Current Clinical Trials in ALS

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1. Clinical trials in ALS: Past & Present
2. Upcoming trials
3. How to prepare

1. ALS Clinical Trials: Past & Present

- THE GOOD:
  - Motivated patients
  - Experienced site staff

biogen idec

EMPOWER

Dexpramipexole

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

Ceftriaxone

CYTOKINETICS

BENEFIT-ALS

Tirasemtiv

gsk GlaxoSmithKline

NOG112264

Ozanezumab

2. ALS Clinical Trials: Past & Present

- THE GOOD:
  - Motivated patients
  - Experienced site staff
- THE BAD:
  - Comparing McIntosh to Granny Smith Apples
  - Limited resources
  - Trial design

In BENEFIT-ALS, 711 patients with amyotrophic lateral sclerosis (ALS) were enrolled into the open-label phase; subsequently 605 patients were randomized 1:1 to double-blind treatment with either *tirasemtiv* or placebo for 12 weeks. As previously announced, BENEFIT-ALS did not achieve its primary efficacy endpoint, the mean change from baseline in the ALS Functional Rating Scale in its revised form (ALSFRS-R). Secondary endpoints evaluated measures of respiratory performance and other measures of skeletal muscle function and fatigability.

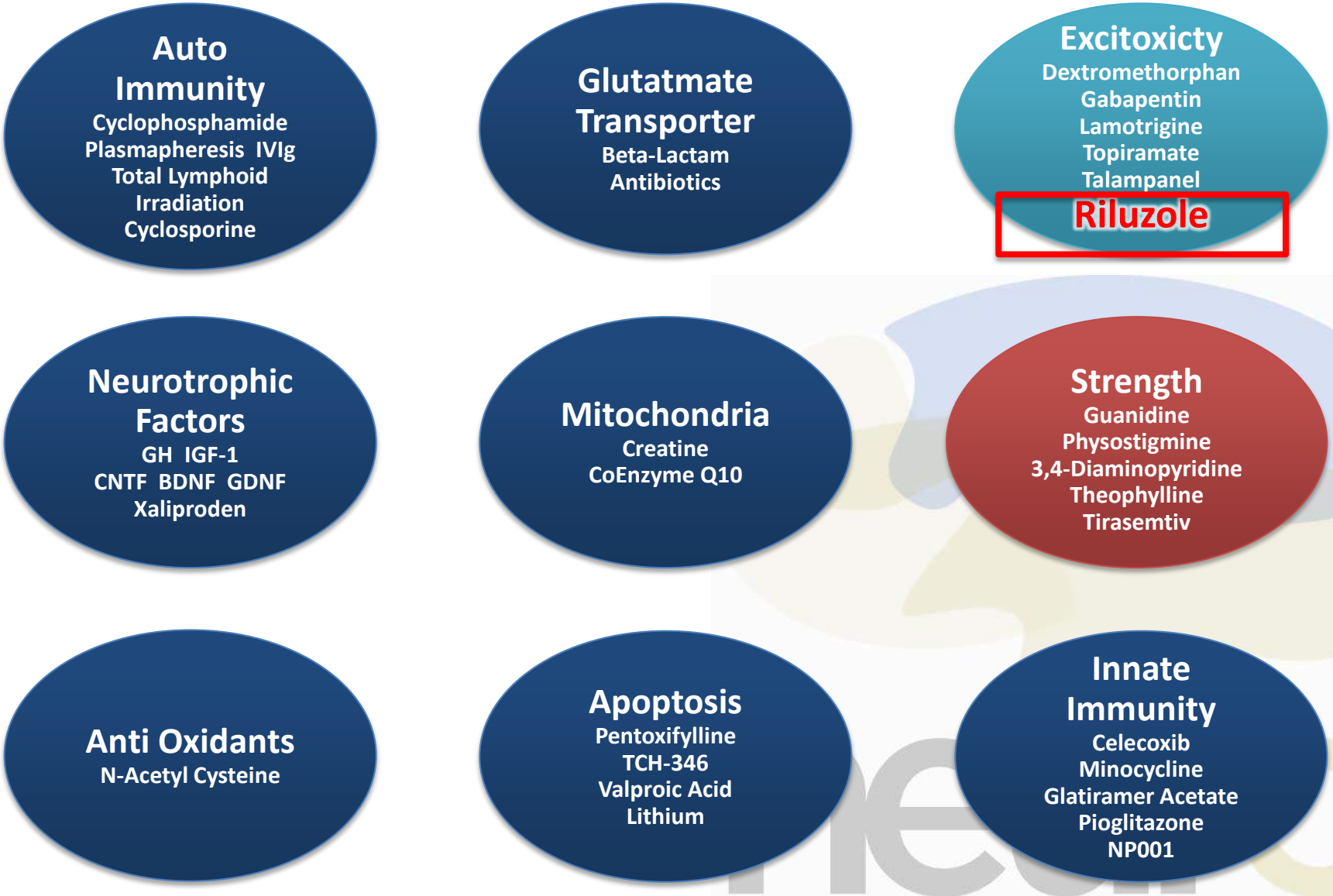
Treatment with *tirasemtiv* resulted in a statistically significant and potentially clinically meaningful reduction in the decline of Slow Vital Capacity (SVC, a measure of the strength of the skeletal muscles responsible for breathing) that has been shown to be an important predictor of disease progression and survival in prior trials of patients with ALS. This pre-specified secondary efficacy endpoint also declined less on *tirasemtiv* than on placebo at each assessment time point.

