www.associazioneasla.org

SCLEROSI LATERALE AMIOTROFICA (SLA): COSA C'E' DA SAPERE

La terapia della SLA

Andrea Calvo

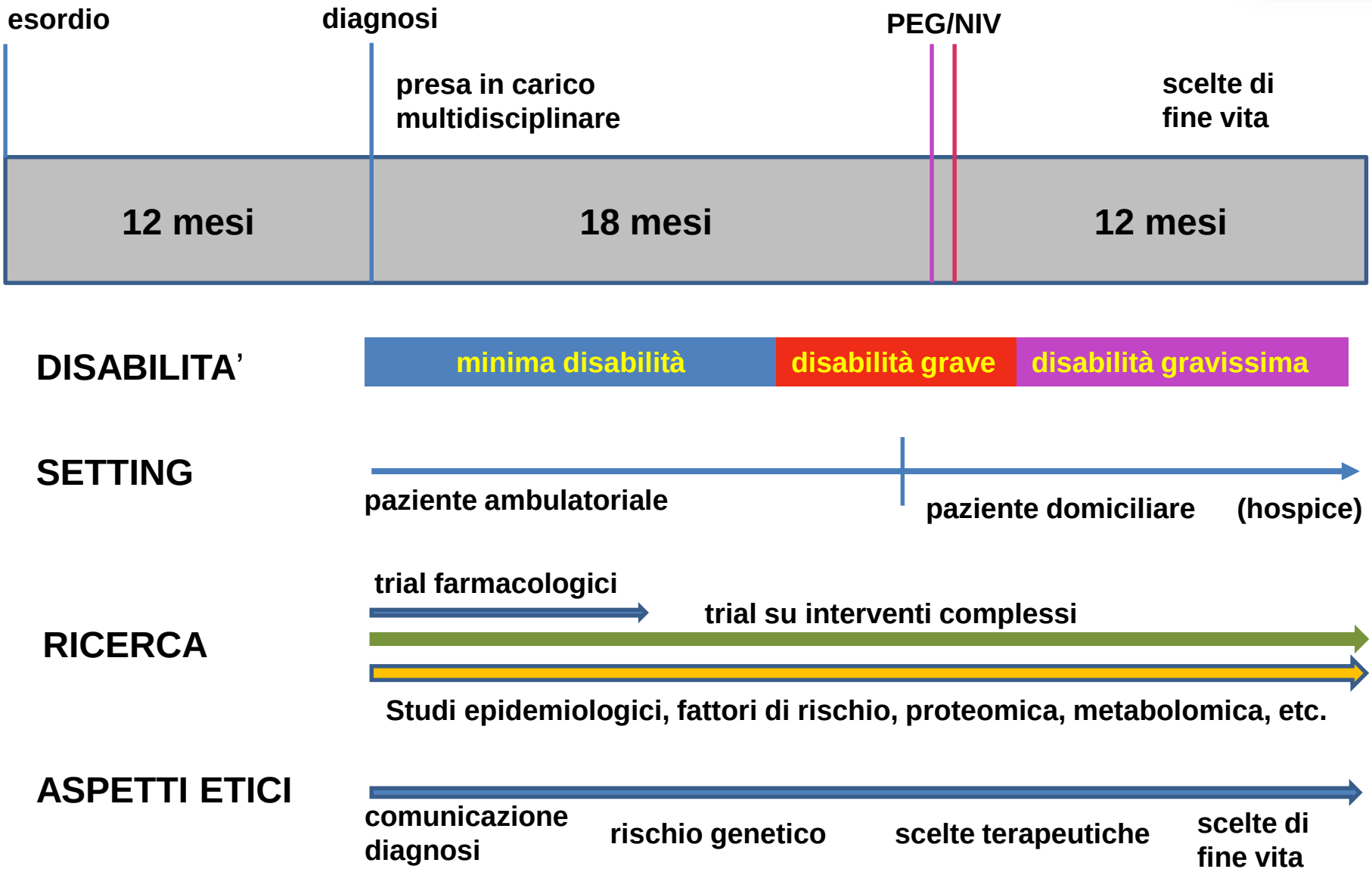
LEGGE 22 DICEMBRE 2017, N. 219 .
NORME IN MATERIA DI CONSENSO INFORMATO E DI DISPOSIZIONI ANTICIPATE DI TRATTAMENTO.

ART. 1. *CONSENSO INFORMATO.*

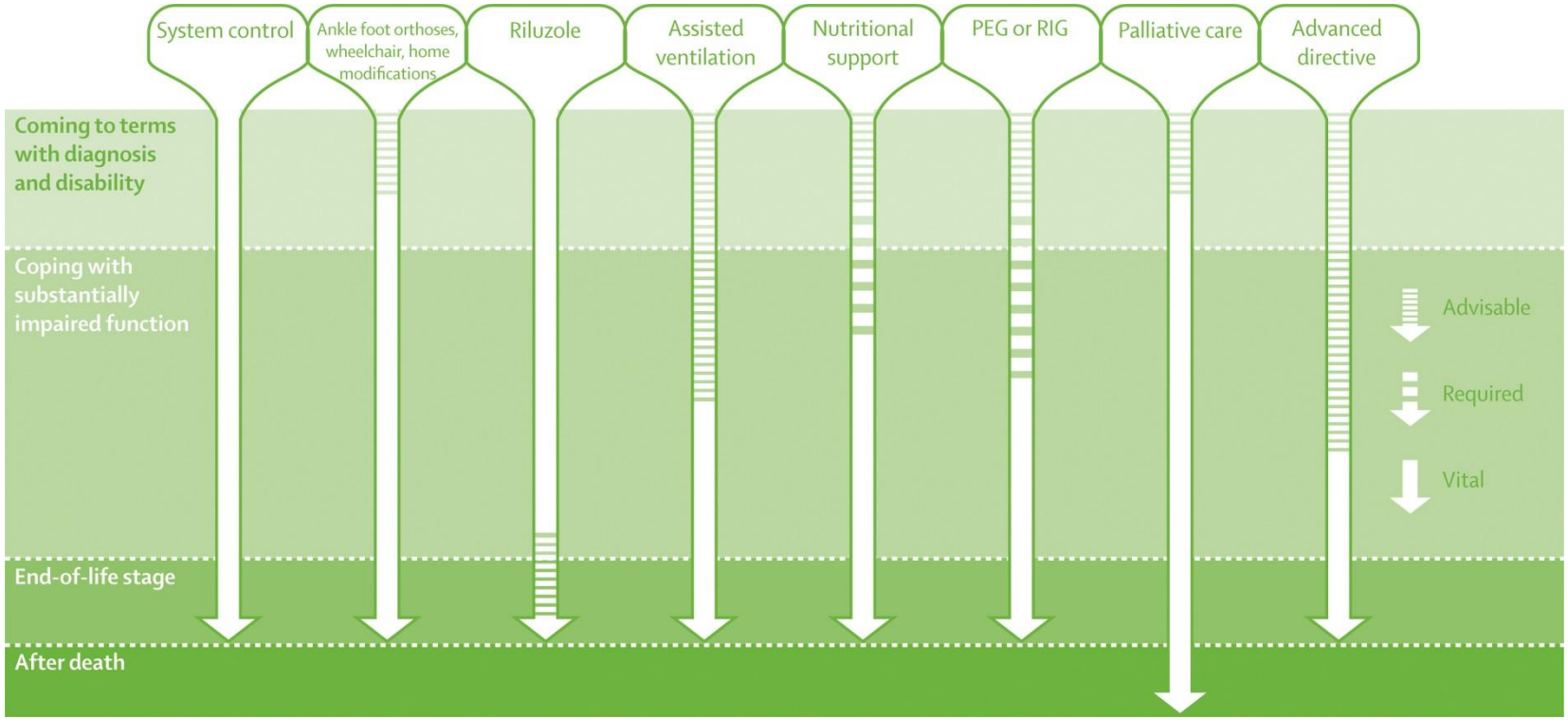
COMMA 8

«IL TEMPO DELLA COMUNICAZIONE TRA MEDICO E PAZIENTE COSTITUISCE TEMPO DI CURA».

