Longer Overall Survival in the CENTAUR Trial:

A Rank Preserving Structural Failure Time Model Adjusts for Crossover from Placebo to PB/TURSO

Applying Lessons from Oncology

Sabrina Paganoni, MD, PhD

Disclosures

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CENTAUR Study Group

MGH 1811

Sabrina Paganoni, MD, PhD
Merit E. Cudkowicz, MD
Eric A. Macklin, PhD
James D. Berry, MD
Suma Babu, MBBS, MPH
Marianne Chase, BA
Derek D'agostino, BA
Michelle McGovern, BS
Joseph Ostrow, BS
Lindsay Pothier, BA
Alexander V. Sherman, MSc
Eric Tustison, BA
Prasha Vigneswaran, MS
Jason Walker, BS
Hong Yu, MS
James Chan, MA
Maria E. St. Pierre, MA
Matthew Eydinov, MS
Rudolph E. Tanzi, PhD
David Schoenfeld, PhD

BARROW Neurological Institute

Shafeeq Ladha, MD
Meghan Hall, MS
Gale Kittle, RN, MPH
Rebecca Randall, MS, RD
Jeremy M. Shefner, MD, PhD

Pentara

Suzanne Hendrix, PhD
Samuel P. Dickson, PhD
Newman Knowlton, MS
Noel Ellison, MS
Kent Hendrix, BS

Statistics•Collaborative

Janet Wittes, PhD
Zi-Fan Yu, ScD

AMYLYX

Joshua Cohen, BSE
Justin Klee, ScB
Kent Leslie, MS
Patrick D. Yeramian, MD, MBA

SWEDISH — Michael Elliott, MD

Hennepin Health — Samuel Maiser, MD

OHSU — Chafic Karam, MD

Wake Forest School of Medicine — James B. Caress, MD

UMASS MEDICAL SCHOOL — Margaret Ayo Owegi, DO

The Ohio State University Wexner Medical Center — Adam Quick, MD

Johns Hopkins Medicine — Jeffrey D. Rothstein, MD, PhD

University of Kentucky College of Medicine — Edward J. Kasarskis, MD, PhD

Sutter Health CPMC — Jon Katz, MD

Liberty Jenkins, MD

Washington University in St. Louis School of Medicine — Timothy M. Miller, MD, PhD

Mount Sinai Beth Israel — Stephen N. Scelsa, MD

USF Health Morsani College of Medicine — Tuan H. Vu, MD

UFHealth University of Florida Health — James Wymer, MD, PhD

University of Michigan Medical School — Stephen A. Goutman, MD

Texas Neurology — Daragh Heitzman, MD

School of Medicine Temple University — Terry Heiman-Patterson, MD

UT Health San Antonio — Carlayne E. Jackson, MD

Penn Medicine — Colin Quinn, MD

Emory University School of Medicine — Christina N. Fournier, MD

Jonathan D. Glass, MD

Ochsner Health System — Kristin Johnson, DO

University of Iowa Hospitals & Clinics — Andrea Swenson, MD

UC Irvine Health — Namita A. Goyal, MD

Neurology Associates, P.C. — Gary L. Pattee, MD

Harvard University — Walter Gilbert, PhD

Patricia L. Andres, MS, DPT

The CENTAUR Trial Was Done in Partnership With the ALS Community

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

NEUROLOGICAL CLINICAL RESEARCH INSTITUTE

BARROW Neurological Institute

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

ALS ASSOCIATION

alsFINDINGaCURE

AMYLYX

177 participants screened
137 participants in CENTAUR

Context for Today's Presentation

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Amylyx Pharmaceuticals Announces Plan to Submit New Drug Application (NDA) for AMX0035 for the Treatment of ALS in the Coming Months

September 15, 2021 08:00 AM Eastern Daylight Time

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Amylyx Pharmaceuticals, Inc. today announced its intention to submit a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for AMX0035 (sodium phenylbutyrate (PB) and taurursodiol (TURSO)) for the treatment of amyotrophic lateral sclerosis (ALS). The decision by the company to submit the application in the coming months follows recent discussions with the FDA, including a pre-NDA meeting held on July 15, 2021.

