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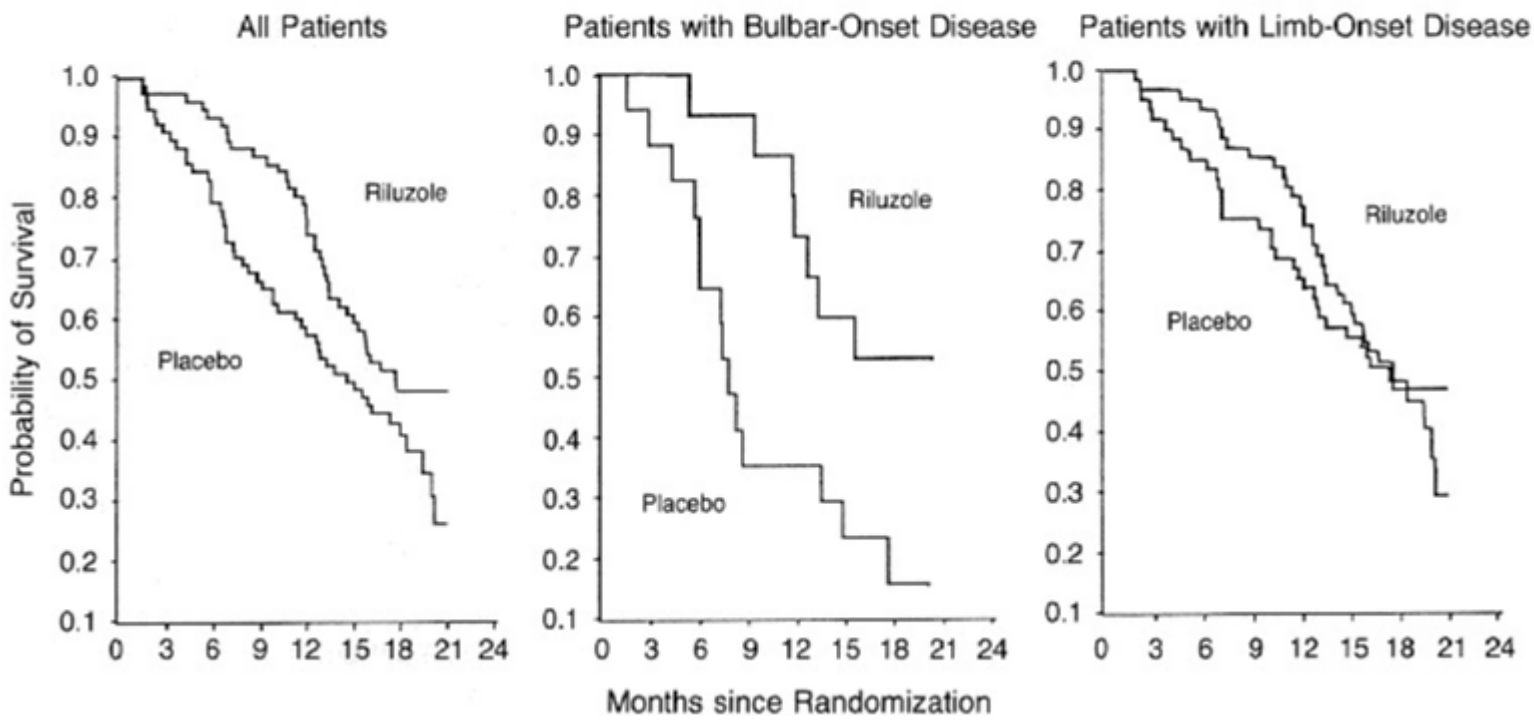
Genève

Options thérapeutiques de la SLA: Riluzole

- Depuis les années 90: **RILUZOLE** (anti-glutamate) était le seul traitement à ralentir la progression de la maladie et prolonger la survie d'environ 30 %



Bensimon G, Lacomblez L, Meininger V. N Engl J Med. 1994

Options thérapeutiques de la SLA: Riluzole

2x50 mg / j

Effets indésirables:

Très fréquents : fatigue, nausées, augmentation des transaminases.

Fréquents : maux de tête, étourdissements, somnolence, fourmillements dans la bouche, diarrhée, douleurs abdominales, vomissements, accélération du cœur.

Options thérapeutiques de la SLA: Edaravone

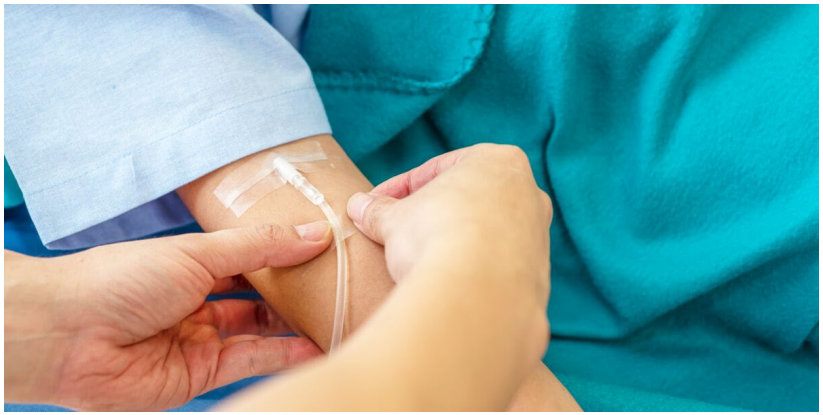
- Autorisé en Suisse depuis 2019: **EDARAVONE iv**: Eliminateur des radicaux libres, diminution de la progression d'environ 30 % dans un groupe bien défini:

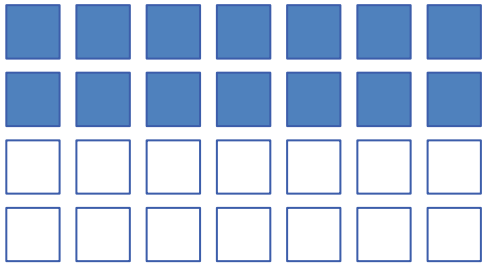
  - Durée de la maladie < 2 ans
  - ALS-FRS: au moins 2 points pour chaque item
  - Capacité vitale > 80 %

