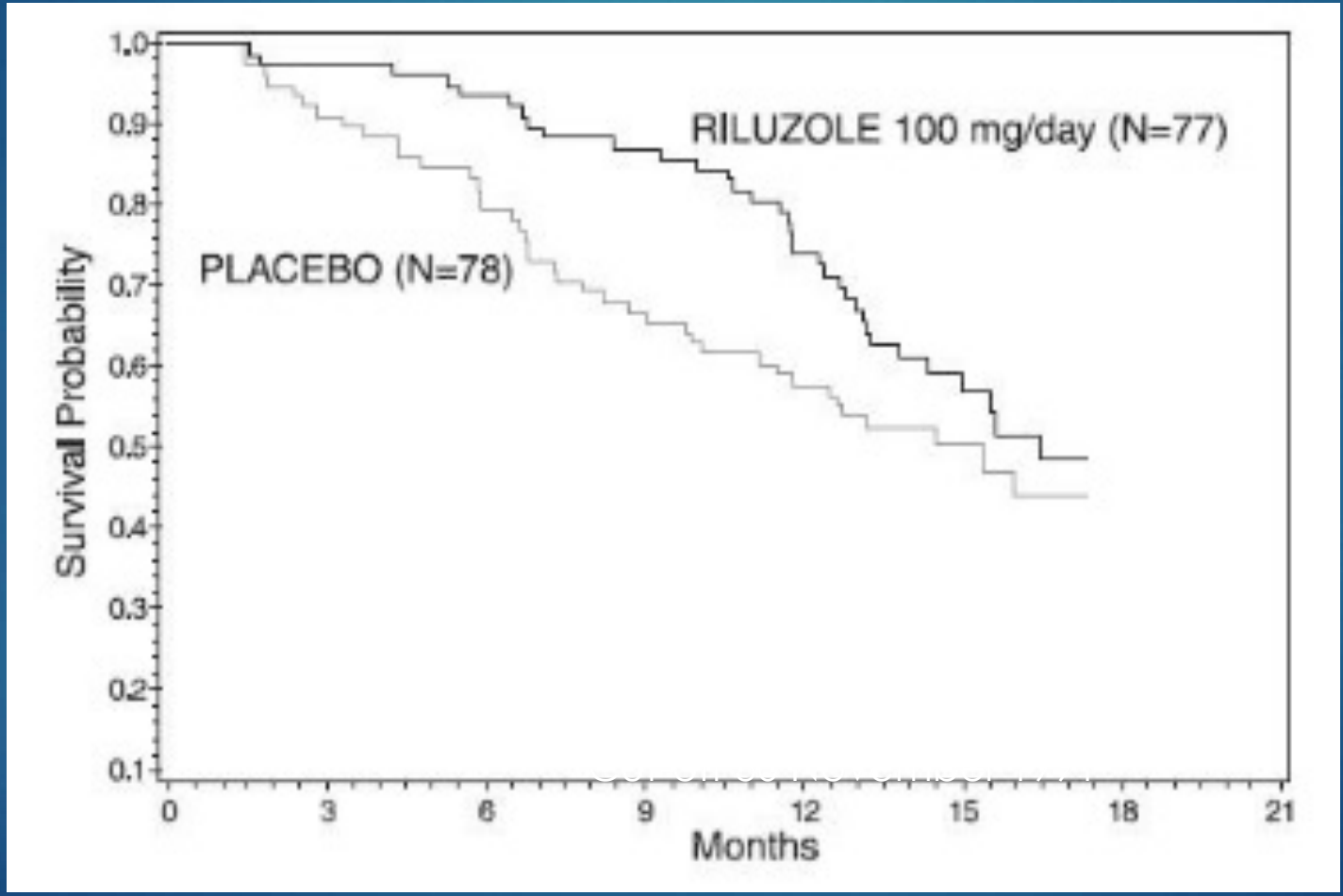
PALLIATIVE CARE/HOSPICE CARE

- Patient and family support & education
- Referral to hospice
- Dignity and comfort
- Symptom management
- Research participation - Autopsy and tissue donation
- Participation in mourning process