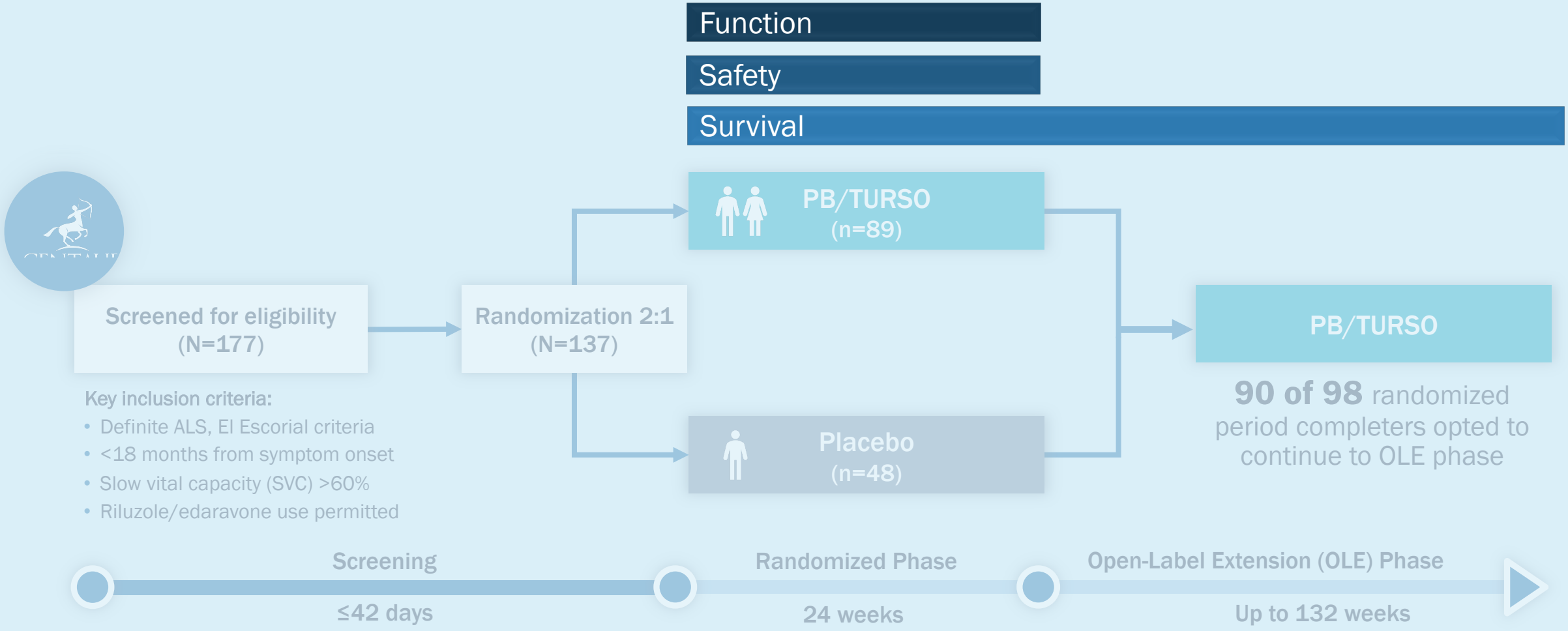
"We are thrilled to move toward the U.S. submission of an NDA for AMX0035 and look forward to continuing to work with the FDA"

Tweet this

"We are thrilled to move toward the U.S. submission of an NDA for AMX0035 and look forward to continuing to work with the FDA," said Joshua Cohen, Co-CEO, Chairman and Co-Founder of Amylyx. "For those living with ALS, time is the most important resource, and we remain focused on advancing AMX0035 through the clinical development process as efficiently as possible," added Justin Klee, Co-CEO, Director and Co-Founder of Amylyx. "We're endlessly grateful for all of the support and efforts of ALS Finding a Cure, the ALS Association, I AM ALS, the Healey & AMG Center at Mass General and the Northeast ALS Consortium, and all CENTAUR trial participants for their critical involvement as we approach this milestone."

- Submission will be supported with safety, function, and long-term survival data from the CENTAUR trial
  - Encompasses a 6-month randomized placebo-controlled phase and an open-label long-term follow-up phase
- **Today's Focus:** How lessons from oncology informed patient-centric study design and analysis methods in the CENTAUR trial (and how they can be applied to future ALS trials)

CENTAUR Study Design[1,2]



1. Paganoni S, et al. *N Engl J Med.* 2020;383:919-930. **2.** Paganoni S, et al. *Muscle Nerve*. 2021;63:31-39.doi:10.1002/mus.27091.