  - "Inclusion criteria identifies patients who would be expected to have a sufficient and measurable deterioration over 6 months in order to see the effect of treatment"

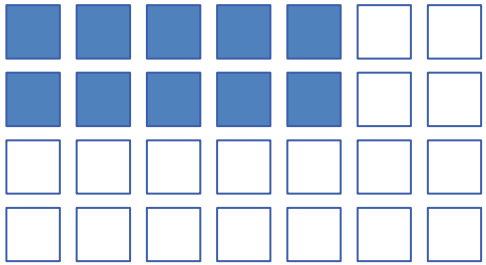
- **Cycle 1:** 60 mg i.v./j, 14 jours consécutives, suivi par 2 semaines sans traitment

- **Cycle 2 (et suivants):** 60 mg i.v./j, **10 jours pendant une période de 14 jours**, suivi par 2 semaines sans traitment





Cycle 1

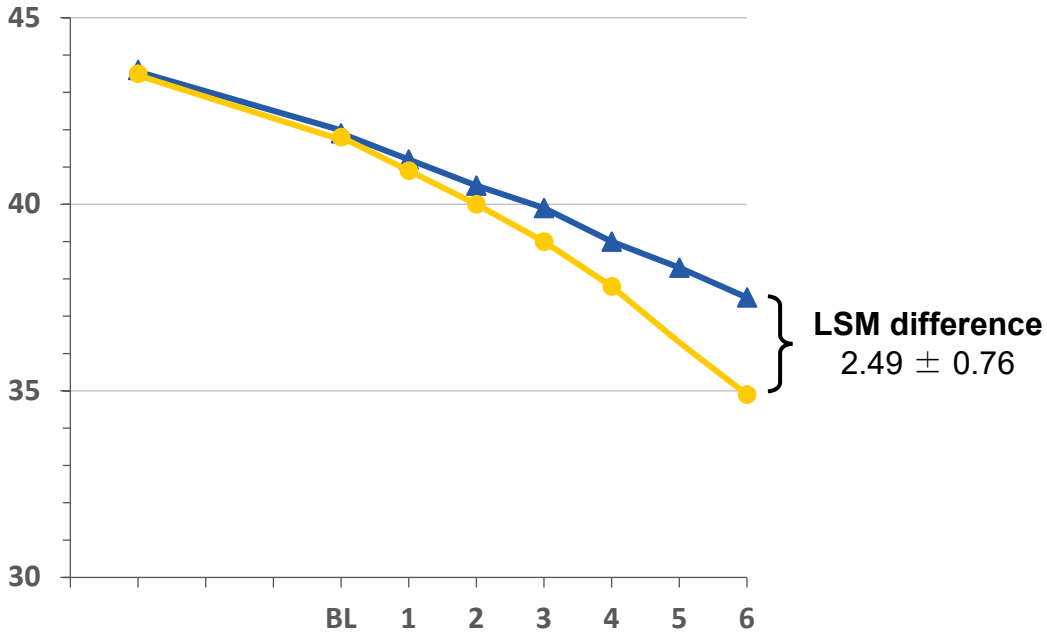


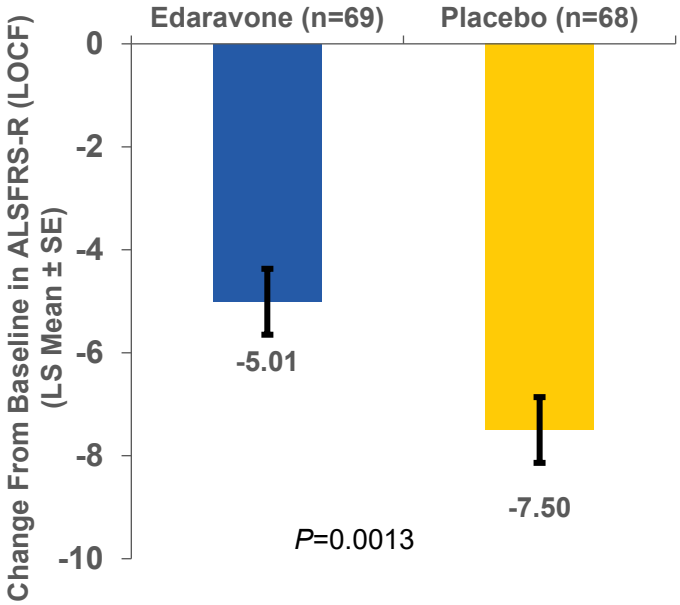
Cycle 2 and thereafter

Edaravone at 60 mg for 60 minutes

[1] Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. Lancet Neurol. 2017; 16(7): 505-512.

Options thérapeutiques de la SLA: Edaravone





EDARAVONE DEMONSTRATED STATISTICAL SIGNIFICANCE ON THE PRIMARY ENDPOINT → 33% LESS PHYSICAL FUNCTIONAL LOSS VS PLACEBO OVER 24-WEEK DOUBLE-BLIND PERIOD

[1] Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. Lancet Neurol. 2017; 16(7): 505-512.

Effets indésirables

Des effets indésirables ont été observés chez environ 10% des personnes traitées

Les effets secondaires les plus fréquents observés lors de l'essai clinique étaient des ecchymoses (contusions) et des troubles de la marche.

Il est également associé à des risques graves qui nécessitent des soins médicaux immédiats, comme l'urticaire, le gonflement ou l'essoufflement, et des réactions allergiques au bisulfite de sodium, un ingrédient du médicament.

Effets secondaires fréquents liés à la voie veineuse (inflammations, fièvre, thromboses...)

UNE NOUVELLE OPTION THÉRAPEUTIQUE POUR LA SLA: MASITINIB (?)

