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Clinical Course of FUS-ALS: A Retrospective Analysis of Clinical and Genetic Modifiers

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INTRODUCTION

Fused-in-sarcoma amyotrophic lateral sclerosis (FUS-ALS) is a genetic subtype of ALS comprising approximately 1% of total cases with highly heterogeneous age of onset, phenotypic presentation, and rate of progression. NH00004 was designed to characterize the clinical course of FUS-ALS in a trial-relevant population to inform development of targeted therapies such as *ulefnersen* (ION363).

METHODS

The **NH00004 Study** was a predominantly retrospective, temporally relevant (onset on or after January 2000) chart review study including 147 subjects with FUS-ALS from 13 global sites. Consistent with *Study ION363-CS1 (FUSION)* genetic eligibility criteria, the primary analysis set (n=118) was defined as individuals with FUS variants classified as pathogenic, likely pathogenic, or variants of uncertain significance with pathogenic characteristics. The results focus on the primary analysis set. Longitudinal data were abstracted from symptom onset through death, ION363 exposure, or end of follow-up.

RESULTS

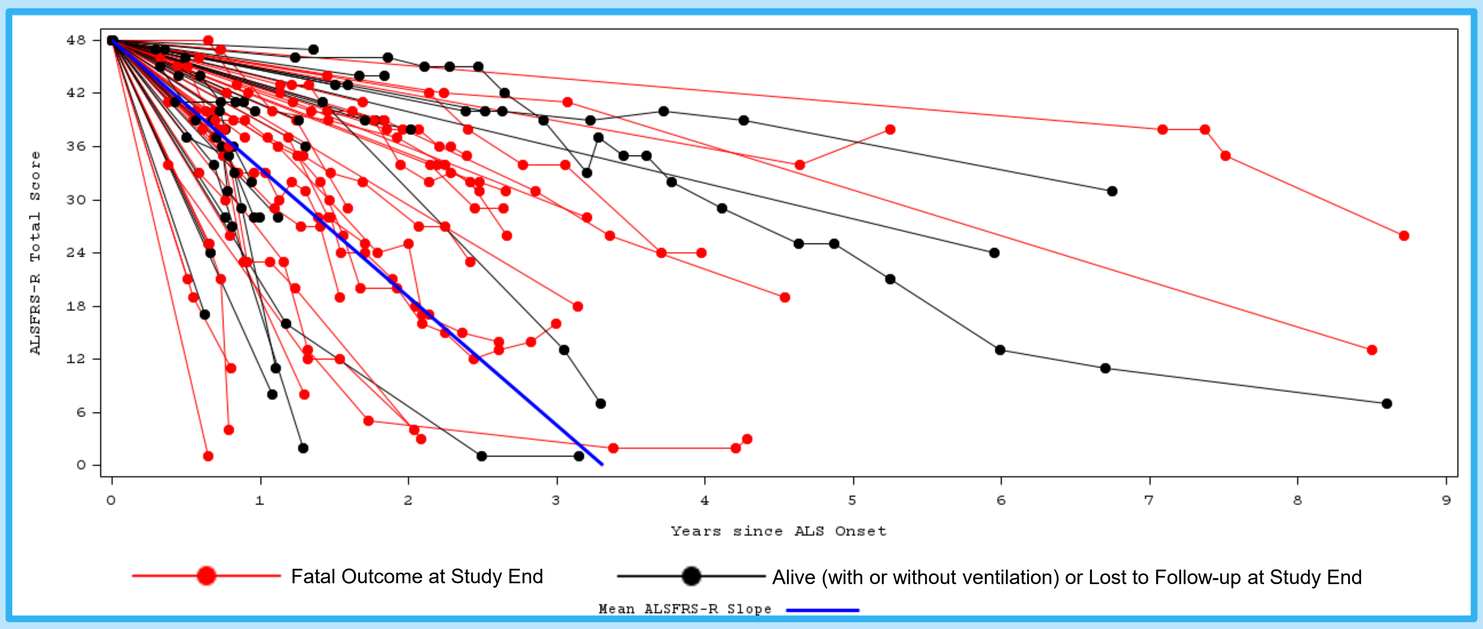
Demographics, ALS Diagnosis, and Disposition