Decorso nella SLA



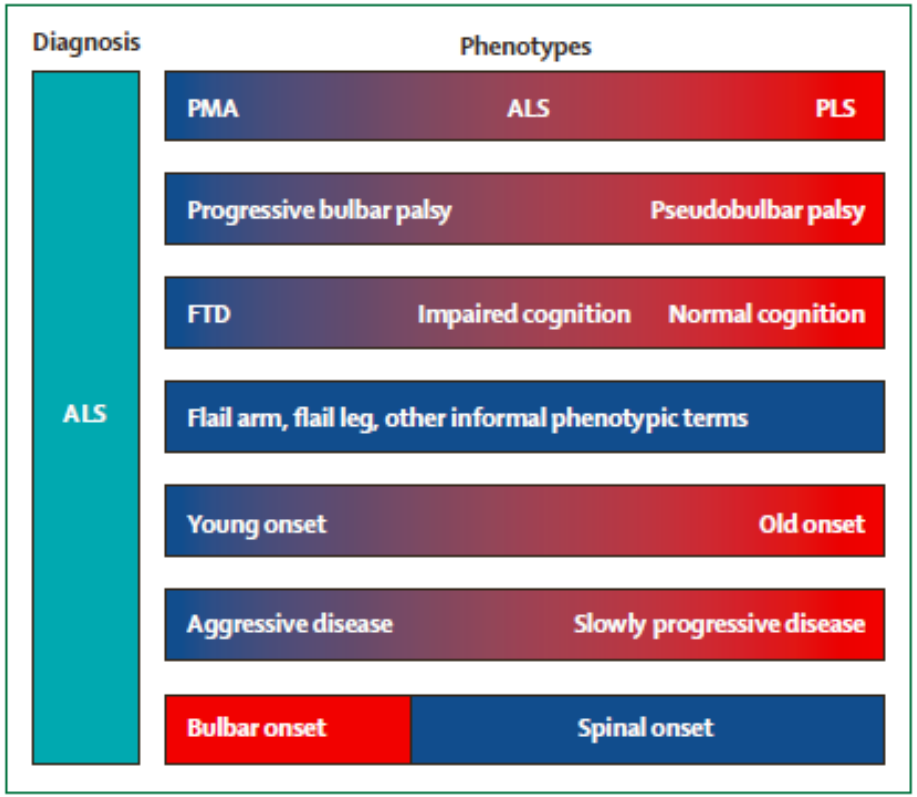
La SLA come modello di cure simultanee

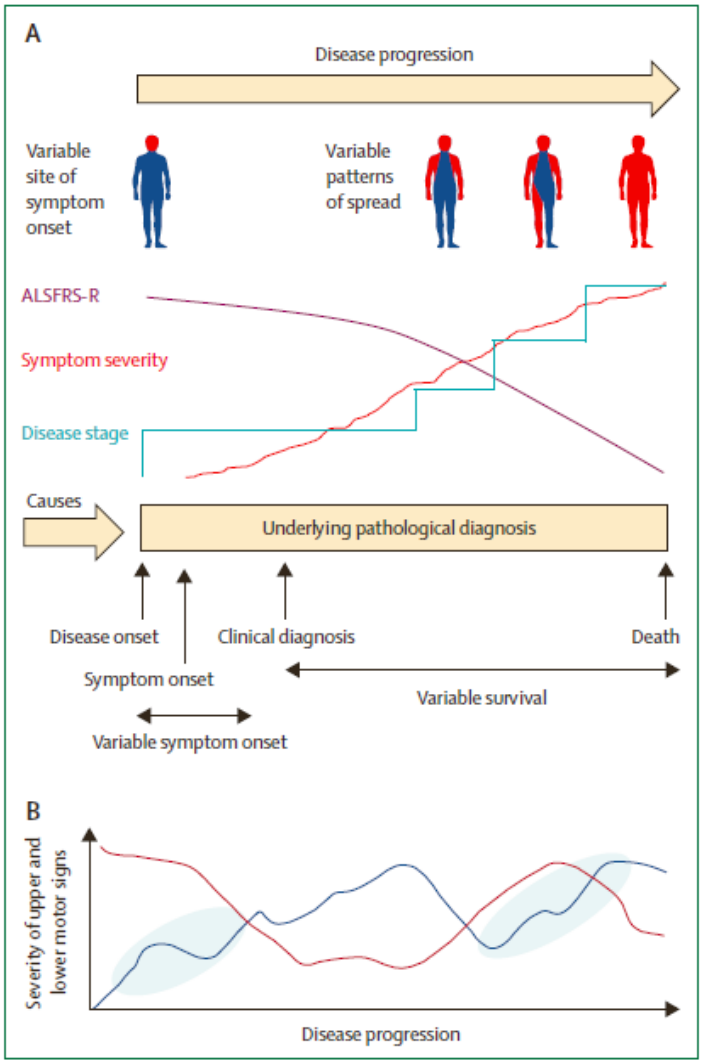


Radunovic et al, Lancet Neurology 2007

La SLA è una malattia o una sindrome?

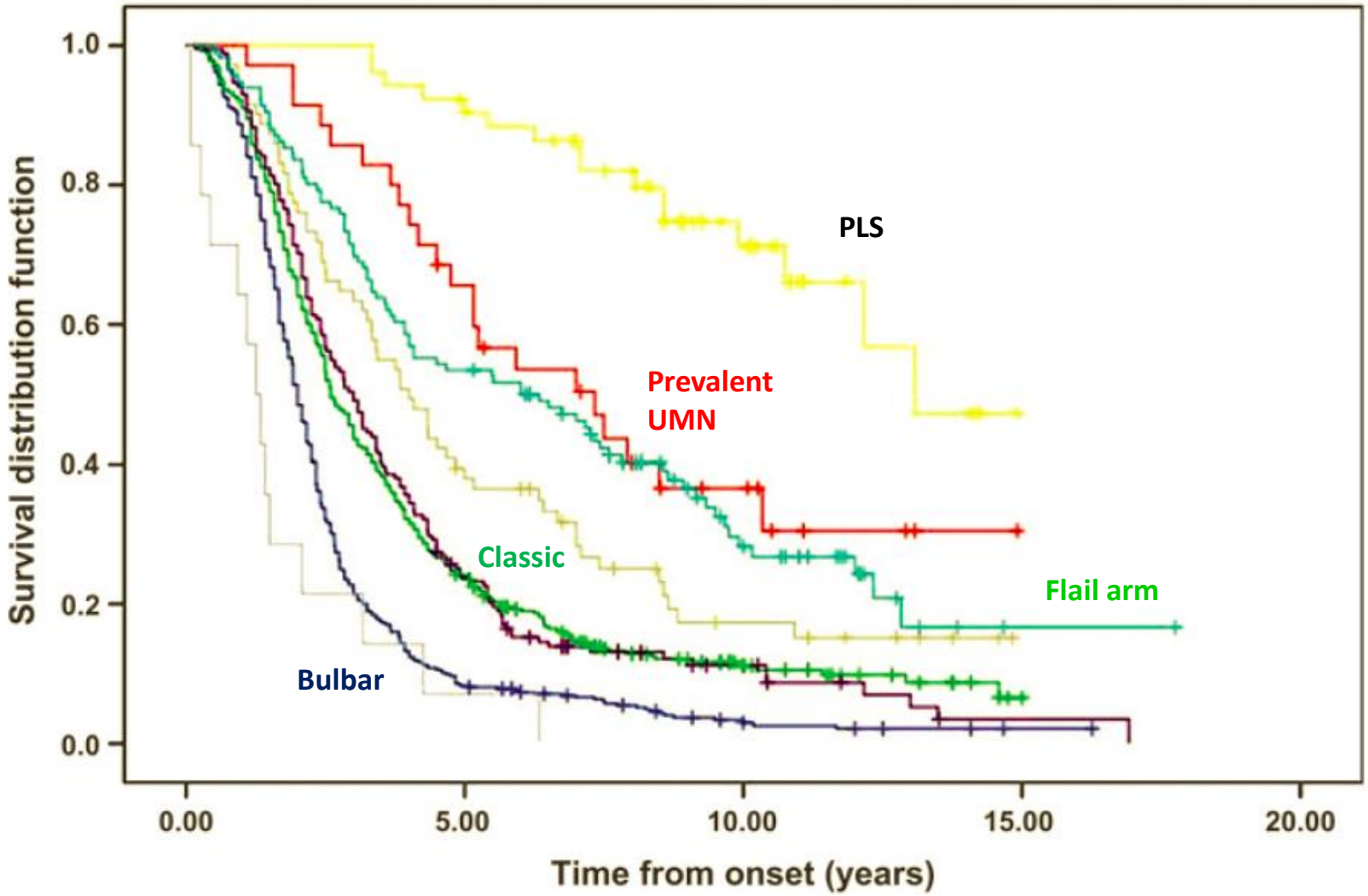
Cosa c'è dietro alla diagnosi di SLA?





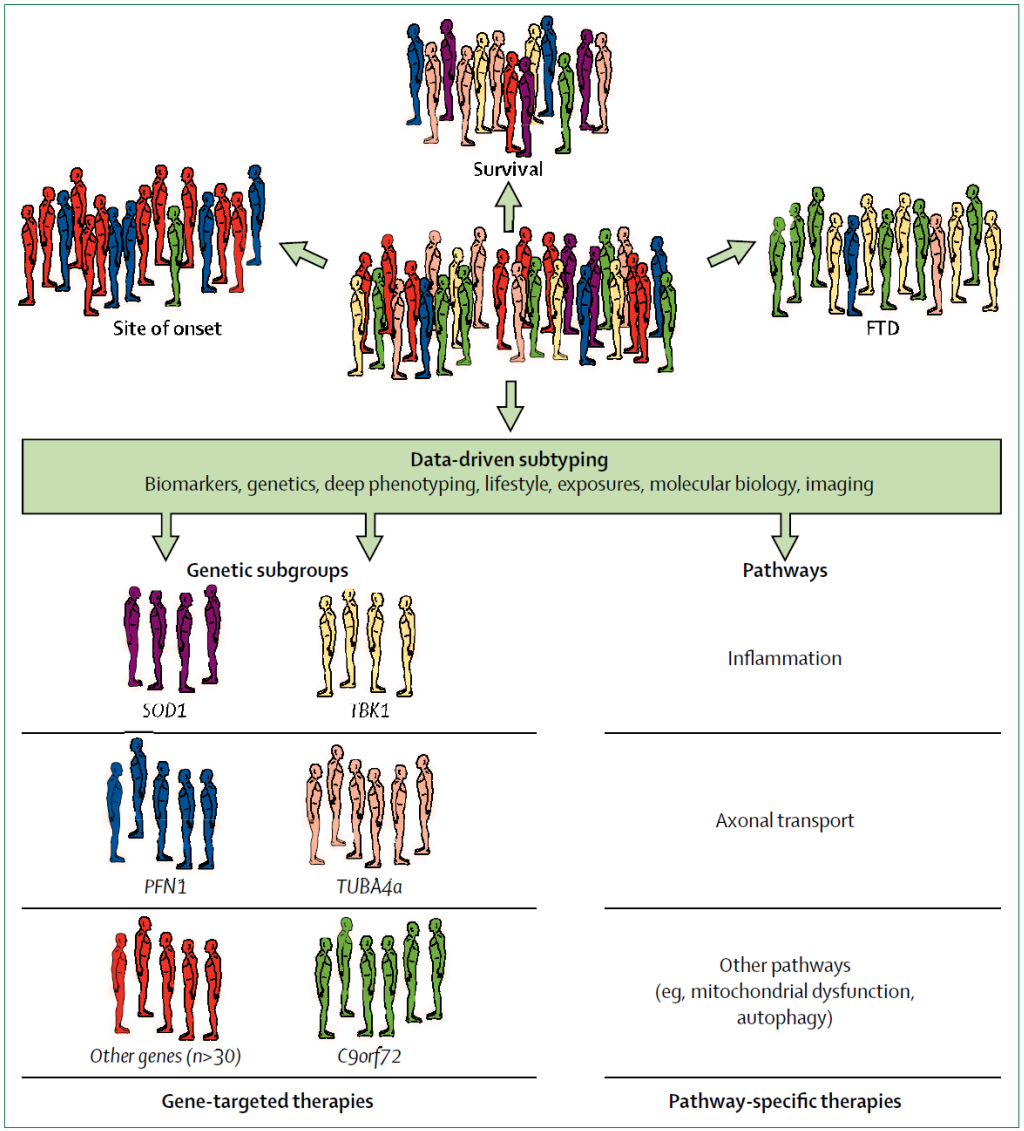
Al-Chalabi, et al, *Lancet Neurology 2016*