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2020; 21: 5–14

Taylor & Francis
Taylor & Francis Group

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RESEARCH ARTICLE

Masitinib as an add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a randomized clinical trial

Therapeutic Advances in Neurological Disorders *Original Research*

Long-term survival analysis of masitinib in amyotrophic lateral sclerosis

Jesus S. Mora, Walter G. Bradley, Delia Chaverri, María Hernández-Barral, Javier Mascias, Josep Gamez, Gisella M. Gargiulo-Monachelli, Alain Moussy, Colin D. Mansfield, Olivier Hermine and Albert C. Ludolph

Ther Adv Neurol Disord
2021, Vol. 14: 1–16
DOI: 10.1177/17562864211030365

Masitinib, an oral tyrosine kinase inhibitor, has demonstrated promising preclinical activity in ALS (SOD1G93A) rat models, exerting neuroprotection via its immunomodulatory properties and in particular through targeting microglia, macrophage and mast cell activity, in both central and peripheral nervous systems

UNE NOUVELLE OPTION THÉRAPEUTIQUE POUR LA SLA: MASITINIB (?)

27% slowing of ALSFRS-R

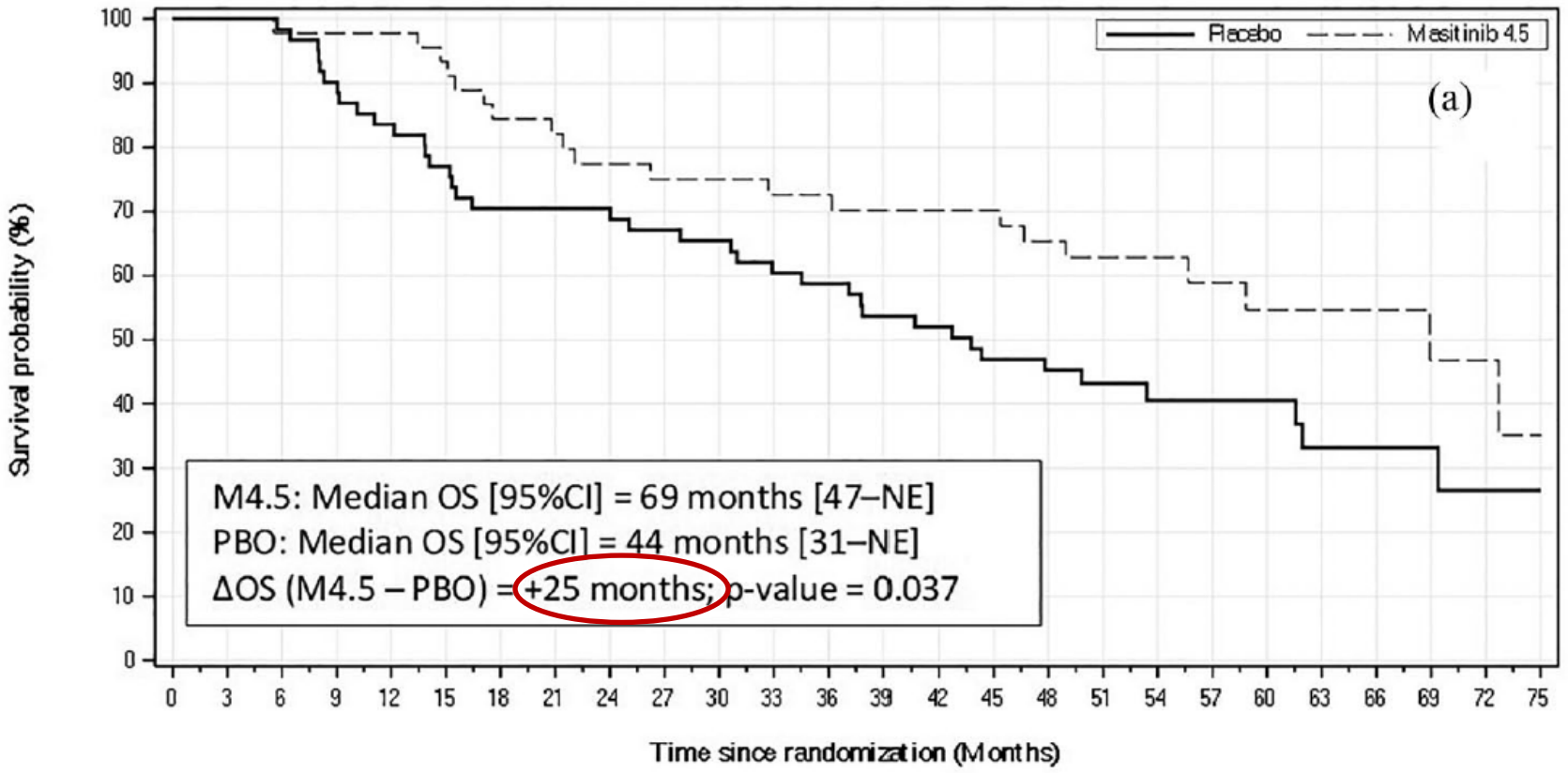
«Normal progressors»