Slow Vital Capacity	Placebo (n = 210)	*Tirasemtiv* (n = 178)	All (N = 388)
Baseline (% Predicted, mean ± SD)	89.7 (17.2)	85.7 (19.3)	87.8 (18.3)
Time Point	Changes from Baseline (Least Square Mean ± Standard Error)		p-value
Week 4	-3.89 (0.62)	-0.99 (0.68)	0.001
Week 8	-5.81 (0.68)	-2.85 (0.77)	0.004
Week 12	-8.66 (0.80)	-3.12 (0.90)	<0.0001
	Slope of decline (Percentage Points per day)		
Week 0 to Week 12	-0.0905	-0.0394	0.0006

2. ALS Clinical Trials: Past & Present

- THE GOOD:
  - Motivated patients
  - Experienced site staff
- THE BAD:
  - Comparing McIntosh to Granny Smith Apples
  - Limited resources
  - Trial design
- THE UGLY:
  - Only 1 positive trial

ALS Clinical Trial Targets



Why is ALS so Difficult to Treat?

REVIEW ARTICLE

Why is ALS so Difficult to Treat?

John Turnbull

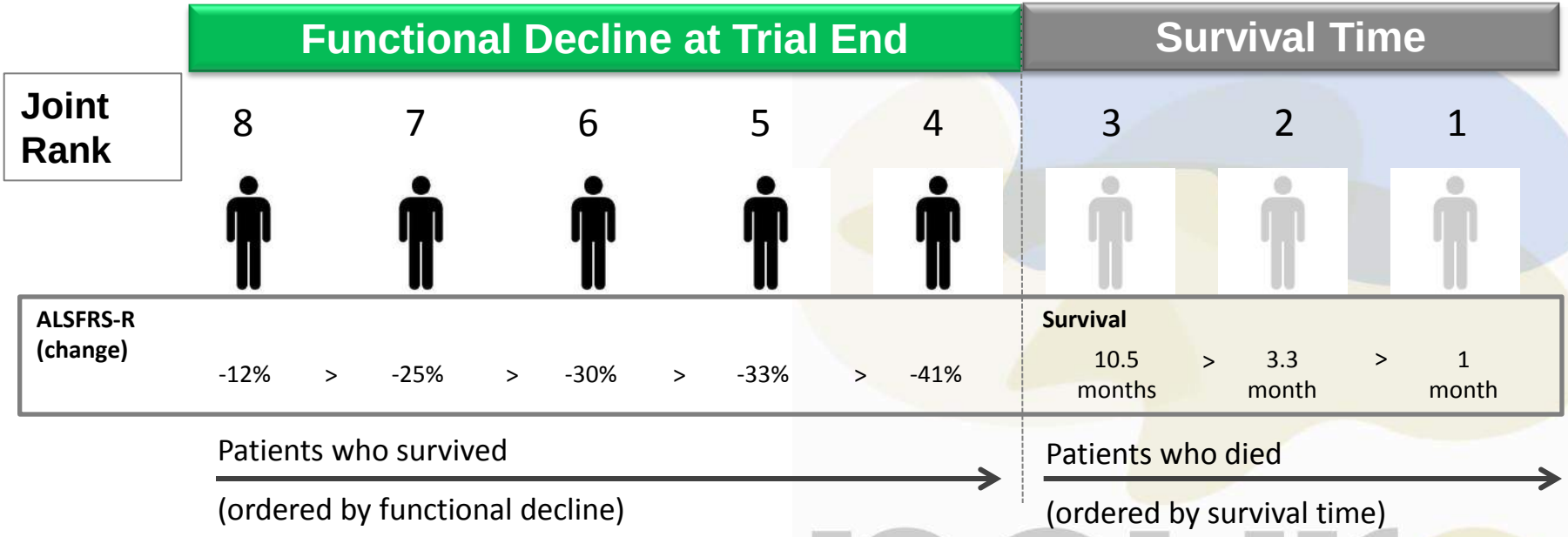
ABSTRACT: Amyotrophic lateral sclerosis (ALS) is proving intractable. Difficulties in pre-clinical studies contribute in small measure to this futility, but the chief reason for failure is an inadequate understanding of disease pathogenesis. Many acquired and inherited processes have been advanced as potential causes of ALS but, while they may predispose to disease, it seems increasingly likely that none leads directly to ALS. Rather, two recent overlapping considerations, both involving aberrant protein homeostasis, may provide a better explanation for a common disease phenotype and a common terminal pathogenesis. If so, therapeutic approaches will need to be altered and carefully nuanced, since protein homeostasis is essential and highly conserved. Nonetheless, these considerations provide new optimism in a difficult disease which has hitherto defied treatment.