Fenotipi clinici e sopravvivenza



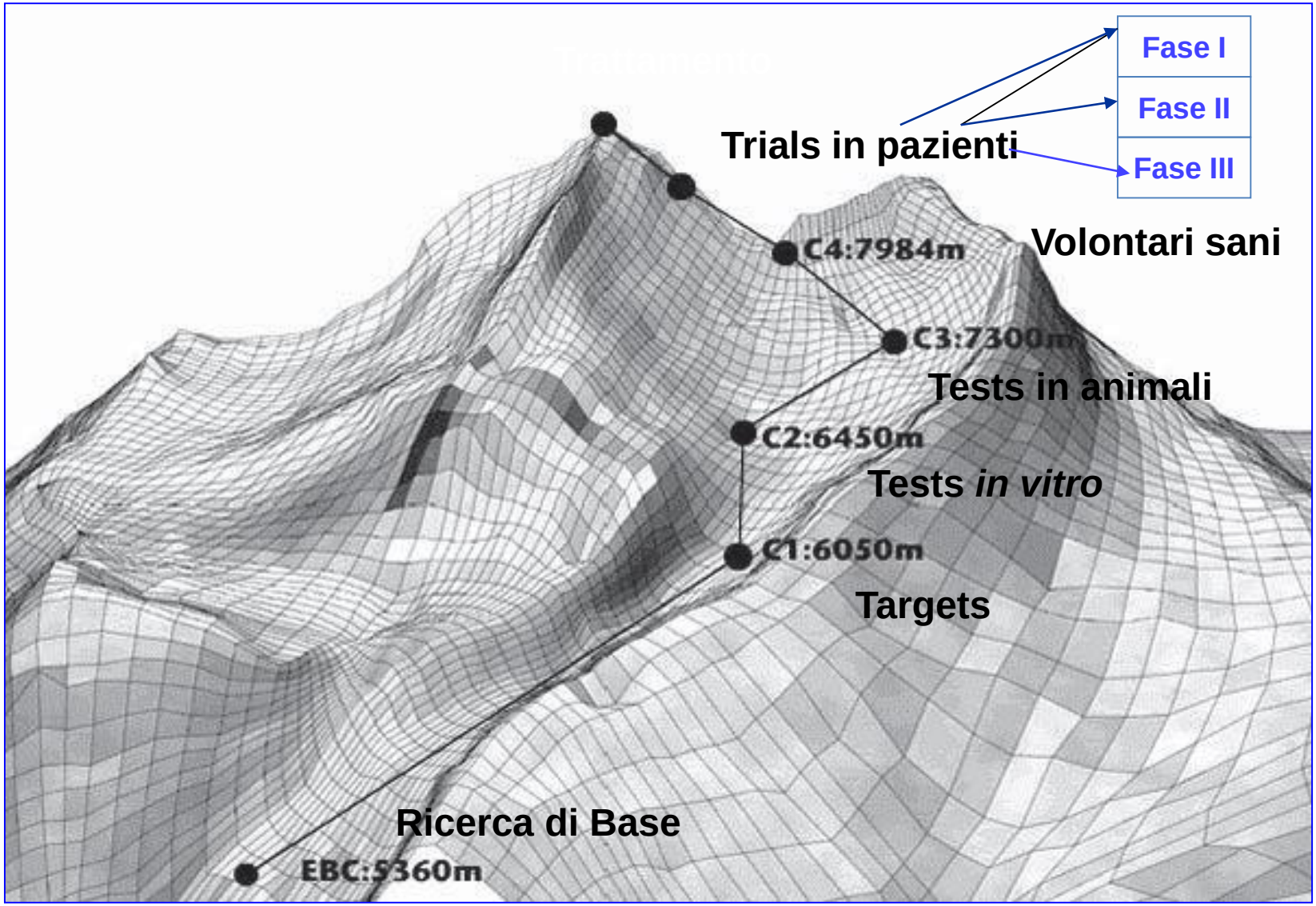
Chiò et al, *J Neurol Neurosurg Psychiatry* 2011

Is it time for precision medicine in ALS?



Van Es et al, Lancet 2017

Fasi dello sviluppo di un farmaco



With thanks to Clare Wood-Allum, University of Sheffield

Challanges of clinical trials and drug development for ALS

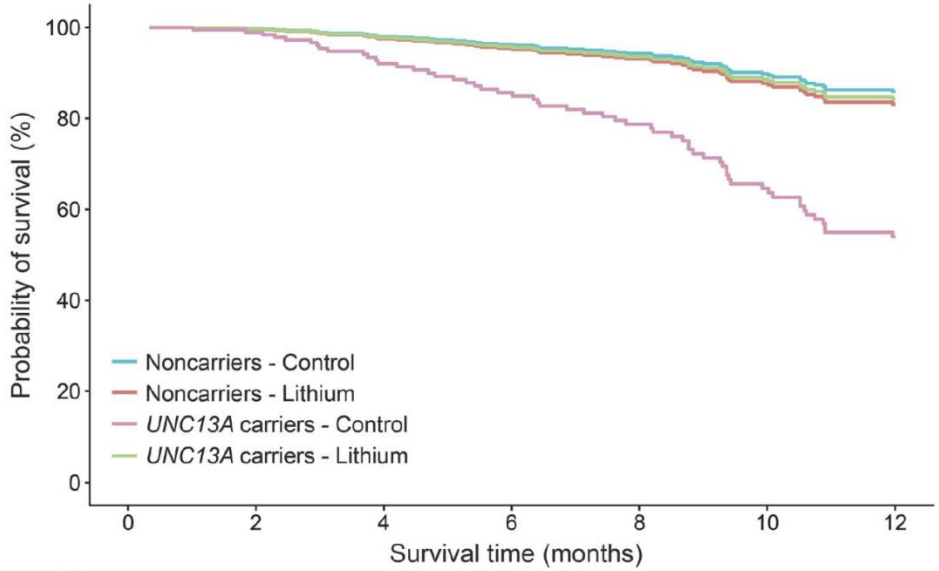
1. Inadequate and problem-related rodent study models
2. Problems related to preclinical experimental designs
3. Genetic complexity of ALS disease needs extensive study of all the genetic models
4. Due to genotypic features discrepancies in recognizing the ALS subtypes
5. Problems in understanding individual models and formulating focused clinical trials
6. Diverse phenotypes with same ALS mutation
7. Diverse phenotypes due to mutations in the same ALS gene
8. Heterogeneity among patients—one does not fit all
9. Pharmacokinetic differences between rodent preclinical trials and human
10. Issues with RCTs faulty designs and methodological issues
11. Lack of distinction between null versus negative effect
12. Lack of focus on clinical significance instead of just statistical significance
13. Insensitive biomarkers
14. Diagnostic delays

Meta-analysis of pharmacogenetic interactions in amyotrophic lateral sclerosis clinical trials

OPEN

Neurology® 2017;89:1-8

Figure 2 Cox proportional hazards model of 12-month survival and the interaction of lithium carbonate with *UNC13A* genotype



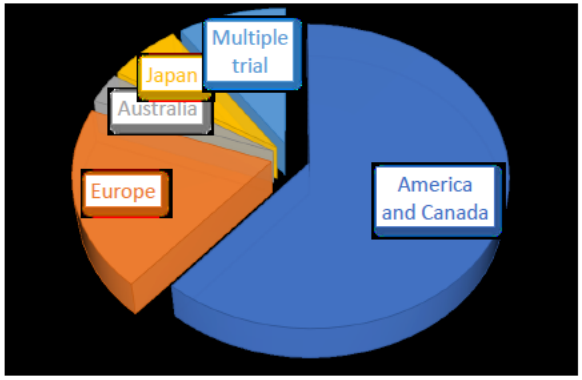
Number at risk							
Noncarriers - Control	114	112	105	96	89	76	69
Noncarriers - Lithium	109	106	94	84	76	68	65
UNC13A carriers - Control	26	25	20	15	13	10	7
UNC13A carriers - Lithium	20	20	19	16	14	12	10

A che punto è la ricerca sulle terapie?