Riluzole - RILUTEK®

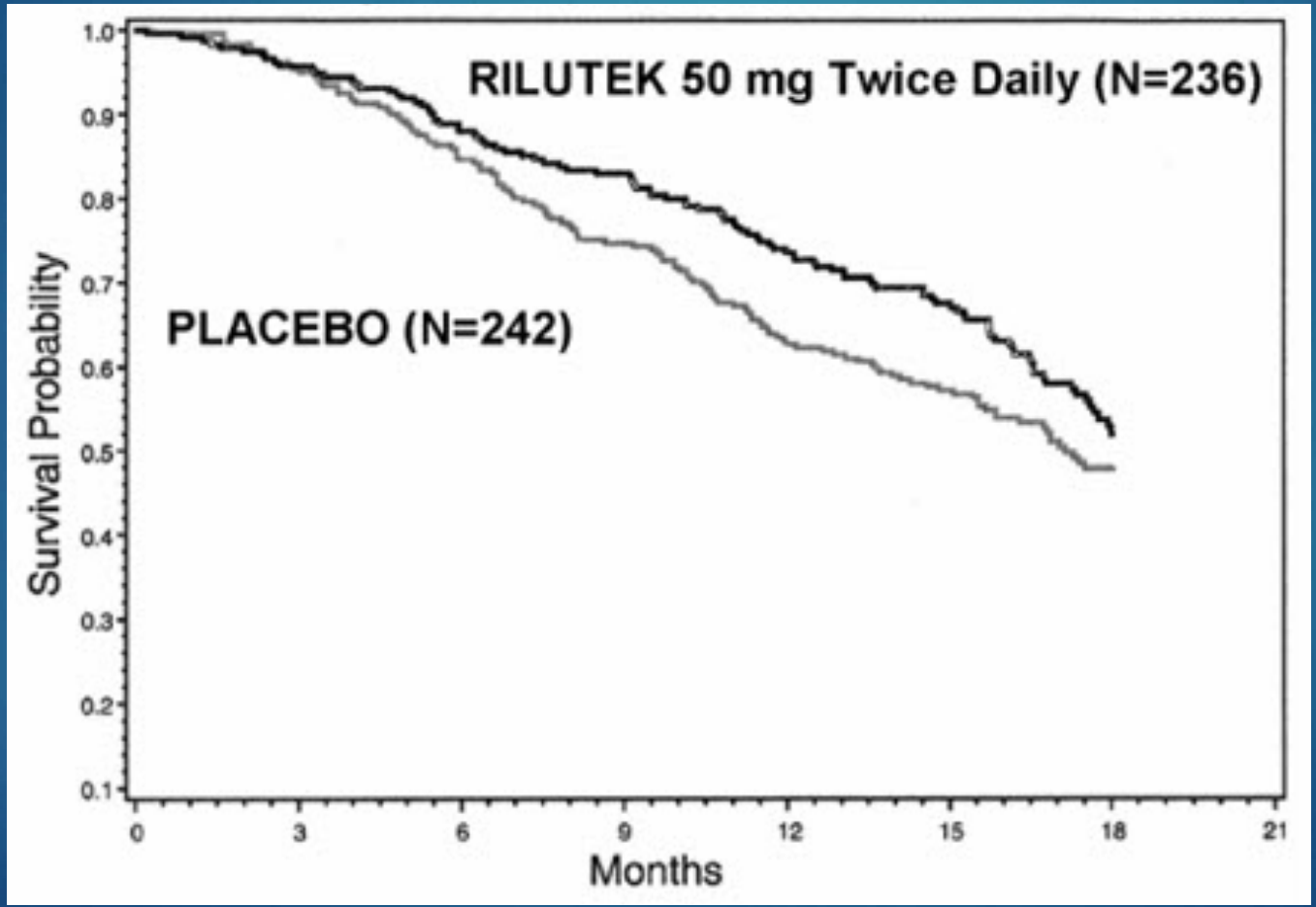
- Clinical trial results – first drug shown to have an effect in ALS
- Mechanism of action – inhibitory effect on glutamate release
- Dosage and Administration – 50mg PO BID 1 hour before meals or 2 hours after meals; statistically significant improved survival
- Storage & Handling – white capsule shaped film coated capsules stored at 20-25 degree C/68-77 degree F ; protect from bright light
- Adverse reactions – increased ALT (SGPT)/AST (SGOT); asthenia; nausea; vomiting; vertigo; somnolence; paresthesia
- Contraindications – history of hypersensitivity to riluzole; liver sensitivity or toxicity
- Patient Education – AST/ALT – baseline/30/60/90 days; yellowing of whites of eyes; fever; respiratory symptoms