ALS-FRS diminution < 1.1 points/mois

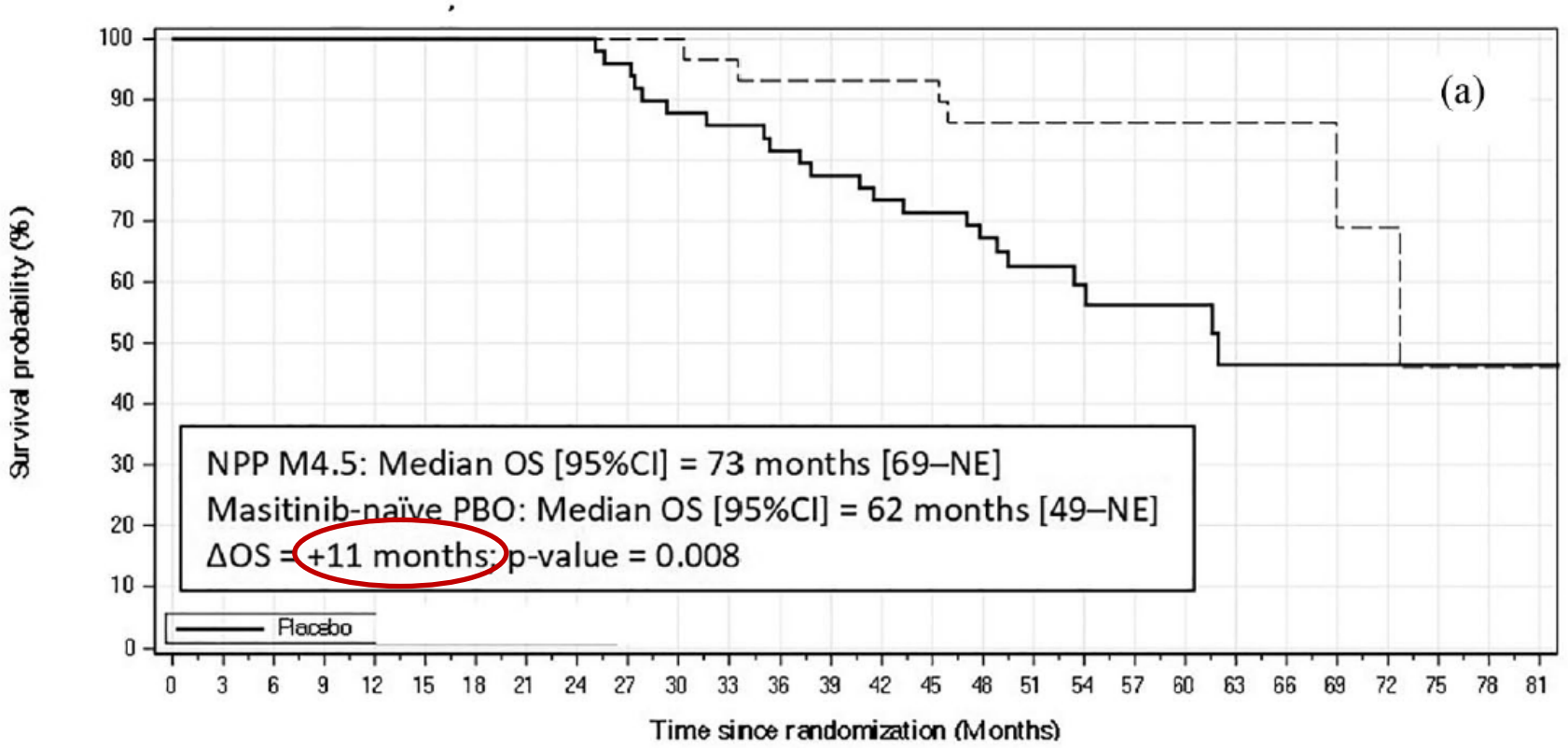
Cohort	MAS (*n*)	PBO (*n*)	Deaths		Median OS (95% CI)		ΔOS (months)	*p*-value (log-rank)
			MAS	PBO	MAS (months)	PBO (months)		
LT-M4.5 (≥2 each baseline ALSFRS-R item, any ΔFS)	50	63	24 (48%)	38 (60%)	69 (44; NE)	44 (31; 62)	+25	0.037
LT-M4.5 (≥2 each baseline ALSFRS-R item, ΔFS < 1.1)	45	62	20 (44%)	38 (61%)	69 (47; NE)	44 (31; 62)	+25	0.037

UNE NOUVELLE OPTION THÉRAPEUTIQUE POUR LA SLA: MASITINIB (?)

ALS-FRS >/= 2 points/item, progression < 1.1 points/mois



UNE NOUVELLE OPTION THÉRAPEUTIQUE POUR LA SLA: MASITINIB (?)



UNE NOUVELLE OPTION THÉRAPEUTIQUE POUR LA SLA: MASITINIB (?)

Completed week-48 visit
M4.5=73/105 (69.5%)
PBO=83/113 (73.5%)

Reason for withdrawal prior to W48
Discontinued due to AE:
M4.5=11/32 (34.4%)
PBO=1/30 (3.3%)
Lack of efficacy:
M4.5=13/32 (40.6%)
PBO=9/30 (30.0%)
Death prior to W48:
M4.5=2/32 (6.3%)
PBO=7/30 (23.3%)
$Other:
M4.5=6/32 (18.8%)
PBO=13/30 (43.3%)

Number (%) of patients with at least one	PBO ($n = 133$) (%)	M4.5 ($n = 129$) (%)	Δ[M4.5] (%)	M3.0 ($n = 131$) (%)	Δ[M3.0] (%)
Rash maculo papular	1 (0.8)	11 (8.5)	7.7	6 (4.6)	3.8
Nausea	6 (4.5)	15 (11.6)	7.1	8 (6.1)	1.6
Respiratory failure	5 (3.8)	13 (10.1)	6.3	9 (6.9)	3.1

Biotech

AB halts masitinib trials after discovering heart disease worry

by Nick Paul Taylor | Jun 2, 2021 8:10am

23/08/2021 – AB Science reçoit la première autorisation (en Norvège) de

reprise des inclusions dans l'étude de phase 3 dans la SLA

UNE NOUVELLE OPTION THÉRAPEUTIQUE POUR LA SLA: PB-TUDCA (?)