	Primary Analysis Set (N=118) mean ± SD [min, **median**, max)
Age at ALS Symptom Onset (years)	38.0 ± 15.31 (12, **38**, 74)
Age at ALS Diagnosis (years)	38.8 ± 15.63 (12, **38**, 74)
Vital Status at End of Observation, (n,%)	
Alive without Permanent Ventilation	12 (10.2)
Permanent Ventilation[a]	13 (11.0)
Dead	83 (70.3)
Lost to Follow-up	10 (8.5)
Invasive Ventilation after ALS onset (n,%)	
Yes	25 (21.2)
No	88 (74.6)
Missing	5 (4.2)

[a] Permanent ventilation is defined as > 22 hours/day of mechanical ventilation (invasive or noninvasive) for > 21 consecutive days; SD = standard deviation

ALS Functional Rating Scale – Revised (ALSFRS-R)

ALSFRS-R linear slope: n = 77 with ≥1 measurement; mean (SD) was -1.2 (1.16) points/month



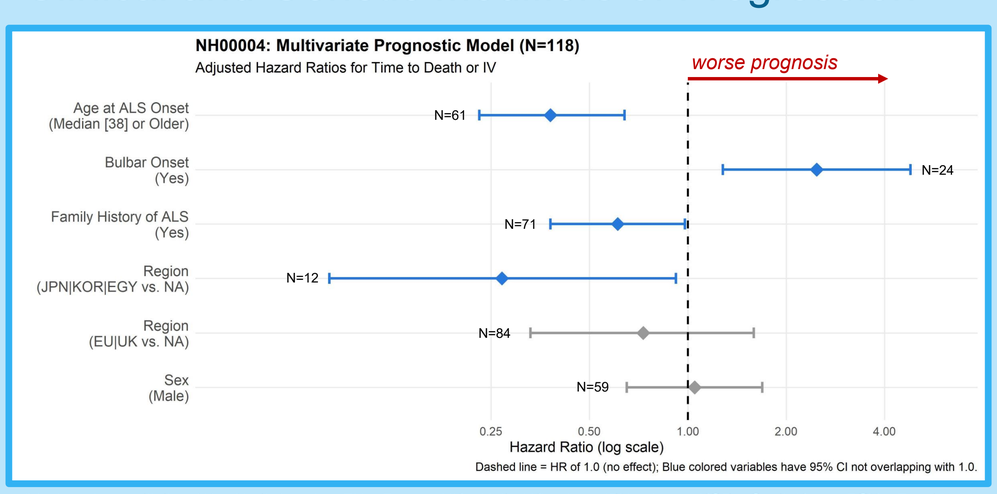
Every subject was assumed to have an ALSFRS-R total score of 48 at ALS symptom onset.

