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Masitinib Shows Prolonged Survival in Amyotrophic Lateral Sclerosis (ALS) Patients with Mild or Moderate Disease Severity at Baseline

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Conflict of Interest Disclosure

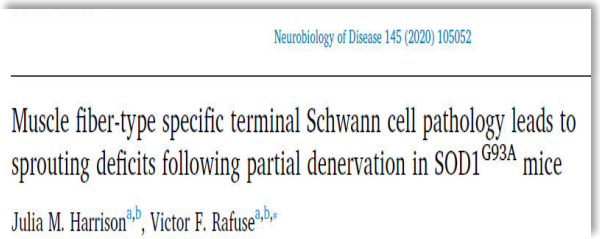
- **Dr. Ludolph is the Steering Committee chair of the current masitinib trial (AB19001, AB Science)**

- Dr. Ludolph has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Novartis. Dr. Ludolph has received personal compensation in the range of $10,000-$49,999 for serving as a Consultant for Biogen . Dr. Ludolph has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Roche Pharma AG . Dr. Ludolph has received personal compensation in the range of $500-$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Biogen. Dr. Ludolph has received personal compensation in the range of $500-$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Roche Pharma. Dr. Ludolph has received personal compensation in the range of $500-$4,999 for serving on a Speakers Bureau for Biologix FZCo.. Dr. Ludolph has received personal compensation in the range of $500-$4,999 for serving on a Speakers Bureau for Biologix FZCo.. Dr. Ludolph has received personal compensation in the range of $500-$4,999 for serving on a Speakers Bureau for Biologix FZCo.. Dr. Ludolph has received personal compensation in the range of $500-$4,999 for serving on a Speakers Bureau for Biogen. Dr. Ludolph has received personal compensation in the range of $500-$4,999 for serving on a Speakers Bureau for Biogen. Dr. Ludolph has received personal compensation in the range of $500-$4,999 for serving on a Speakers Bureau for Biogen. Dr. Ludolph has received personal compensation in the range of $500-$4,999 for serving on a Speakers Bureau for Teva.

Masitinib modulates inflammation

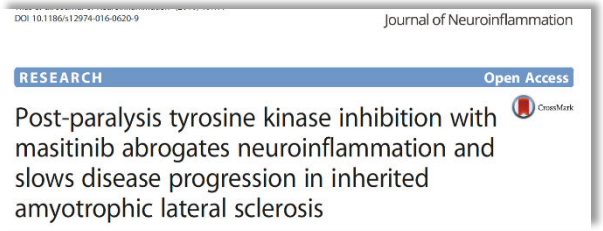
- **Masitinib exerts a potential protective effect on the central nervous system**
  - Regulates microglia, cells with well-known pathogenic role during ALS progression
  - Reduction of microgliosis and aberrant glial cells through CSF-1R inhibition

- **Masitinib exerts a protective effect on the peripheral nervous system**
  - Mast cell infiltration and degranulation contribute to neuromuscular pathology in post-paralytic SOD1G93A rats
  - Masitinib-induced mast cell inhibition significantly reduced rate of motor and neuromuscular junction (NMJ) deficits
  - Mast cell infiltration was observed in muscle and sciatic nerve of ALS patients


Neurobiology of Disease 145 (2020) 105052

Muscle fiber-type specific terminal Schwann cell pathology leads to sprouting deficits following partial denervation in SOD1^{G93A} mice

Julia M. Harrison[a,b], Victor F. Rafuse[a,b,*]


Journal of Neuroinflammation

RESEARCH Open Access

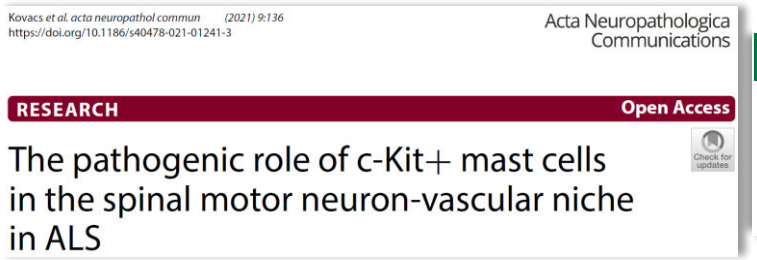
Post-paralysis tyrosine kinase inhibition with masitinib abrogates neuroinflammation and slows disease progression in inherited amyotrophic lateral sclerosis

- **Mechanistic evidence suggests masitinib would provide better outcomes if administered early in disease course**
  - Masitinib significantly reduced terminal Schwann cell loss and preserved motoneuron sprouting capacity