KAPLAN-MEIER SURVIVAL CURVE STUDY 216 – STUDY I



Source: http://products.sanofi.us/rilutek/rilutek.pdf

KAPLAN-MEIER SURVIVAL CURVE STUDY 301 – STUDY II

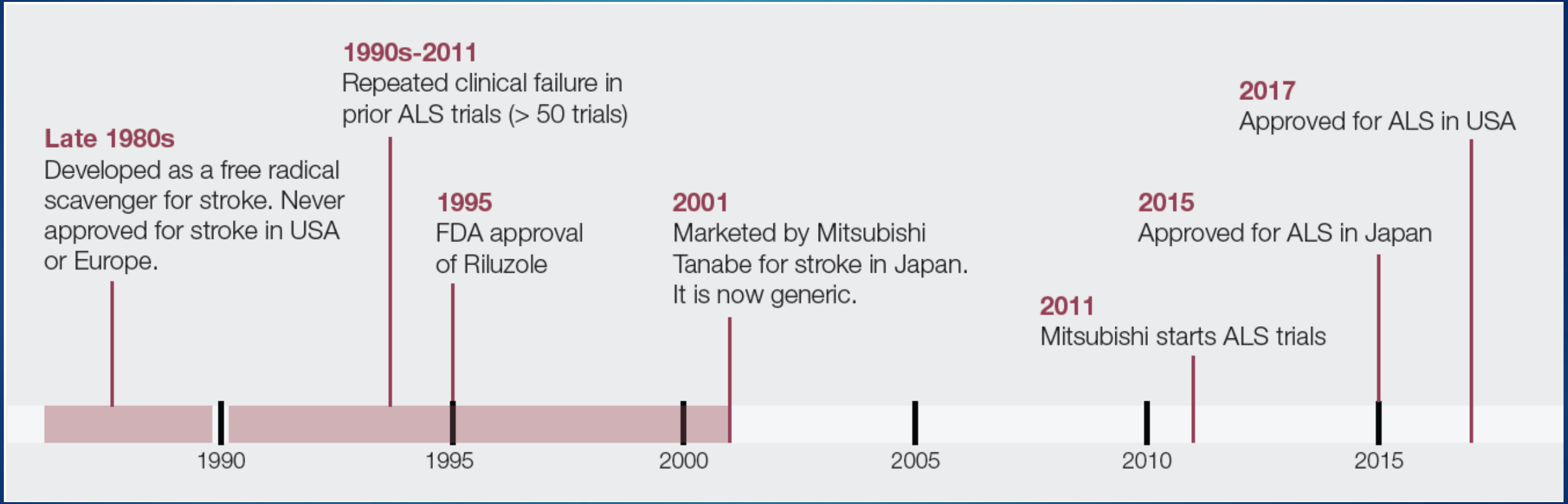


Source: http://products.sanofi.us/rilutek/rilutek.pdf

Edaravone - RADICAVA®

- Clinical trial results – first drug approved for ALS in 22 years
- Mechanism of action – antioxidant
- Dosing & Administration - Regimen is in cycles – 30mg/100ml (0.3mg/ml) single dose bag – 2 bags to a package – clear colorless sterile solution
  - Initial treatment cycle - 60mg IV QD for first 14 days; then 14 days with no drug
  - Subsequent cycles - 60mg IV for 10 out of 14 days; then 14 days with no drug
- Storage & Handling – store at 25 degree C/77 degree F – excursions permitted from 15-30 degree C/59-86 degree F; protect from light; Store in overwrapped package to protect from oxygen degradation until time of use. O2 indicator will turn blue/purple if O2 has exceeded acceptable levels. Once overwrap package is opened use within 24 hours.
- Adverse reactions – Bruising, gait disturbance, headache, dermatitis
- Contraindications – Hypersensitivity Reactions; Sulfite Allergic Reactions; Contains sodium bisulfite
- Patient Education – PICC/PORT Access line care & maintenance; IV Administration procedure; side effects – hives/itching; trouble breathing/wheezing; trouble swallowing; dizziness; swelling of lips/tongue/face; trouble walking.