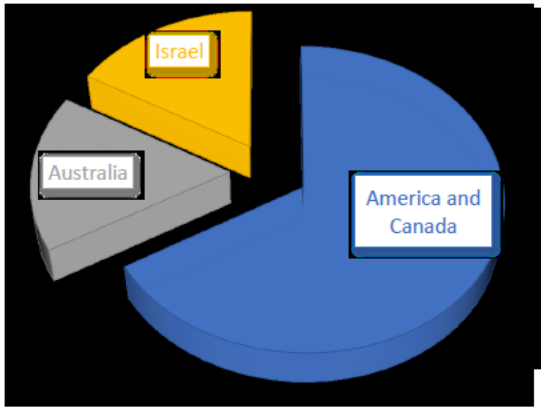
U.S. National Library of Medicine
ClinicalTrials.gov

Ongoing Clinical Trials in ALS
(57 studies)

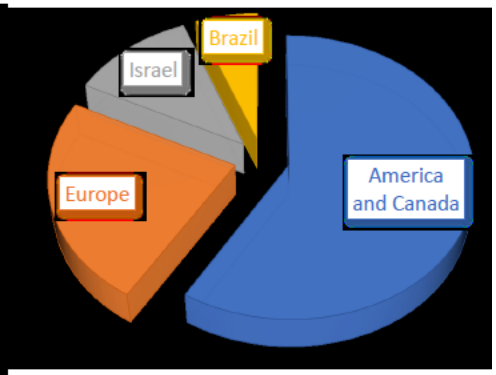
Ongoing pharmacological clinical trials phases 2 and 3 (31 studies)



Ongoing pharmacological clinical trials in phase 1 (9 studies)

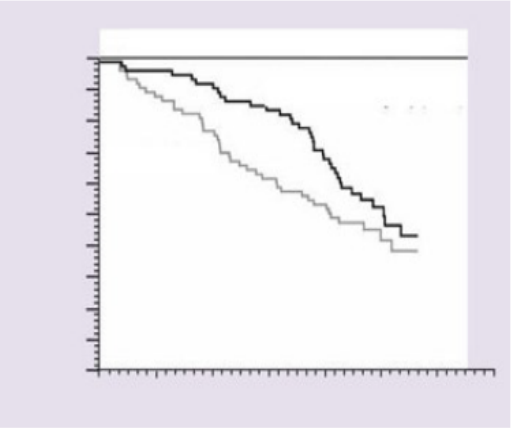


Ongoing stem cell clinical trials (17 studies)



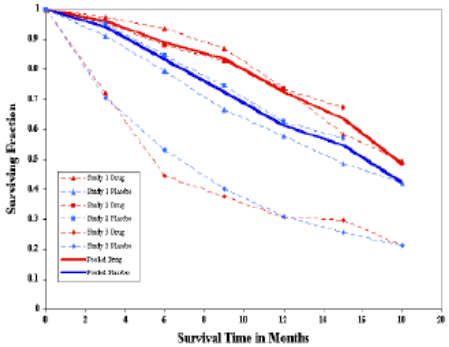
Riluzole

The Lancet 18,1996,247

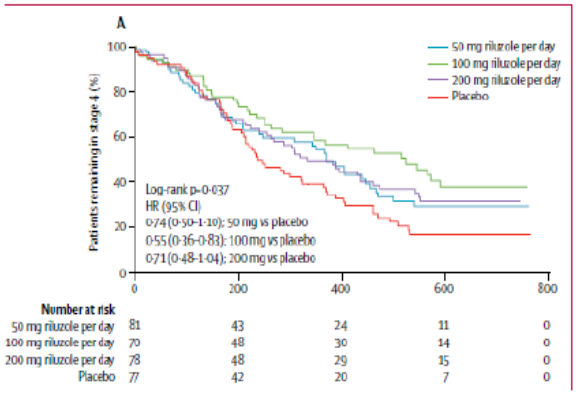


Published Online: 14 MAR 2012

Figure 2. Pooled survival time in months. Solid lines show pooled results from the two trials that were homogeneous.



www.thelancet.com/neurology Published online March 7, 2018



Authors' conclusions

Riluzole 100 mg daily is reasonably safe and probably prolongs median survival by about two to three months in patients with amyotrophic lateral sclerosis.

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Authors' conclusions

Riluzole 100 mg daily significantly prolongs survival in the last stage rather than by slowing the entire disease course

Edaravone

ALS and Frontotemporal degeneration 2014 Dec;15(7-8):610-7

Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients

Koji Abe, Yasuto Itoyama, Gen Sobue, Shoji Tsuji, Masashi Aoki, Manabu Doyu, Chikuma Hamada, Kazuoki Kondo, Takatomo Yoneoka, Makoto Akimoto, Hiide Yoshino & on behalf of The Edaravone ALS Study Group

www.thelancet.com/neurology Vol 16 July 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†*

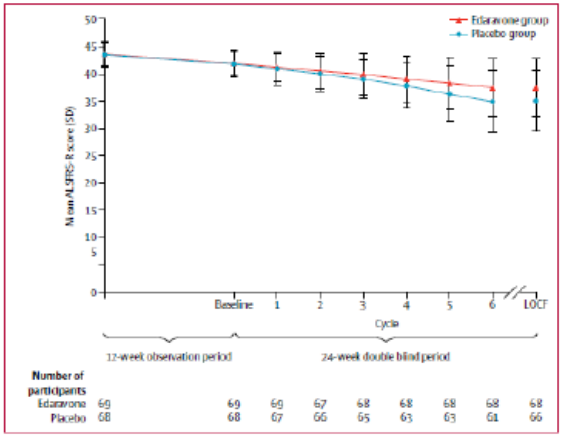
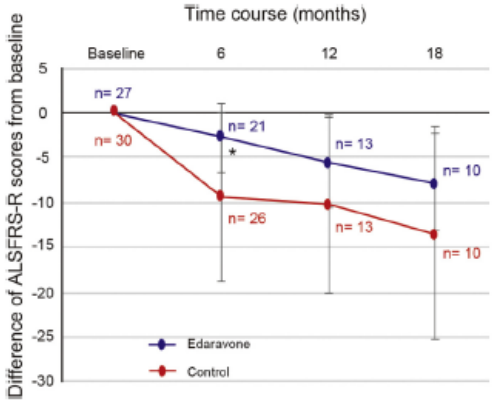


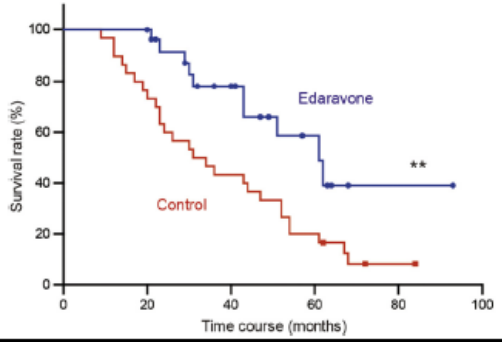
Figure 2: Mean ALSFRS-R scores during treatment

eNeurologicalSci 11 (2018) 11–14

Long-term effects of edaravone on survival of patients with amyotrophic lateral sclerosis

Masamitsu Okada[a,b], Satoshi Yamashita[b,*], Hidetsugu Ueyama[a,*], Masatoshi Ishizaki[a], Yasushi Maeda[a], Yukio Ando[b]





SOCIETÀ ITALIANA DI NEUROLOGIA

Gruppo di studio Malattie del Motoneurone

SCHEDA EDARAVONE

CENTRO MEDICO

Your answer

TIPO SCHEDA

- SCHEDA INIZIO TRATTAMENTO
- SCHEDA DI CONTROLLO TRIMESTRALE

NUMERO DI CICLO DI TRATTAMENTO

Your answer

DATA TRATTAMENTO

DD MM YYYY

/ / 2018

CODICE PAZIENTE

Your answer

SESSO

- MASCHIO
- FEMMINA

DATA DI NASCITA

DD MM YYYY

/ / 2018

PUNTEGGIO ALSFRS-R

Your answer

MISURAZIONE CAPACITA' VITALE FORZATA (FVC)