ORIGINAL ARTICLE

Trial of Sodium Phenylbutyrate–Taurursodiol for Amyotrophic Lateral Sclerosis

S. Paganoni, E.A. Macklin, S. Hendrix, J.D. Berry, M.A. Elliott, S. Maiser, C. Karam, J.B. Caress, M.A. Owegi, A. Quick, J. Wymer, S.A. Goutman, D. Heitzman, T. Heiman-Patterson, C.E. Jackson, C. Quinn, J.D. Rothstein, E.J. Kasarskis, J. Katz, L. Jenkins, S. Ladha, T.M. Miller, S.N. Scelsa, T.H. Vu, C.N. Fournier, J.D. Glass, K.M. Johnson, A. Swenson, N.A. Goyal, G.L. Pattee, P.L. Andres, S. Babu, M. Chase, D. Dagostino, S.P. Dickson, N. Ellison, M. Hall, K. Hendrix, G. Kittle, M. McGovern, J. Ostrow, L. Pothier, R. Randall, J.M. Shefner, A.V. Sherman, E. Tustison, P. Vigneswaran, J. Walker, H. Yu, J. Chan, J. Wittes, J. Cohen, J. Klee, K. Leslie, R.E. Tanzi, W. Gilbert, P.D. Yeramian, D. Schoenfeld, and M.E. Cudkowicz

Mécanismes d'action proposés:

Sodium phenylbutyrate (inhibiteur de la histone deacetylase): diminution du stress cellulaire et de la toxicité du reticulum endoplasmatique par "up-"regulation de protéines "heat shock" proteins et chaperone pour des petites molecules.

Taurursodiol: rétablissement des déficits bioénergétiques des mitochondries, augmentation du seuil apoptotique (auto-destruction) des cellules

a 2:1 ratio to receive sodium phenylbutyrate–taurursodiol (3 g of sodium phenylbutyrate and 1 g of taurursodiol per sachet) or matching placebo, orally or through a feeding tube for a planned duration of 24 weeks. (For details re-

for eligibility, of whom 137 were randomly assigned to a trial group: 89 to sodium phenylbutyrate–taurursodiol and 48 to placebo (Fig. 1).

Outcome	Least-Squares Mean Change per Month†		Least-Squares Mean at Week 24†‡		
	Sodium Phenylbutyrate–Taurursodiol (N=87)	Placebo (N=48)	Sodium Phenylbutyrate–Taurursodiol (N=87)	Placebo (N=48)	Least-Squares Difference (95% CI)†§
Primary outcome					
ALSFRS-R total score	−1.24±0.12	−1.66±0.16	29.06±0.78	26.73±0.98	2.32 (0.18 to 4.47)¶

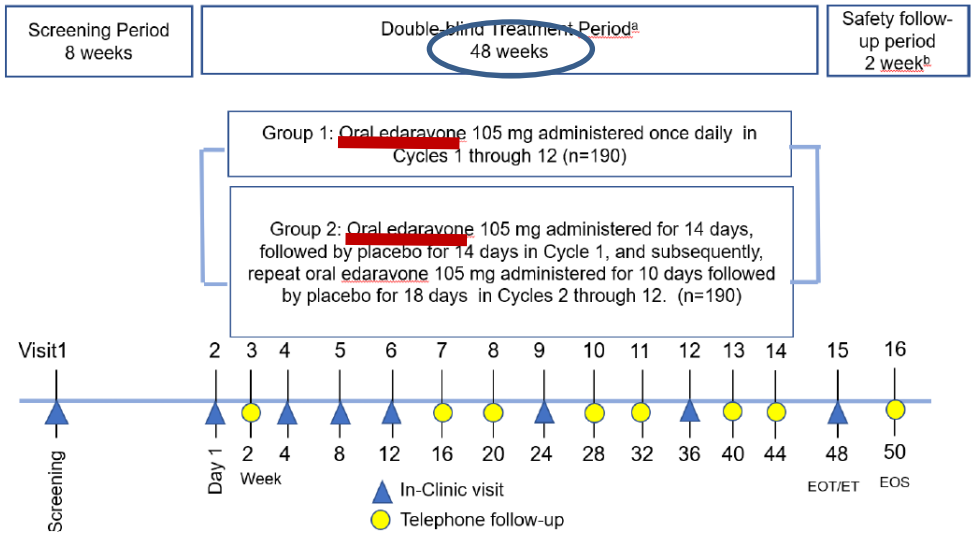
Table 3. Summary of Adverse Events That Occurred during the Treatment Period.*

Variable	Sodium Phenylbutyrate–Taurursodiol (N = 89)	Placebo (N = 48)
Adverse events		
≥1 Adverse event — no. (%)	86 (97)	46 (96)
No. of distinct events	618	328
Trial regimen interrupted owing to adverse event — no. (%)	13 (15)	6 (12)
Dose reduced owing to adverse event — no. (%)	4 (4)	0
Trial regimen discontinued owing to adverse event — no. (%)	17 (19)	4 (8)
Adverse event considered to be related to intervention	13 (15)	1 (2)
Adverse event considered to be unrelated to intervention	4 (4)	3 (6)
Serious adverse events		
≥1 Serious adverse event — no. (%)	11 (12)	9 (19)
No. of distinct events	14	10
Death — no. (%)	5 (6)	2 (4)
≥1 Serious adverse event considered to be related to intervention — no. (%)	1 (1)	1 (2)
Trial regimen discontinued owing to serious adverse event — no. (%)	1 (1)	3 (6)
Serious adverse event considered to be related to intervention	0	0
Serious adverse event considered to be unrelated to intervention	1 (1)	3 (6)
Adverse events with ≥5% incidence in either group — no. (%)†		
Gastrointestinal disorders	60 (67)	29 (60)
Musculoskeletal and connective-tissue disorders	38 (43)	21 (44)
Injury, poisoning, and procedural complications	35 (39)	23 (48)
Nervous-system disorders	33 (37)	19 (40)
Infections and infestations	28 (31)	21 (44)
Respiratory, thoracic, and mediastinal disorders	29 (33)	10 (21)
General disorders and administration-site conditions	20 (22)	13 (27)
Skin and subcutaneous-tissue disorders	16 (18)	8 (17)
Psychiatric disorders	14 (16)	9 (19)
Renal and urinary disorders	10 (11)	8 (17)
Metabolism and nutrition disorders	10 (11)	4 (8)
Cardiac disorders‡	7 (8)	0
Eye disorders	5 (6)	1 (2)

EDARAVONE PER OS: ETUDE DE MITSUBISHI TANABE, PHASE III

Inclusion Criteria:

1. Subjects must provide a signed and dated informed consent form (ICF) to participate in the study. Subjects must be able (in the judgment of the Investigator) to understand the nature of the study and all risks involved with participation in the study. Subjects must be willing to cooperate and comply with all protocol restrictions and requirements.
2. Subjects will be male or female, ≥ 18 to 75 years of age at the time the ICF is signed.
3. Subjects will be diagnosed with Definite ALS or Probable ALS according to the El Escorial revised criteria (Appendix 1) for the diagnosis of ALS.
4. Subjects with a baseline score ≥ 2 points on each individual item of the ALSFRS- R at screening and baseline visits (Appendix 2).
5. Subjects have a screening and baseline %forced vital capacity (FVC) ≥ 70%.
6. Subjects with 1 to 4 points decline for 8 weeks in ALSFRS-R total score between screening and baseline visits.
7. Subjects whose first symptom of ALS has occurred within 2 years of providing written informed consent.