PNAS

Phenotypically aberrant astrocytes that promote motoneuron damage in a model of inherited amyotrophic lateral sclerosis

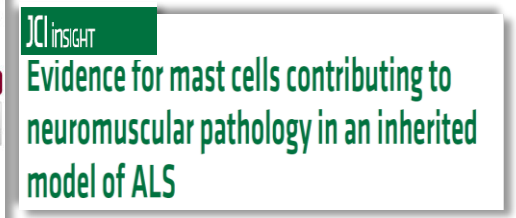
Pablo Díaz-Amarilla[a], Silvia Olivera-Bravo[a], Emiliano Trias[a], Andrea Cragnolini[b], Laura Martínez-Palma[c], Patricia Cassina[c], Joseph Beckman[d,e], and Luis Barbeito[a,b,1]


Kovacs et al. acta neuropathol commun (2021) 9:136
https://doi.org/10.1186/s40478-021-01241-3

Acta Neuropathologica Communications

RESEARCH Open Access

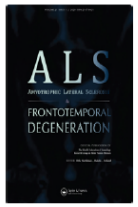
The pathogenic role of c-Kit+ mast cells in the spinal motor neuron-vascular niche in ALS


JCI insight

Evidence for mast cells contributing to neuromuscular pathology in an inherited model of ALS

Study AB10015 overview

- **Study AB10015 was a placebo controlled phase 3 trial of masitinib in ALS**
  - Masitinib 4.5 mg/kg/d administered as an add-on to riluzole significantly slowed the rate of functional decline in ALS patients having an ALSFRS-R progression rate from onset to baseline (ΔFS) of <1.1 points/month
  - The safety and risk profile of masitinib was manageable in patients with ALS



Taylor & Francis

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: 2167-8421 (Print) 2167-9223 (Online) Journal homepage: https://www.tandfonline.com/loi/iafd20

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

Jesus S. Mora, Angela Genge, Adriano Chio, Conrado J. Estol, Delia Chaverri, Maria Hernández, Saúl Marín, Javier Mascias, Gabriel E. Rodriguez, Monica Povedano, Andrés Paipa, Raul Dominguez, Josep Gamez, Maria Salvado, Christian Lunetta, Carlos Ballario, Nilo Riva, Jessica Mandrioli, Alain Moussy, Jean-Pierre Kinet, Christian Auclair, Patrice Dubreuil, Vincent Arnold, Colin D. Mansfield, Olivier Hermine & on behalf of the AB10015 STUDY GROUP

https://doi.org/10.1080/21678421.2019.1632346

- **Double blind, placebo controlled, randomized 1:1:1, oral BID, 48 weeks**
  - Masitinib 4.5 mg/kg/day + riluzole
  - Masitinib 3.0 mg/kg/day + riluzole
  - Placebo + riluzole
- **Main Inclusion Criteria**
  - Sporadic or familial ALS
  - Stable dose of riluzole
  - Disease duration ≤36 mo, FVC ≥60%
- **Primary endpoint**

  Change in the ALSFRS-R score at 48 weeks (ΔALSFRS-R)
- **Primary efficacy population**

  Cohort receiving masitinib 4.5 mg/kg/d with ΔFS <1.1
- **394 patients, 9 countries, 34 sites**

Long-term follow-up of study AB10015

Objectives:

1. Perform long-term survival analysis on a post-hoc survival dataset

- **Overall survival (OS) was a key efficacy endpoint of study AB10015**
- At time of unblinding, OS data were too immature to interpret

❖Estimate survival in an enriched population that excludes severe and/or very severe patients

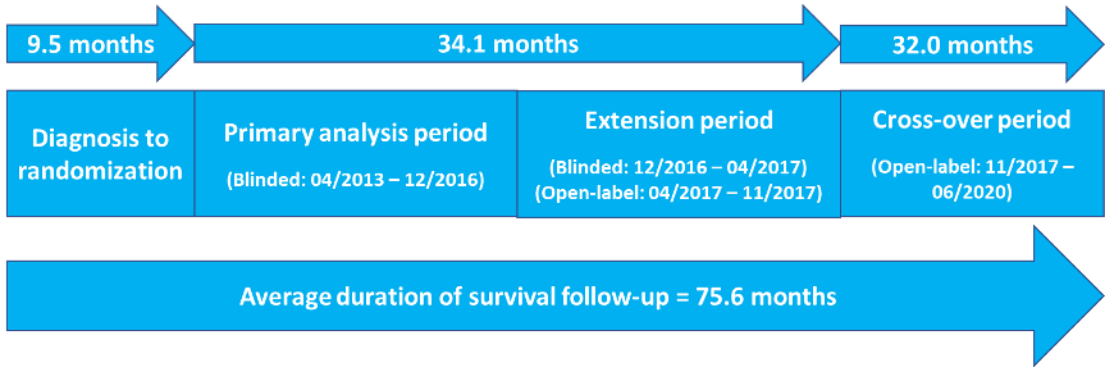
- Consistent with the idea (current ALS trial recommendations) to select ALS patients as early as possible in the course of their disease
- The moderate (non severe) ALS subgroup* is similar to prospectively defined patient population for ongoing confirmatory study AB19001