Your answer

PUNTEGGIO ALSAQ-5

Your answer

EVENTI AVVERSI

Your answer

DATA FINE TERAPIA

DD MM YYYY

/ / 2018

CAUSA FINE TERAPIA

Your answer

DATA SOSPENSIONE TERAPIA

DD MM YYYY

/ / 2018

CAUSA SOSPENSIONE TERAPIA

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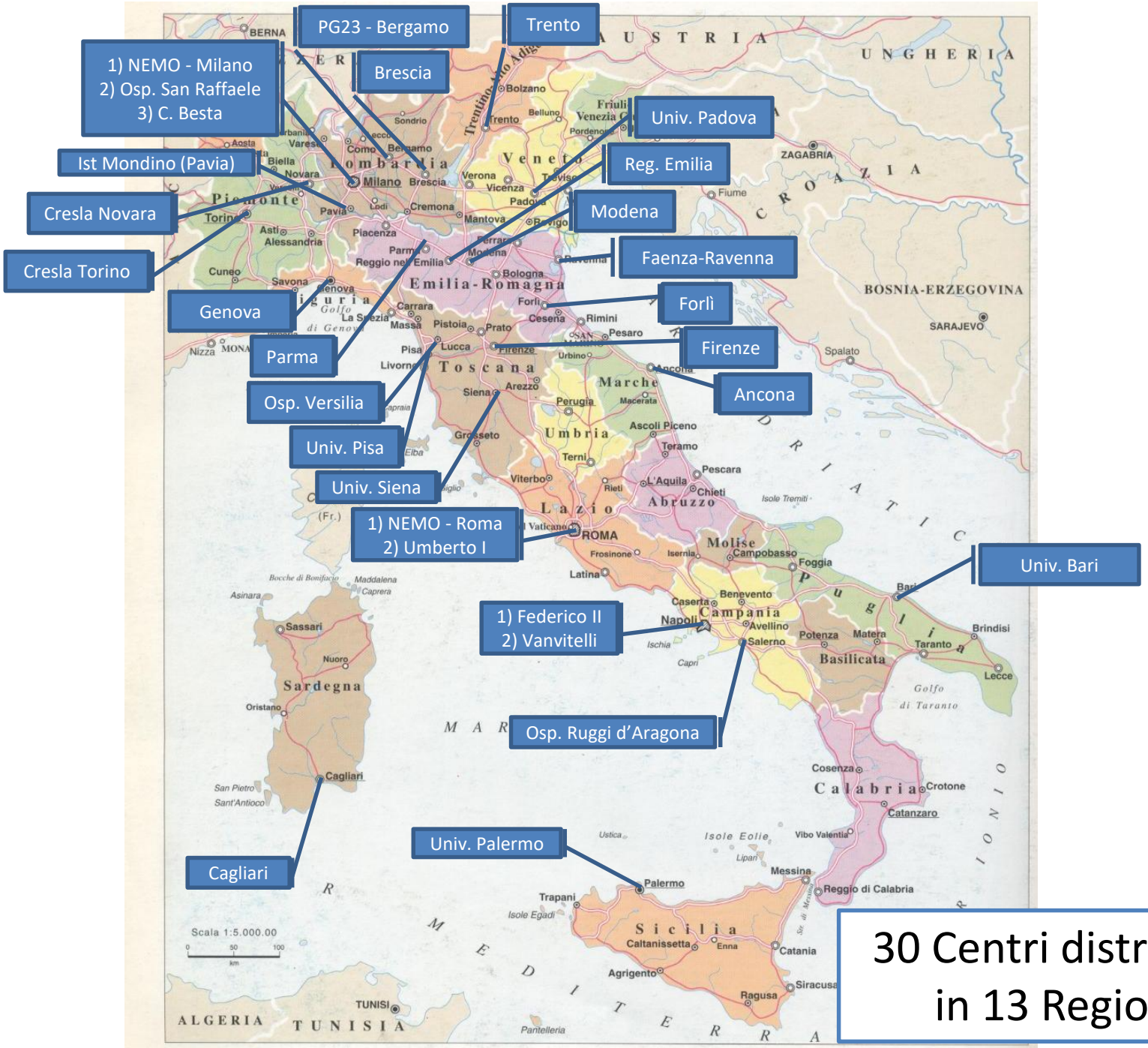
SUBMIT

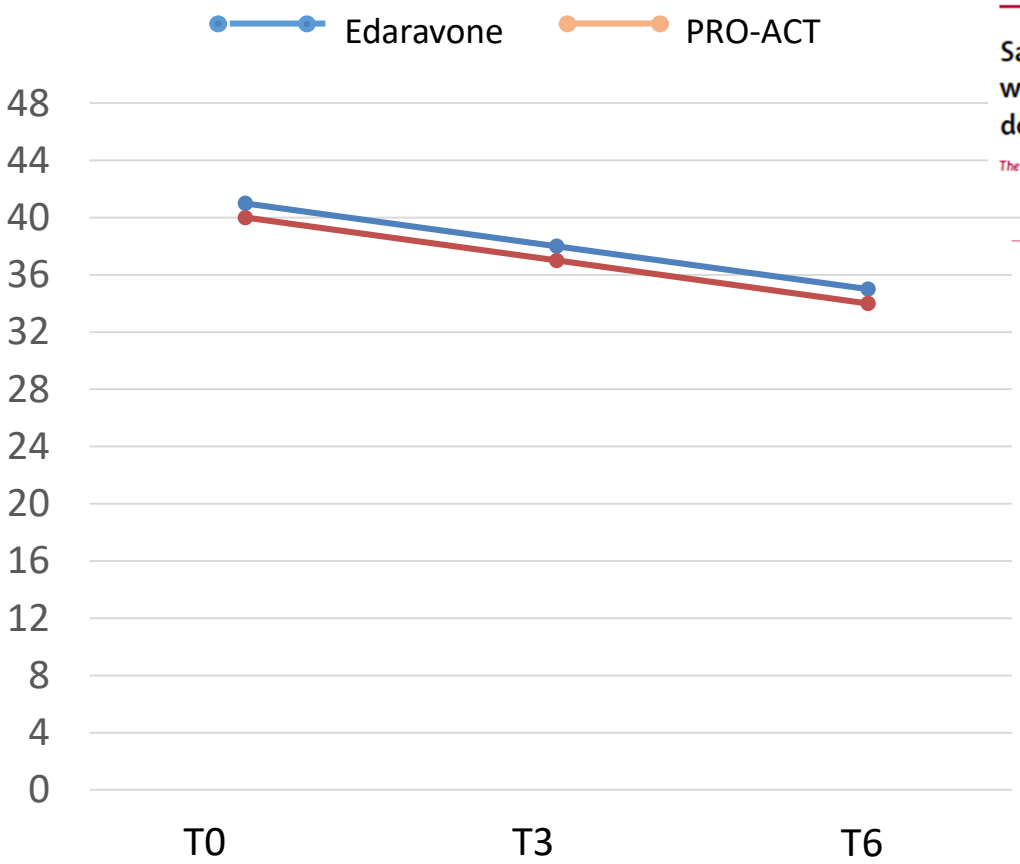


30 Centri distribuiti in 13 Regioni

CENTRO CLINICO NEMO MILANO

C.R.E.SLA Torino

ALSFRSr



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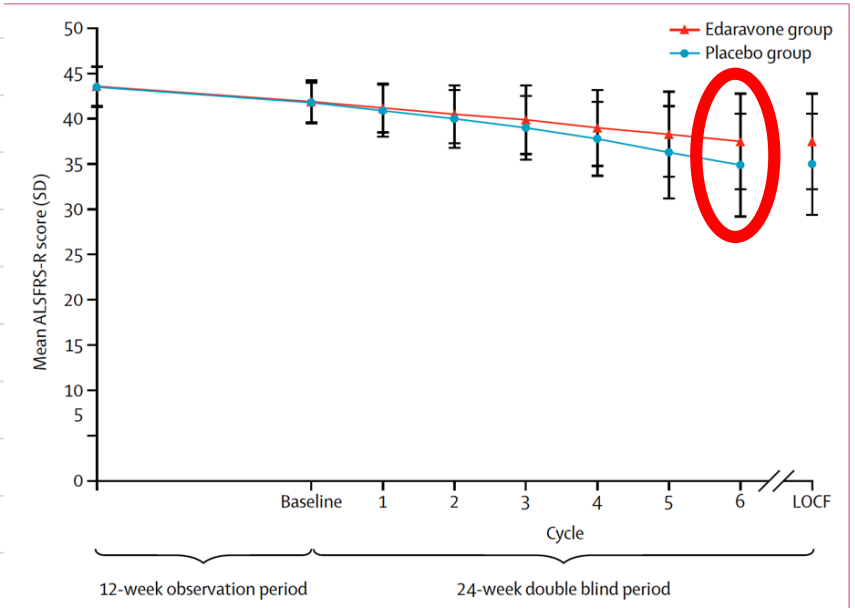
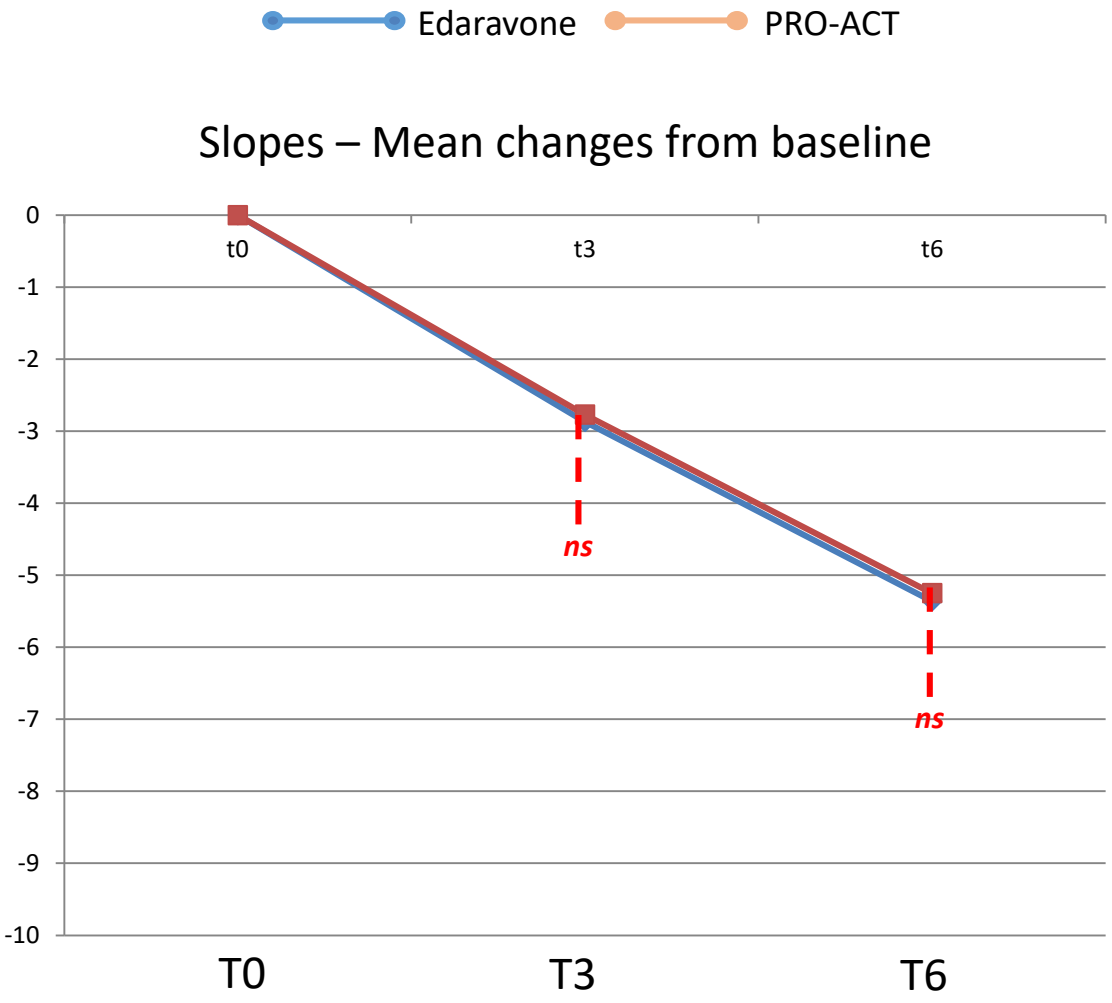


ALSFRSr


Edaravone
PRO-ACT
Slopes – Mean changes from baseline
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
t0
t3
t6
ns
ns
T0
T3
T6

Cytotherapy, 2016; ■■: ■■–■■

International Society for Cellular Therapy
ISCT®

Intraspinal stem cell transplantation for amyotrophic lateral sclerosis: Ready for efficacy clinical trials?