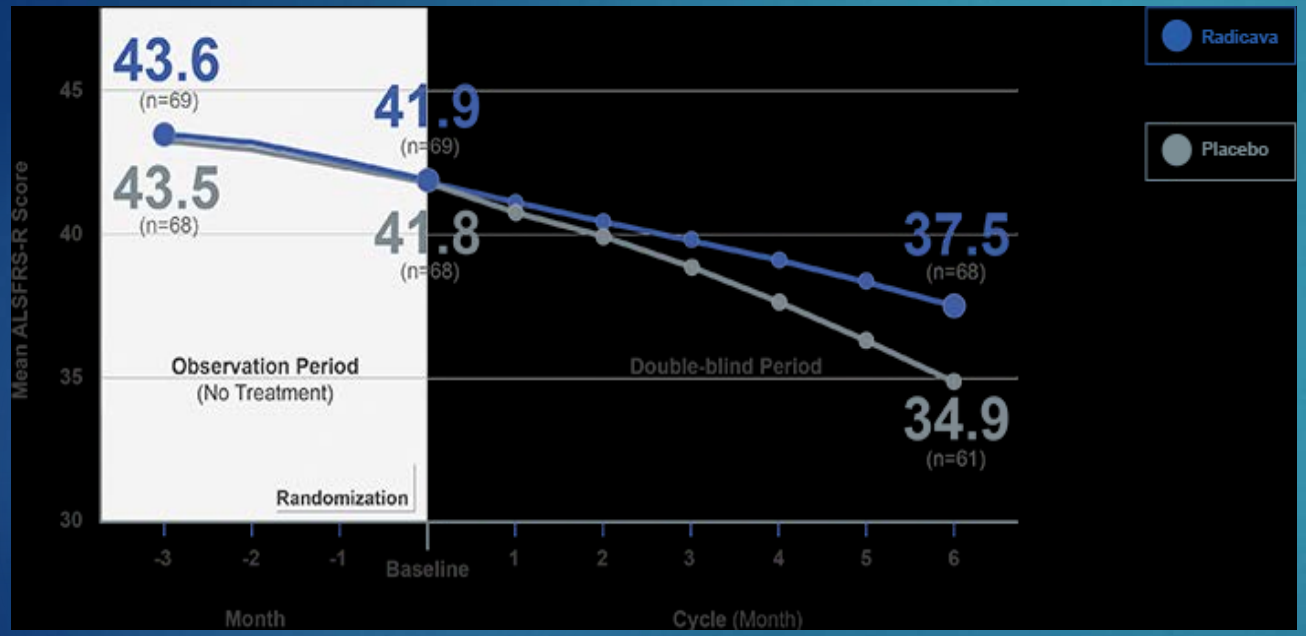
HISTORY OF RADICAVA® DEVELOPMENT



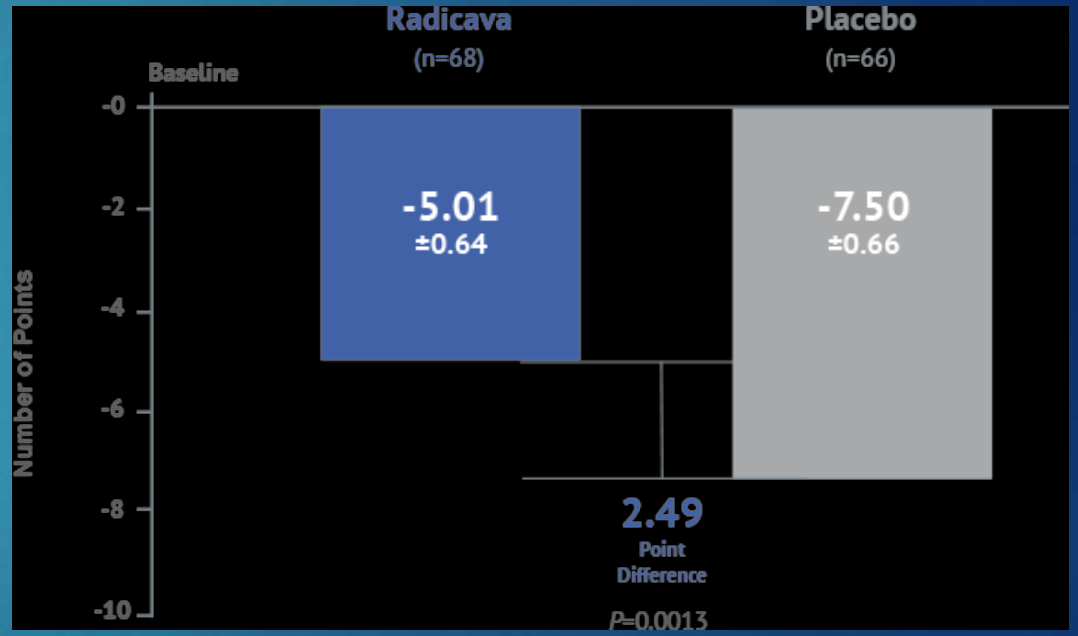
Source: *Cell*, 2017; Volume 171: p. 725