Enriched patient populations analyzed (ΔFS <1.1)

	ALS (functional) severity at baseline		ALSFRS-R score
1	*Moderate ALS	No complete loss or severe impairment of function	≥2 on each item
2	Moderate–Severe ALS	No complete loss of function	≥1 on each item
3	Moderate–Severe–Very Severe	Corresponds to population of study AB10015	any score

Long-term survival study design

- **Cut-off date for survival data: 14 June 2020, in 100 % of patients survival status**
- **Survival (vital) status collected from each participating investigational site (patients still alive at the time of analysis censored at the date of last contact)**



- **Survival analysis of all patients randomized in study AB10015 for an average observation period of 75 months (date of diagnosis – cut-off)**
- **Follow-up incorporated a masitinib treatment 'compassionate use' with inclusion of 59 pts from masitinib arms and 25 pts (crossover) from the placebo arm**
- **95% of patients had survival status verified less than 7 months prior to cut-off**

	PBO (n)	M4.5 (n)	M3.0 (n)	Total (n)
Overall (mITT) population	133	130	131	394
Survival status <7 mo prior to cut-off	128 (96%)	122 (94%)	124 (95%)	374 (95%)
Survival status older than 7 mo	5 (4%)	8 (6%)	7 (5%)	20 (5%)

- **Results reported here are based on the hard database lock (9/2021)**

Long-term survival analysis results

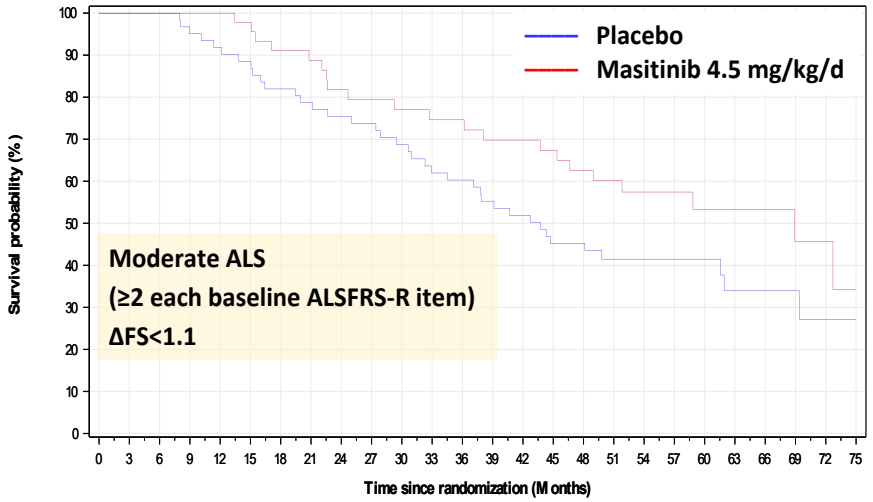
❖ Median overall survival analysis

	N		Deaths		Median OS [95%CI]		ΔOS	P-
	MAS	PBO	MAS	PBO	MAS	PBO	(months)	value
Moderate ALS (ΔFS<1.1)	45	62	21 (47%)	38 (61%)	69 [45;NE]	44 [33;62]	+25	< 0.05
Moderate/Severe ALS (ΔFS<1.1)	85	104	44 (52%)	66 (63%)	53 [36;NE]	43 [31;49]	+10	< 0.05
Moderate/Severe/Very severe ALS (ΔFS<1.1)	106	114	60 (57%)	73 (64%)	46 [33;69]	40 [30;48]	+6	NS

❖ Hazard ratio (HR) analysis

	HR [95%CI]	Reduced Risk	P-value
Moderate ALS (ΔFS<1.1)	0.56 [0.32–0.96]	44%	< 0.05