NAZEM ATASSI[1], ETTORE BEGHI[2], MIGUEL BLANQUER[3], NICHOLAS M. BOULIS[4], ROBERTO CANTELLO[5], CLAUDIA CAPONNETTO[6], ADRIANO CHIÒ[7], STEPHEN B. DUNNETT[8], EVA L. FELDMAN[9], ANGELO VESCOVI[10,11], LETIZIA MAZZINI[12] ON BEHALF OF THE ATTENDEES OF THE INTERNATIONAL WORKSHOP ON PROGRESS IN STEM CELLS RESEARCH FOR ALS/MND*

Specific issues with SC-based treatments inevitably lead to small trials.

Main problems:

- the capacity to produce sufficiently large number of standardized cells meeting safety and quality standard
- the higher risk related to surgical delivery
- the high costs

Solutions?

- to increase sample
- to find selective biomarkers related to cellular activity
- the creation of international network

Foetal Neural Stem Cells Transplantation in ALS
(EudraCT: 2009-014484-39)

NEXT STEP

A Phase II Randomized, Dose Escalation Safety and Efficacy Study of Human Foetal Neural Stem Cell Transplantation for ALS

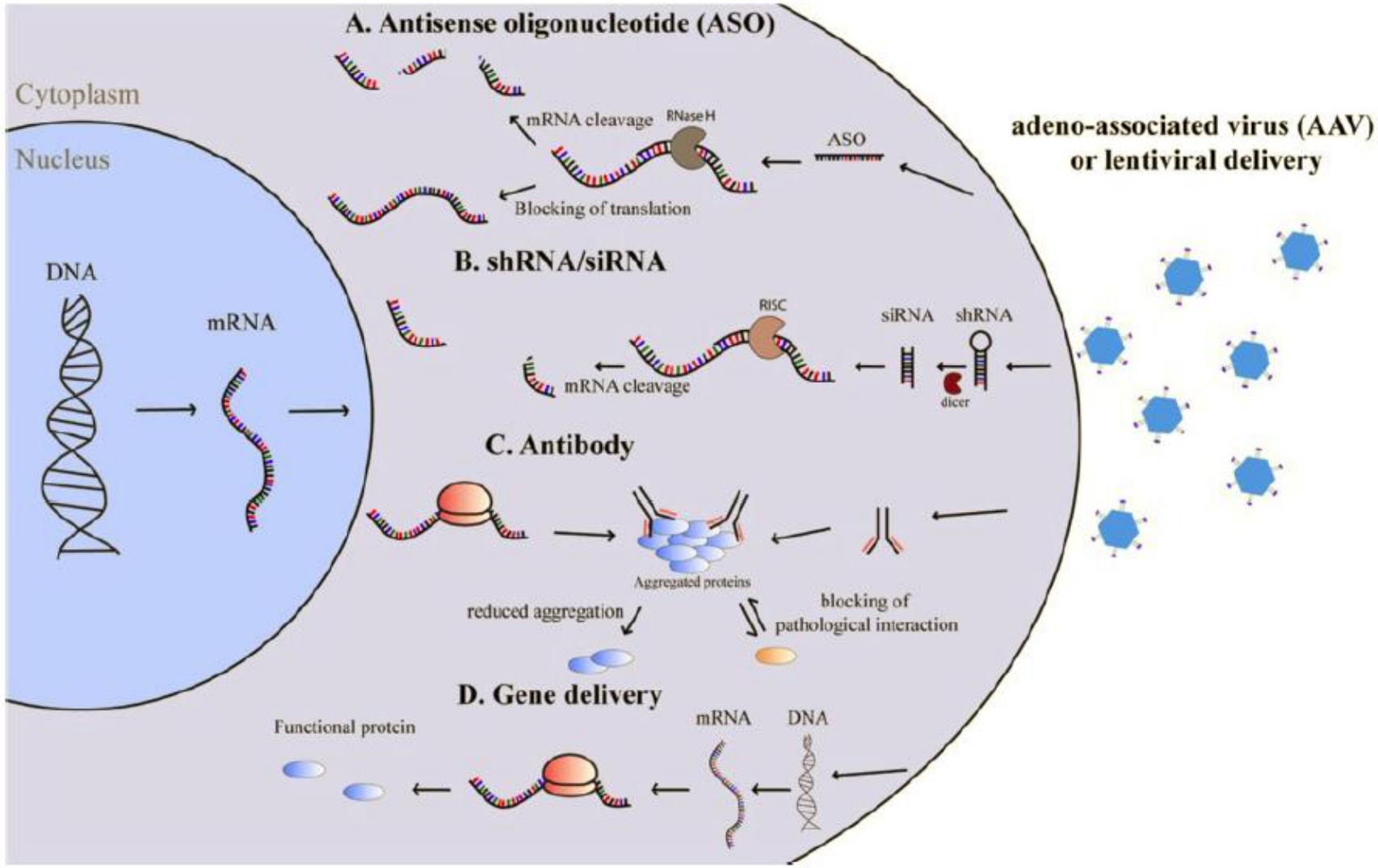
Primary Objective: to measure the effect of different hNSCs doses transplanted into the cervical spinal cord of ALS patients and **to determine the safety of the maximum tolerated dose**.

Secondary Objectives:

1. to collect data on the efficacy

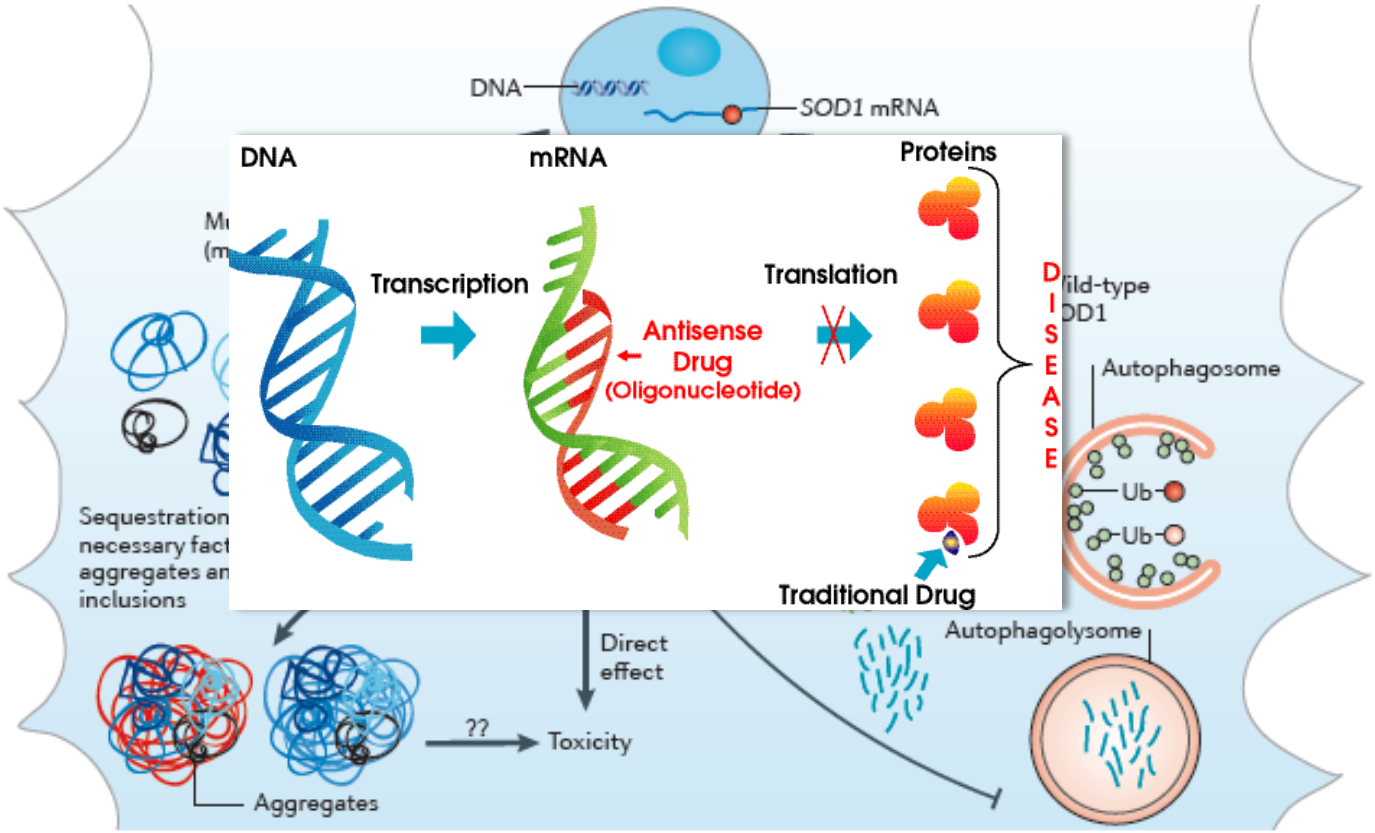
Terapia genica

Potenziali obiettivi della terapia genica nella SLA



Picher-Martel et al, *Acta Neuropathol Comm* 2016

Potenziali meccanismi patogenetici della SOD1 misfolded



Robberecht and Philip, *Nature Rev Neurol* 2013

An antisense oligonucleotide against *SOD1* delivered intrathecally for patients with *SOD1* familial amyotrophic lateral sclerosis: a phase 1, randomised, first-in-man study