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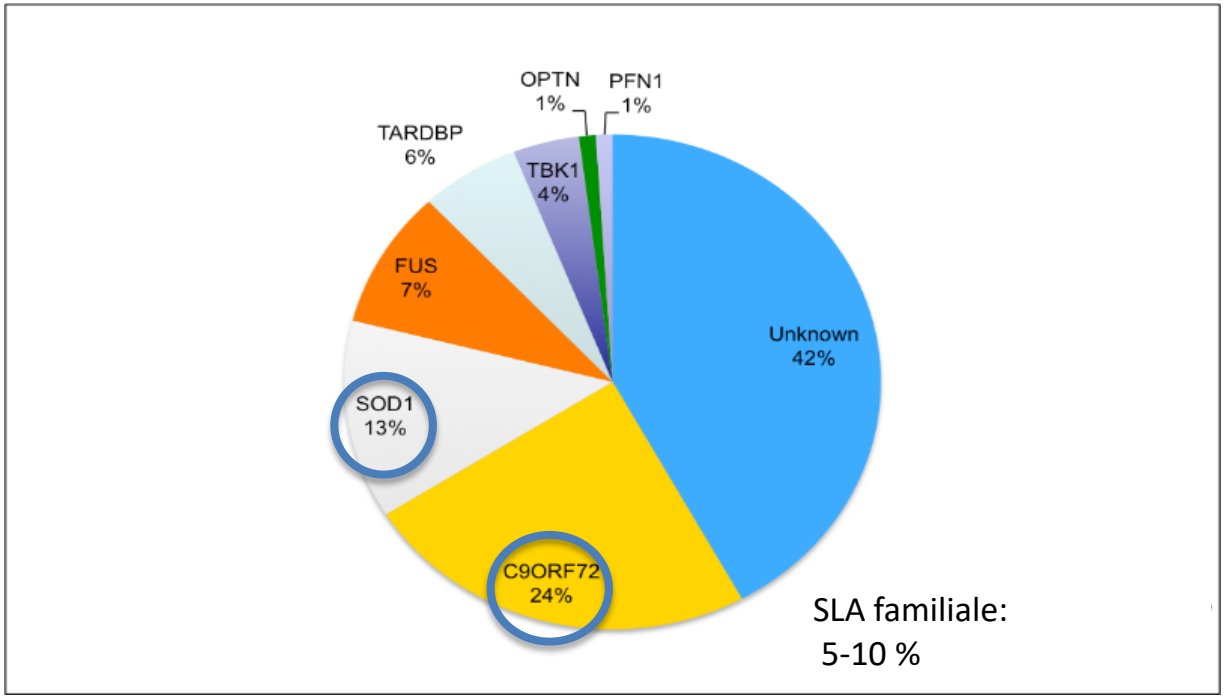
UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