Time-to-Event Analysis

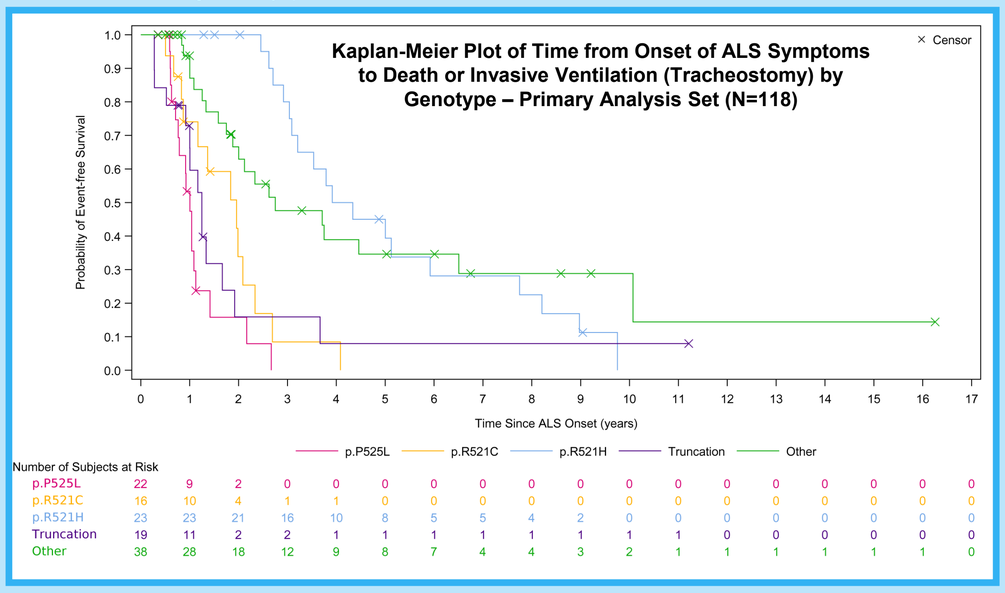
	N	Median Time (months) from Onset to Diagnosis	Median Time (years) from Onset to Death	Median Time (years) from Onset to Death/IV	Observation Time–Adjusted Event Rate (events per 100 subject-years) NIV	IV	PEG	NIV, IV, or PEG
All subjects	118	8.4	2.69	2.12	11.4	6.0	9.1	26.5
Age at onset								
< 25 years	27	5.5	1.42	1.04	15.1	16.8	20.2	52.2
≥ 25 years	91	9.0	3.04	2.69	10.6	3.8	6.8	21.2
< Median (38 years)	57	7.0	1.67	1.09	16.0	15.2	19.2	50.5
≥ Median (38 years)	61	10.0	3.54	3.54	8.8	0.9	3.5	13.2
Family history of ALS								
No or Don't Know	47	8.0	1.96	1.17	13.0	10.9	17.4	41.3
Yes	71	8.7	3.04	2.70	10.3	2.8	3.7	16.9
FUS variant								
Pathogenic / likely pathogenic	106	8.3	2.62	–	–	–	–	–
Variants of uncertain (unknown) significance	12	10.8	10.07	–	–	–	–	–
p.P525L	22	6.2	1.09	1.00	18.6	13.9	18.6	51.0
p.R521C	16	8.2	1.96	1.96	22.9	7.6	11.4	41.9
p.R521H	23	13.3	4.13	4.13	7.6	0.0	0	7.6
Site of ALS onset								
Bulbar	24	5.4	1.42	1.04	16.7	21.4	35.7	73.9
Axial	29	8.0	2.62	1.26	7.3	8.4	10.5	26.2
Limb	90	8.8	2.70	2.62	12.0	4.7	6.7	23.3
Sex								
Male	59	8.4	2.46	1.92	13.8	6.6	8.2	28.5
Female	59	8.4	2.92	2.62	8.4	5.2	10.3	23.8
Riluzole reported	53	9.9	2.62	2.17	12.7	5.4	9.7	27.8

Subjects could have more than one site of ALS onset reported. IV = invasive ventilation, NIV = non-invasive ventilation, PEG = percutaneous endoscopic gastrostomy

Clinical and Genetic Modifiers of Progression



IV = invasive ventilation, NA = North America, EU = Europe, UK = United Kingdom, JPN = Japan, KOR = South Korea, EGY = Egypt, Age at ALS onset refers to age of first symptom of ALS.



Potential Genotype-Phenotype Relationships

p.P525L mutation was associated with earlier age at onset (mean 20.1 vs. 42.1 years), bulbar site of onset (41% vs. 16%), shorter time to death/IV (median 1.00 vs. 2.69 years), and higher observation time-adjusted event rates for non-invasive ventilation, IV and PEG (51 vs. 23 events per 100 subject-years) compared to other mutations.

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CONCLUSIONS

1. Earlier age at onset, bulbar onset, and no family history of ALS (i.e., likely *de novo* mutations) are important and inter-related prognostic factors associated with shorter time from ALS onset to death or IV in patients with FUS-ALS.
2. The NH00004 study provides a well-curated dataset aligned with interventional eligibility criteria to serve as an untreated reference group when evaluating potential therapeutics for this ALS subpopulation with high unmet need.