Timothy M Miller, Alan Pestronk, William David, Jeffrey Rothstein, Ericka Simpson, Stanley H Appel, Patricia L Andres, Katy Mahoney, Peggy Allred, Katie Alexander, Lyle W Ostrow, David Schoenfeld, Eric A Macklin, Daniel A Norris, Georgios Manousakis, Matthew Crisp, Richard Smith, C Frank Bennett, Kathie M Bishop, Merit E Cudkowicz

ISIS SOD1Rx

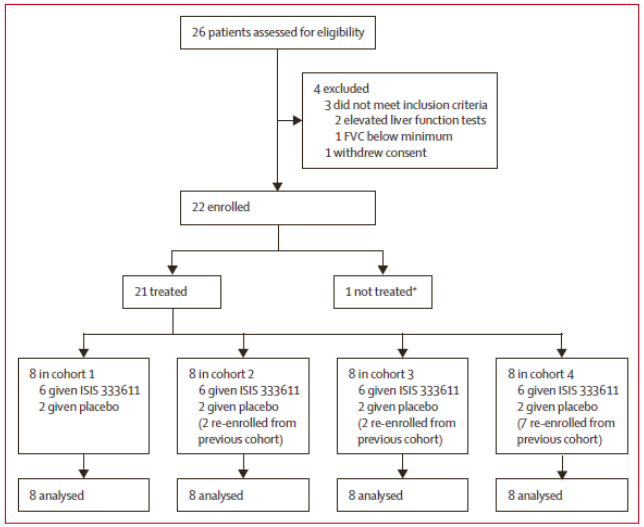


Figure 1: **Trial profile**
FVC=forced vital capacity. *Not treated because of failed placement of intrathecal catheter.

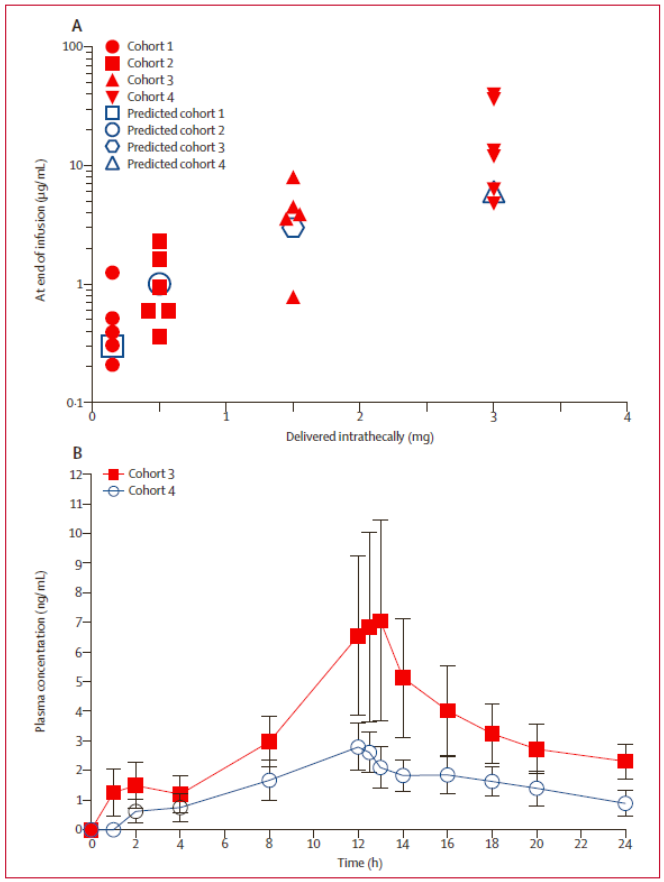


Figure 2: **CSF and plasma concentrations of ISIS 333611**
Delivered and measured concentrations in the CSF (A) and plasma concentrations over time (B). Plasma concentrations for cohorts 1 and 2 were below the limit of detection of the assay. The CSF draw was unsuccessful for one patient in cohort 1 and one patient in cohort 3.

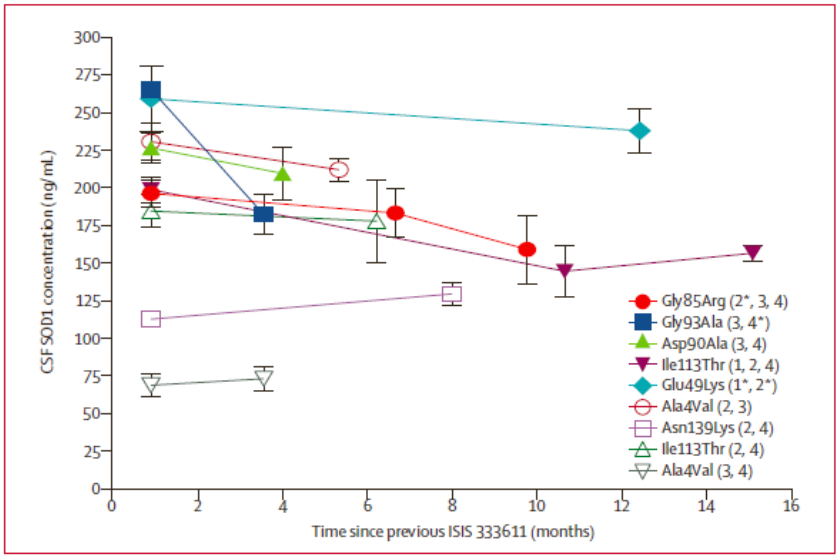


Figure 3: **SOD1 protein concentrations in CSF of patients enrolled in more than one cohort**
Measured by ELISA. SOD1 mutation and cohort number are shown for each patient. *Placebo group for that cohort.

Gene Therapy

A Study to Assess the Safety, Tolerability, and Pharmacokinetics of BIIB078 in Adults With C9ORF72-Associated Amyotrophic Lateral Sclerosis

Sponsors and Collaborators
Biogen

Study Type :Interventional (Clinical Trial)
Estimated Enrollment :59 participants
Allocation:Randomized
Intervention Model:Sequential Assignment
Masking:Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:Treatment
Official Title:**A Phase 1 Multiple-Ascending-Dose** Study to Assess the Safety, Tolerability, and Pharmacokinetics of BIIB078 Administered Intrathecally to Adults With C9ORF72-Associated Amyotrophic Lateral Sclerosis
Actual Study Start Date :September 10, 2018
Estimated Primary Completion Date :November 29, 2020
Estimated Study Completion Date :November 29, 2020

Locations

United States, California
Research Site Recruiting
La Jolla, California, United States, 92093-0949
United States, Florida
Research Site Not yet recruiting
Miami, Florida, United States, 33136
United States, Maryland
Research Site Recruiting
Baltimore, Maryland, United States, 21205
United States, Massachusetts
Research Site Recruiting
Boston, Massachusetts, United States, 02114
United States, Missouri
Research Site Not yet recruiting
Saint Louis, Missouri, United States, 63110
United States, Nebraska
Research Site Not yet recruiting
Lincoln, Nebraska, United States, 68506
United States, Tennessee
Research Site Recruiting
Knoxville, Tennessee, United States, 37920
Canada, Quebec
Research Site Not yet recruiting
Montreal, Quebec, Canada, H3A 2B4

Altri trials in Italia

Titolo: **STUDIO MULTICENTRICO, A DOPPIO CIECO, CONTROLLATO CON PLACEBO, A GRUPPI PARALLELI SUL TRATTAMENTO CON *FILGRASTIM* NELLA SCLEROSI LATERALE AMIOTROFICA (STEMALS-II)**

Acronimo: **STEMALS II**

EudraCT N.: **2014-002228-28**

Fase Studio: **II**

Promotore e Centro Coordinatore: Prof. Adriano Chiò - CRESLA, SCDU Neurologia 2, Dipartimento di Neuroscienze "Rita Levi Montalcini", Università degli Studi di Torino e Azienda Ospedaliera Città della Salute e della Scienza di Torino

UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Modena

RAPAMYCIN (SIROLIMUS) TREATMENT FOR AMYOTROPHIC LATERAL SCLEROSIS

ARISLA
AGENZIA DI RICERCA PER LA SCLEROSI LATERALE AMIOTROFICA

JESSICA MANDRIOLI

Dipartimento Integrato di Neuroscienze
Nuovo Ospedale Civile S. Agostino-Estense
Modena

Acronimo: RAP-ALS
EudraCT N: 2016-002399-28
Fase Studio: II
Centro Coordinatore: MODENA

Protocollo: L'effetto di RNS60 sui biomarcatori della SLA.