ALSFRS-R SCORES IN RADICAVA® AND PLACEBO GROUPS

Mean Change in ALSFRS-R Score

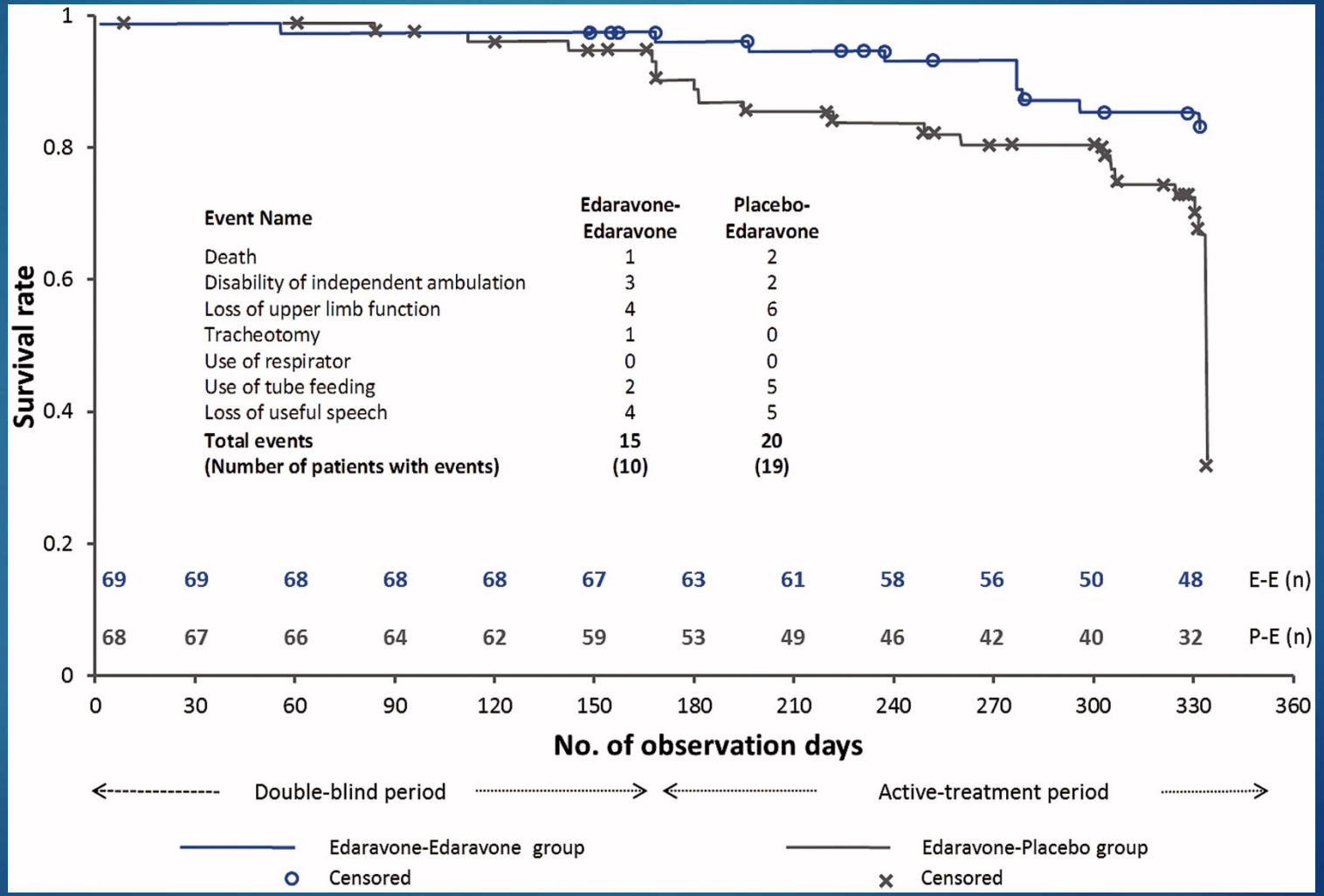


Change in ALSFRS-R Score from Baseline



Source: https://www.radicava.com/hcp/efficacy-and-safety/#effect-on-physical-function

SURVIVAL RATE WITH RADICAVA®



Source: *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 2017; 18: 55-63

RADICAVA® CHALLENGES

- M T PHARMA – distributor – manufactured in Japan NOT US
- Third Party: Searchlight Enrollment Company
- Home Infusion vs. Outpatient Infusion
  - Home: Agreement may not exist
  - Outpatient: Agreement may not exist; Most require patients to be independent; provider needs to have privileges at site
- Current Clinic Visits for all Patients to update/monitor clinical care & educate on Radicava prescribing process & expectations
- Method of Infusion: PIV vs. Midline vs. Central line/PICC or PORT
- Staffing – Neurology Clinic, Insurance companies, Home Care/Infusion companies
- Some insurances will only approve for patients who mimic phase II study participants (FVC > 80%, Onset < 2yrs, ALSFRS-R > 40, etc.)

MULTIDISCIPLINARY HEALTH CARE TEAM OF SPECIALISTS

- Physician
- Nurse Clinician
- Psychologists
- Social Worker
- Home Health Care
- Home Care Infusion Center
- Palliative Care/Hospice Care
- Physical Therapist
- Occupational Therapist
- Respiratory Therapist
- Nutritionist
- Speech-Language Specialist