❖ Kaplan-Meier survival analysis



❖ Baseline characteristics from enriched populations were balanced

Impact of enrichment on ΔALSFRS-R & PFS

- **Enriched populations showed consistency of treatment-effect on the main dataset of study AB10015: ΔALSFRS-R at week 48 (primary endpoint) & PFS (secondary endpoint)**
- **Long-term OS, ΔALSFRS-R and PFS showed the same pattern of greater treatment-effect when masitinib was initiated at an earlier stage of disease**

Increasing benefit

Consistent Pattern

Masitinib 4.5 mg/kg/d vs placebo (ΔFS<1.1)		Moderate / Severe / Very Severe ALS (M4.5=106; PBO=114)	Moderate / Severe ALS (M4.5=85; PBO=104)	Moderate ALS (M4.5=45; PBO=62)
ΔALSFRS-R *mLOCF* **(Primary analysis)**	**Delay in progression**	**-27%**	**-31%**	**-42%**
	Diff. of mean	**3.39**	**4.04**	**4.68**
	p-value	0.016	0.006	0.018
ΔALSFRS-R (sensitivity) *Multiple Imputation*	Diff. of mean	**3.44**	**3.52**	**3.94**
	p-value	0.020	0.027	0.068
ΔALSFRS-R (sensitivity) *Jump to Reference*	Diff. of mean	**2.80**	**3.01**	**3.33**
	p-value	0.039	0.040	0.088
Median PFS (Secondary analysis)	**Gain in Median PFS**	**+ 4 months**	**+ 9 months**	**+ 13 months**
	Median [95% CI]	20 [14,30] vs 16 [11,19]	25 [17,NE] vs 16 [11,19]	30 [22,NE] vs 17 [11,33]
	p-value	0.016	0.006	0.060
Median OS (Long term survival)	**Gain in Median OS**	**+ 6 months**	**+10 months**	**+ 25 months**
	Median OS [95% CI]	46 [33,69] vs 40 [30,48]	53 [36,NE] vs 43 [31,49]	69 [45,NE] vs 44 [33,62]
	Reduced risk	**23%**	**30%**	**44%**
	Hazard Ratio [95% CI]	0.77 [0.55,1.10]	0.70 [0.48,1.03]	0.56 [0.32,0.96]

Increasing benefit

ALS prior to any complete loss of function

- **New analyses based on *ALS population with >0 on each item of the ALSFRS-R***
  - **Unlike previous analyses, includes both 'Normal' (ΔFS <1.1) and 'Fast' (ΔFS ≥1.1) Progressors**
  - **Accounts for ~80% of the AB10015 population; balanced baseline characteristics**
  - **Exclusion of these pts is justified in the context of treating neurodegenerative disease and consistent with masitinib's neuroprotective mechanism**
- **Treatment-effect seen across multiple endpoints, including:**
  - **Significant CAFS (joint rank analysis of function and survival)** – 18.4% relative benefit in favor of masitinib (p=0.035).
    - Significant also for ΔALSFRS-R alone at W48 (p=0.027)
    - Median OS not reached at study cut-off
  - **Long-term (LT) median OS showed a trend of +8 months** (46.0 [30; 69] vs 38.0 [29; 49]) (p=0.068) in favor of masitinib (adjusting for placebo pts who switched to masitinib)
  - Statistically significant on **respiratory function** (ΔFVC) and **quality of life** (ΔALSAQ-40)

	Relative benefit (masitinib vs control)	p-value
CAFS	**18.4%**	**0.035**
ΔALSFRS-R	**25%**	**0.027**
Median OS*	Not reached	n/a
LT median OS**	**+8 months**	**0.068**
ΔFVC	**20.4%**	**0.022**
ΔALSAQ-40	**19.8%**	**0.025**

* Study cut-off: December 2016. **LT OS cut-off: June 2020; adjusted for pts switching to masitinib (censored at crossover)

Summary

Masitinib significantly prolonged OS relative to control, provided that patients have not suffered severe impairment of ALSFRS-related functionality at the time of treatment initiation

- **Masitinib is most effective in patients with 'Moderate ALS' and prior to any complete loss of function (defined as a score of zero on any item of the ALSFRS-R)**
- **Both of these enriched patient populations have demonstrated consistent treatment effects across measures of physical function, QoL and survival**
- **Findings are consistent with masitinib's neuroprotective mechanism of action [Harrison et al. Neurobiol Dis. 2020]**
- **Confirmatory phase 3 trial (AB19001; NCT03127267) is ongoing, *recruiting the same population that is expected to derive greatest benefit from masitinib***

We thank all patients, their families, and investigators of study AB10015