PERSPECTIVE FUTURE:
« THÉRAPIE GÉNÉTIQUE » DES MALADIES DU MOTONEURONE

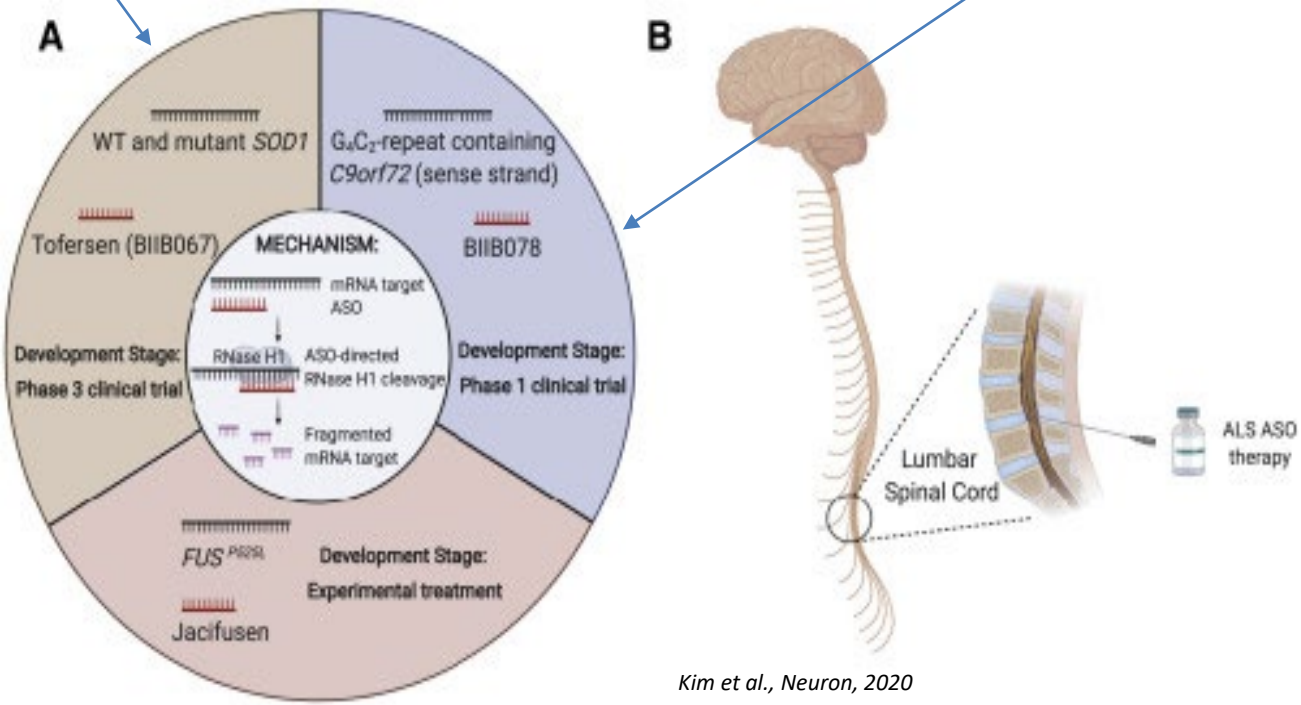


SLA familiale:
5-10 %

PERSPECTIVE FUTURE:
« THÉRAPIE GÉNÉTIQUE » DES MALADIES DU MOTONEURONE

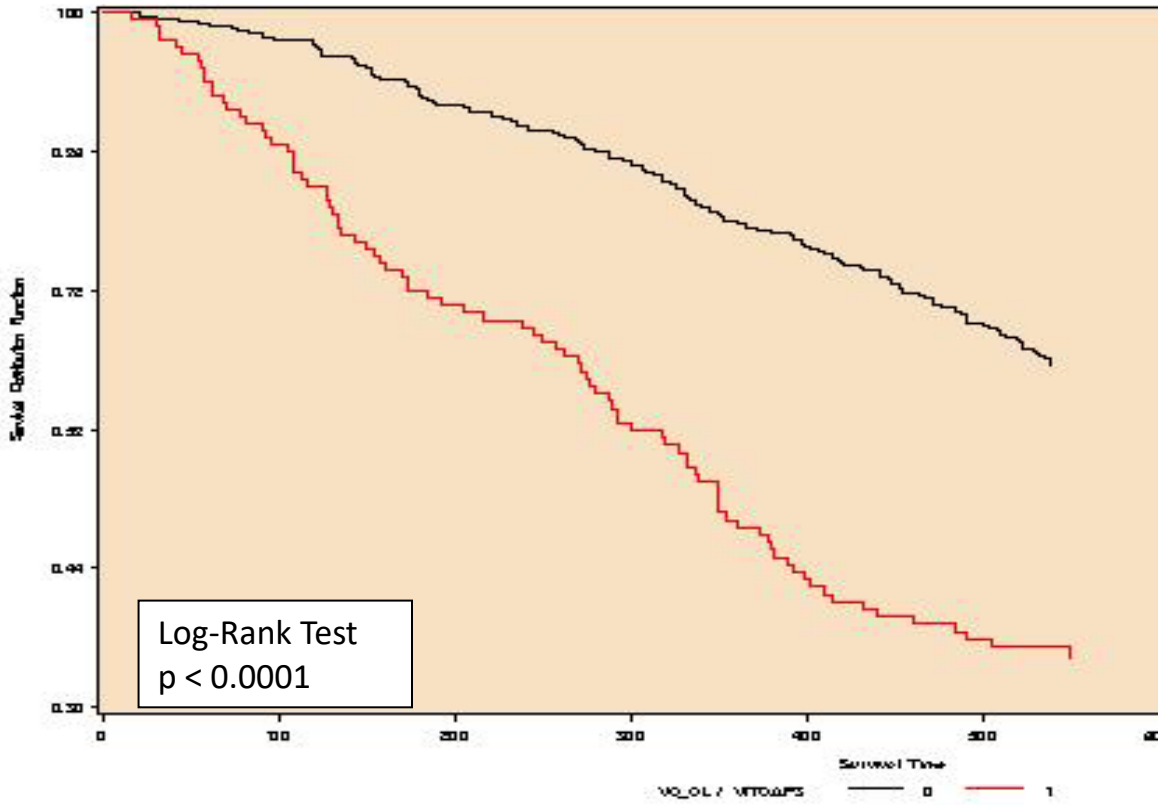
SOD1: Etude terminée, **programme d'accès précoce**!