Collaboration with Home Care/Home Infusion Companies with Multidisciplinary Clinical Care Team

- Home Safety Evaluation
- Home Physical Therapy
- Home Occupational Therapy
- Home Speech/Swallowing Therapy
- Home Social Worker
- Home Respiratory Therapist
- Radicava – PICC/PORT care – patient education / demonstration – ongoing monitoring & assessments
- Enteral Nutrition
- Respiratory Equipment & monitoring – Bipap, Compliance use data, Cough assist device, suction machine, Vest
- Durable Medical Equipment –cane, rollator walker, handrails/safety bars, wheelchairs manual/power, patient lifting devices, hospital bed, recliner lift chair, stairglide
- Accessible Van & ramps

NON-PROFIT ORGANIZATIONS INFORMATION & REFERRAL

- Amyotrophic Lateral Sclerosis Association
  - Phone: (800) 782-4747
  - Email: alsinfo@alsa-national.org
  - Website: www.alsa.org
- Muscular Dystrophy Association
  - Phone: (800) 572-1717
  - Email: mda@mdausa.org
  - Website: www.mda.org
- Amytrophic Lateral Sclerosis Society of Canada
  - Phone: (800) 267-4257
  - Website: www.als.ca
- Muscular Dystrophy Canada
  - Phone: (416) 488-0030
  - Email: info@muscle.ca
  - Website: www.muscle.ca

SUMMARY

- Enhanced your core knowledge and skills to effectively manage ALS patients throughout their disease process

- Provided an overview of current treatment regimens, complimentary therapies, and methods to identify and treat symptoms associated with disease progression.

Questions ?