CENTAUR Results Summary[1]

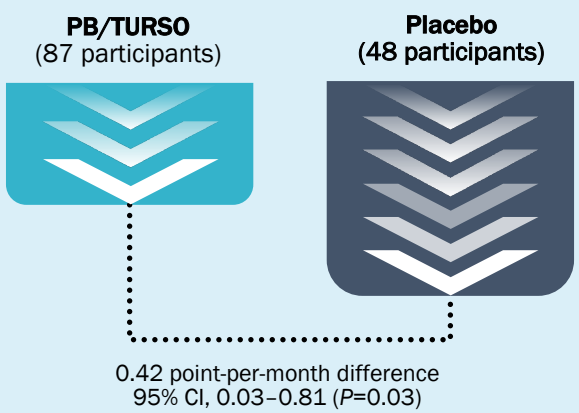
FUNCTION[1]

ALSFRS-R

Difference of

2.32 points

at the end of the 6-month study



SAFETY[1]

While there were similar rates of adverse events and discontinuations recorded in the PB/TURSO and placebo groups during the 24-week randomized phase, GI events occurred with greater frequency (≥2%) in the AMX0035 group

GI events included diarrhea, nausea, salivary hypersecretion, and abdominal discomfort

77% of participants were on riluzole or edaravone at or prior to study entry[1]

1. Paganoni S, et al. *N Engl J Med.* 2020;383:919-930.

Challenge 1

Collecting robust survival data in a 6-month randomized phase

Lesson 1: Participant Locating Service

Collecting robust survival data in a 6-month randomized phase

Oncology Lesson:
Utilize a participant locating service to collect long-term survival data on all participants

Lesson 1: Participant Locating Service

A search of public records by participant locating service OmniTrace successfully confirmed vital status for all but **2** (135/137) participants as of July 2020[a]

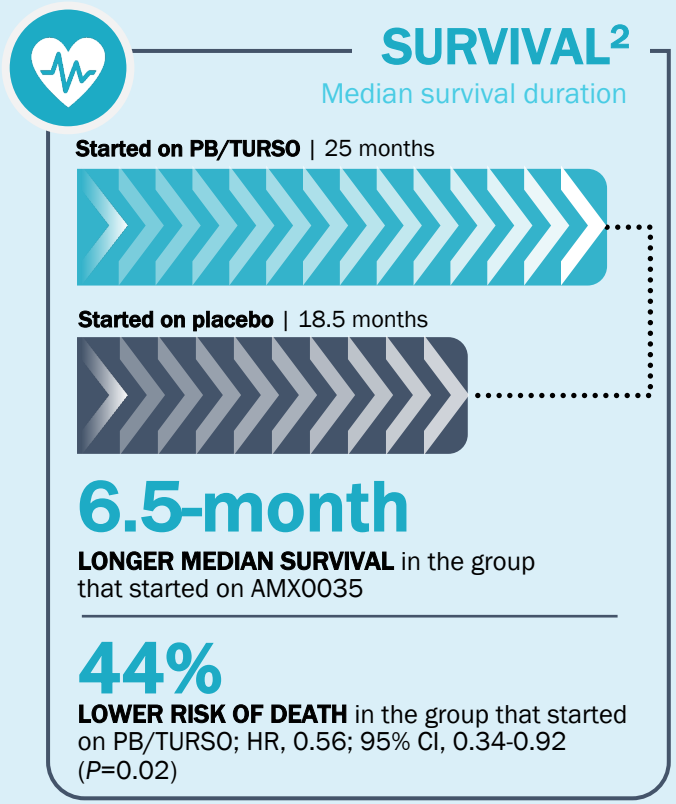
How it works[2]

- Searching publicly available records and databases
- Appropriate protocol language / patient consent required
- In the United States, search turnaround time can be as little as 24-48 hours

[a] The 2 participants that could not be confirmed as of July 2020 were censored at the date of last contact with their clinical site

1. Paganoni S, et al. *Muscle Nerve*. 2020. https://doi.org/10.1002/mus.27091 2. https://www.omnitrace.com/ltfu-patient-search/

CENTAUR Results Summary[1]