Building Better Trials

- Lack of biomarkers
- Heterogeneous patient population
- Phase II Trial Paradox
  → Endpoints

Joint-rank Scoring: Theoretical Trial

- At the end of the trial, functional decline OR survival time is determined for each patient
- All patients are ranked on the same scale, from best to worst outcome, and given a rank number
- Unblinding occurs after the ranks have been assigned; means of rank in each group are compared



Cudkowicz ME, et al. *Nat Med*. 2011;17(12):1652–1656.

2. Upcoming Trials

- Biogen-ISIS SOD1+ & C9orf72+
- *Withania somnifera* (NIALS)
- Cytokinetics Phase 3 *tirasemtiv*
- Neuraltus Phase 3
- Stem cells
- GSK *ozanezumab* Phase 3?

Non-treatment projects

- Canadian Neuromuscular Disease Registry (www.cndr.org)
- CALS Neuroimaging consortium MRI study
- Brain Bank

Translational Research

Research Grants

Arthur J. Hudson Translational Team Grant

The 2014 vision of ALS Canada is “Within ten years, ALS will be a treatable disease.” To that end, ALS Canada's Strategic Plan for Research (2014-2017) established the goal to develop, through a national network, at least one novel therapeutic strategy to slow the progression of ALS. As a mechanism to achieve that goal, the Arthur J. Hudson Translational Team Grant has been established.

3. How to prepare?

- Montreal Neurological Institute as a key site
  - → Infrastructure of the CRU
  - → Research background
  - → Dr. Rouleau as director
- "Harvard model" clinical research program
  - → "register" trial patients at the Neuro
  - → Study visits occur at the Neuro, followed for care elsewhere

QUESTIONS??

Thank you!!

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