C9: Etude en cours



Kim et al., Neuron, 2020

CRITÈRE PRONOSTIC: FONCTIONS PULMONAIRES



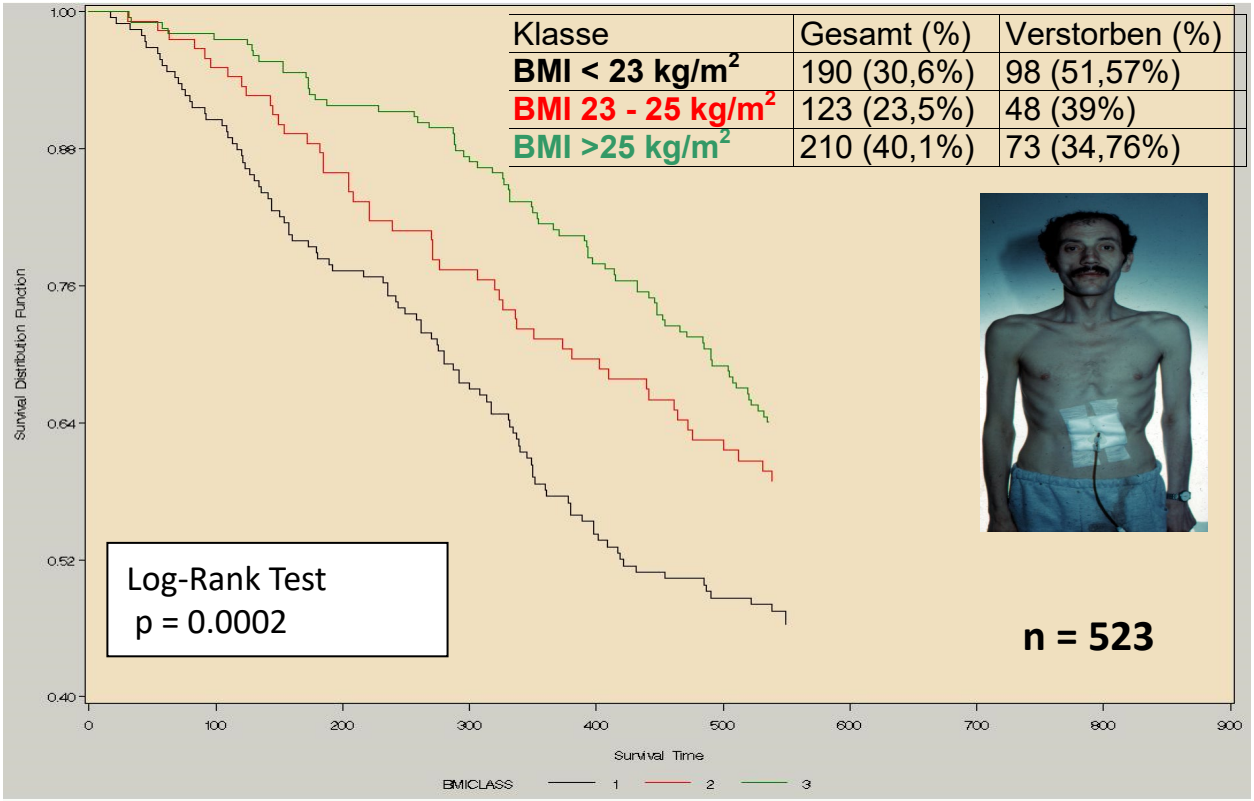
VC ≥ 60%

VC < 60%

n = 523

Dorst J. et al.

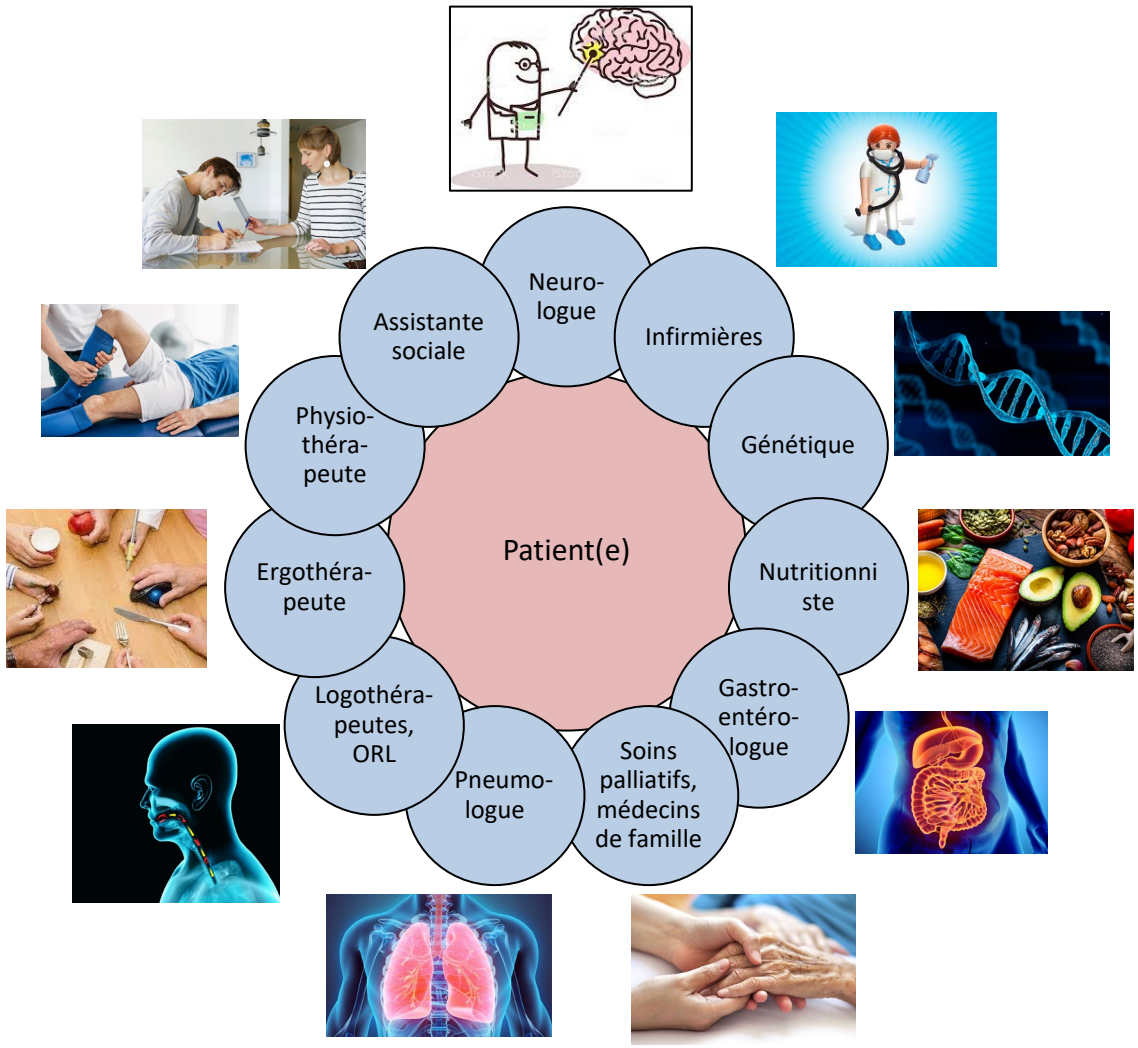
CRITÈRE PRONOSTIC: RAPPORT DE MASSE CORPORELLE (BMI)



Klasse	Gesamt (%)	Verstorben (%)
BMI < 23 kg/m^2	190 (30,6%)	98 (51,57%)
BMI 23 - 25 kg/m^2	123 (23,5%)	48 (39%)
BMI >25 kg/m^2	210 (40,1%)	73 (34,76%)

Dorst J., et al.

Centre pour la SLA et maladies apparentées
L'approche multidisciplinaire aux HUG



Merci à toute l'équipe du centre SLA des HUG!!!

Questions?