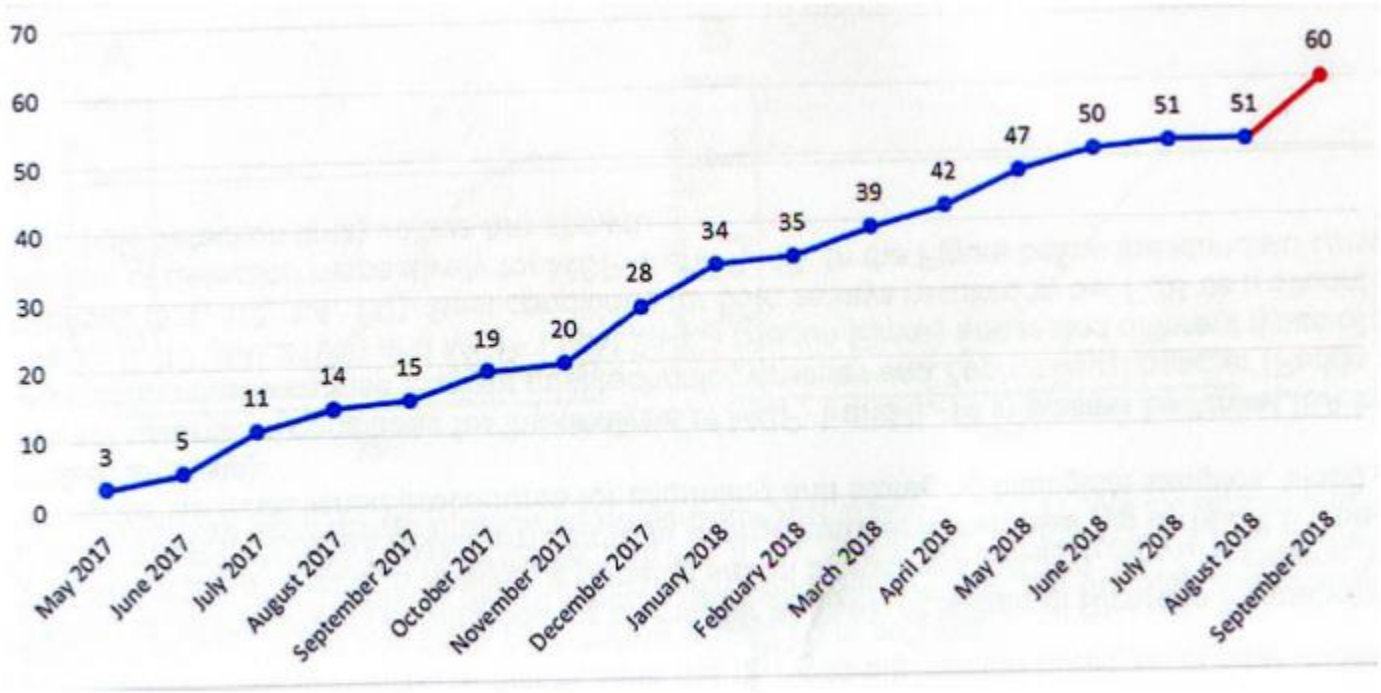
Ve

EudraCT: 2016-002382-62

Acronimo: RNS60-ALS

Promotore dello studio: IRCCS - Istituto di Ricerche Farmacologiche Mario Negri

Coordinatore dello studio: Dr. Ettore Beghi, IRCCS- Istituto di Ricerche Farmacologiche Mario Negri, Milano. **Co-Coordinatore:** Dr.ssa Letizia Mazzini, Dipartimento di Neurologia, Ospedale Universitario "Ospedale Maggiore della Carità" Novara



TITOLO DELLO STUDIO: **MISFOLDING PROTEICO, SCLEROSI LATERALE AMIOTROFICA E GUANABENZ: STUDIO RCT DI FASE III CON DISEGNO DI FUTILITA'**

ENTE PROMOTORE: IRCCS Fondazione Istituto Neurologico "Carlo Besta" - Milano.

PRODOTTO IN STUDIO: Guanabenz acetato

CODICE STUDIO: PROMISE

GUANABENZ ACETATO è un farmaco originariamente utilizzato per curare l'ipertensione ed uscito dal commercio in quanto non era efficace per quello scopo. Nel corso degli ultimi due anni, studi di laboratorio hanno dimostrato che la SLA è caratterizzata dall'accumulo di materiale (proteine) tossico nelle cellule moto neuronali che degenerano causando i sintomi della malattia e la sua progressione. Nei modelli di cellule e negli animali che si usano per capire i meccanismi della SLA e per avere informazioni preliminari su possibili farmaci utili anche nell'uomo, ***GUANABENZ ACETATO*** ha dimostrato di bloccare l'accumulo di quel materiale tossico nelle cellule e di migliorare la malattia negli animali.

REFALS

REFALS: studio di fase III sull'effetto di LEVOSIMENDAN sulla funzione respiratoria nella SLA

Disegno dello studio: muticentrico, randomizzato, doppio cieco, gruppo placebo, a gruppi paralleli,

Centro Coordinatore Italiano : UO Neurologia- Università di Pisa: Prof. Gabriele Siciliano

Cosa è il levosimendan: farmaco già utilizzato per lo scompenso cardiaco congestizio, con effetto inotropo positivo (attraverso i canali del calcio) e con effetto vasodilatatore attraverso canali potassio ATP dipendenti.

Obiettivo primario: SVC supina a 12 settimane

Obiettivi secondari:

1. ALSFRS-R e sopravvivenza a 48 settimane (CAFS)
2. tempo di insorgenza di “evento respiratorio” nelle 48 settimane
3. Clinical Global Impression of change (CGI) nelle 48 settimane
4. Scala di Borg supina a 12 settimane
5. Rallentamento del declino della funzione respiratoria(ALSFRS-R) nelle 48 settimane

A Phase III, Randomized, Placebo-Controlled Trial of Arimoclomol in Amyotrophic Lateral Sclerosis, Followed by a Long-Term, Open-Label Extension on Arimoclomol Treatment

Draft Trial Outline

Product Name/Number:	Arimoclomol
Protocol Number:	ORARIALS-01
Development Phase	Phase III
Protocol Title:	A Phase III, Randomized, Placebo-Controlled Trial of Arimoclomol in Amyotrophic Lateral Sclerosis, Followed by a Long-Term, Open-Label Extension on Arimoclomol Treatment
Indication:	Amyotrophic Lateral Sclerosis (ALS)
Planned Number of Subjects:	Up to 250 subjects are planned for enrollment

Safety and efficacy of tauroursodeoxycholic acid (TUDCA) as add-on treatment in patients affected by amyotrophic lateral sclerosis (ALS)

Funded by Horizon 2020

SC1-PM-08-2017 – New therapies for rare diseases – Project 755094

Sinossi

Titolo	Sicurezza ed efficacia dell'acido tauroursodeossicolico (TUDCA) come trattamento aggiuntivo nei pazienti affetti da sclerosi laterale amiotrofica (SLA)
Sponsor	Humanitas Mirasole S.p.A.
Coordinatore dello Studio	Prof . Alberto Albanese
Acronimo identificativo	TUDCA-ALS

UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena

COLCHICINE TREATMENT FOR AMYOTROPHIC LATERAL SCLEROSIS

AriSLA
AGENZIA DI RICERCA PER LA SCLEROSI LATERALE AMIOTROFICA

JESSICA MANDRIOLI

Dipartimento Integrato di Neuroscienze
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Modena

Acronimo: co-ALS
EudraCT N: 2017-004459-21
Fase Studio: II
Centro Coordinatore: MODENA

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FECAL MICROBIOTA TRANSPLANTATION FOR AMYOTROPHIC LATERAL SCLEROSIS

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Acronimo: FETR-ALS

Centro Coordinatore: MODENA

To cure rarely

To treat often

To care always

COMPAGNIA di San Paolo

FONDAZIONE CASSA DI RISPARMIO DI CUNEO

FONDAZIONE CRT

REGIONE PIEMONTE

Ministero della Salute

REGIONE AUTONOMA DELLA SARDEGNA

FONDAZIONE VIALLI E MAURO PER LA RICERCA E LO SPORT ONLUS

ITALIA FIGC

ARISLA

Fondazione Magnetto

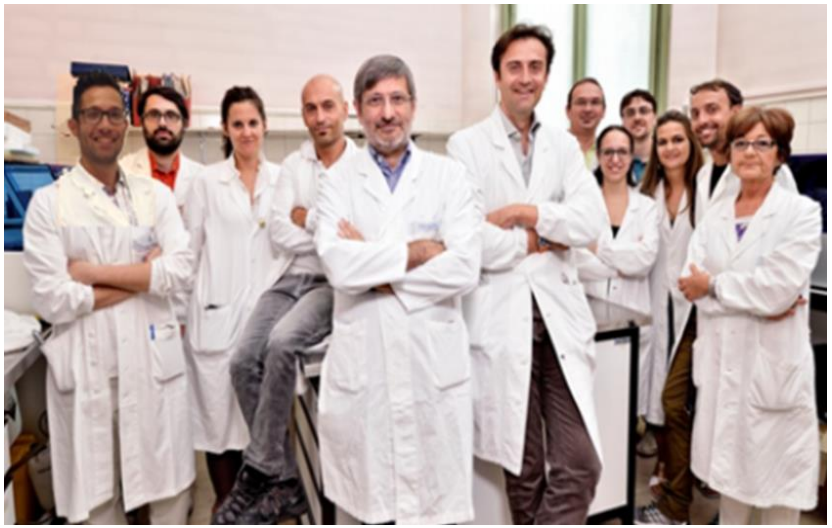
A.P.A. S.L.A.

FONDATION THIERRY LATRAN

SOPHIA

euroMOTOR

Neurinox

SEVENTH FRAMEWORK PROGRAMME

Centro Regionale Esperto per la SLA di Torino (CRESLA)