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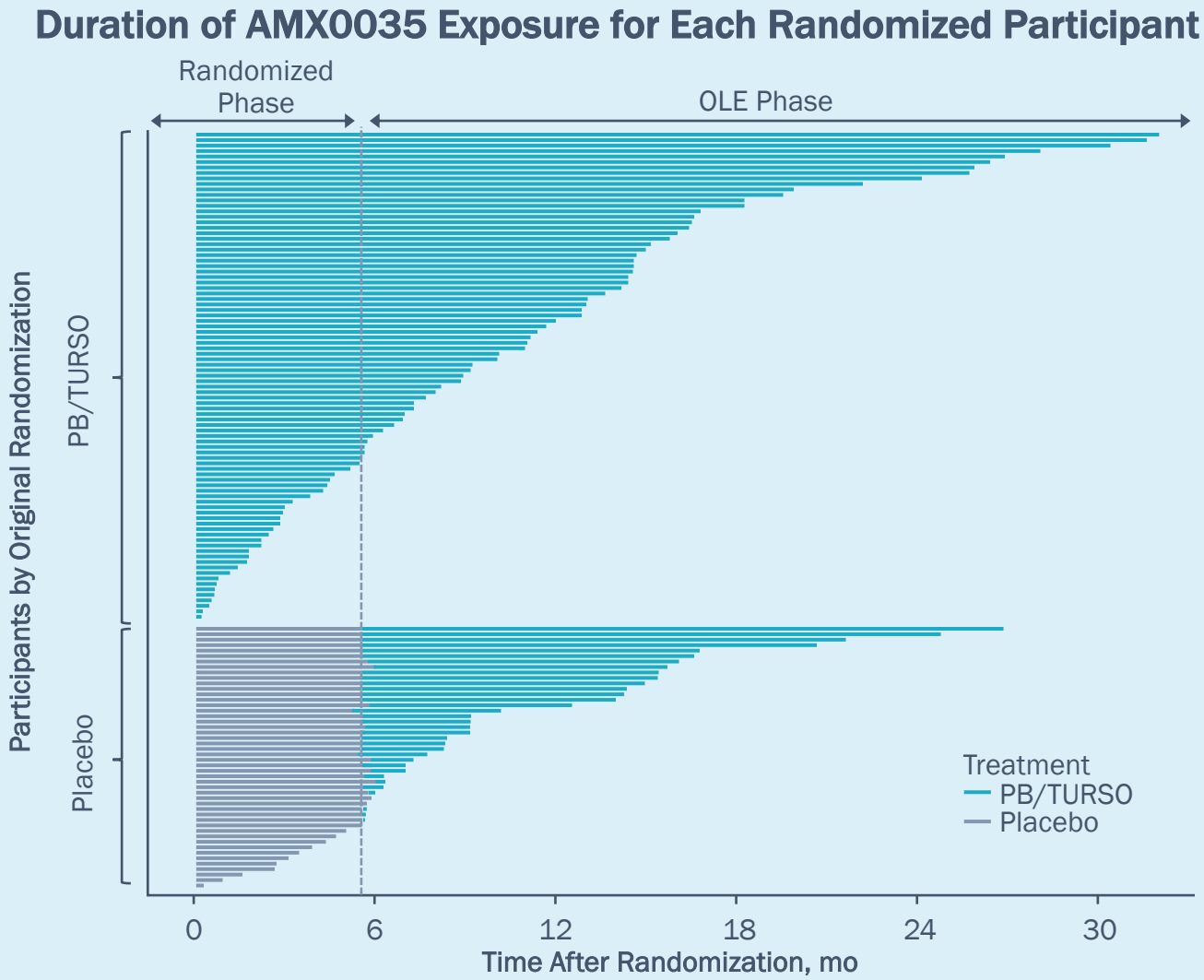
1. Paganoni S, et al. *Muscle Nerve*. 2021;63:31-39.doi:10.1002/mus.27091.

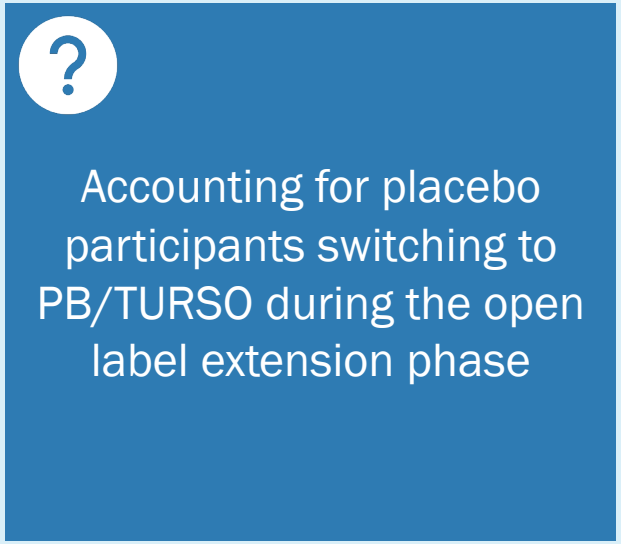
The Majority of Participants Starting on Placebo in CENTAUR Received PB/TURSO During the OLE Phase

- In CENTAUR, the pre-specified overall survival analysis was not designed to evaluate if participants that started on placebo and switched to PB/TURSO in the OLE phase received any survival benefit[1]
  - 71% (34/48) of participants starting on placebo switched to PB/TURSO during the OLE phase

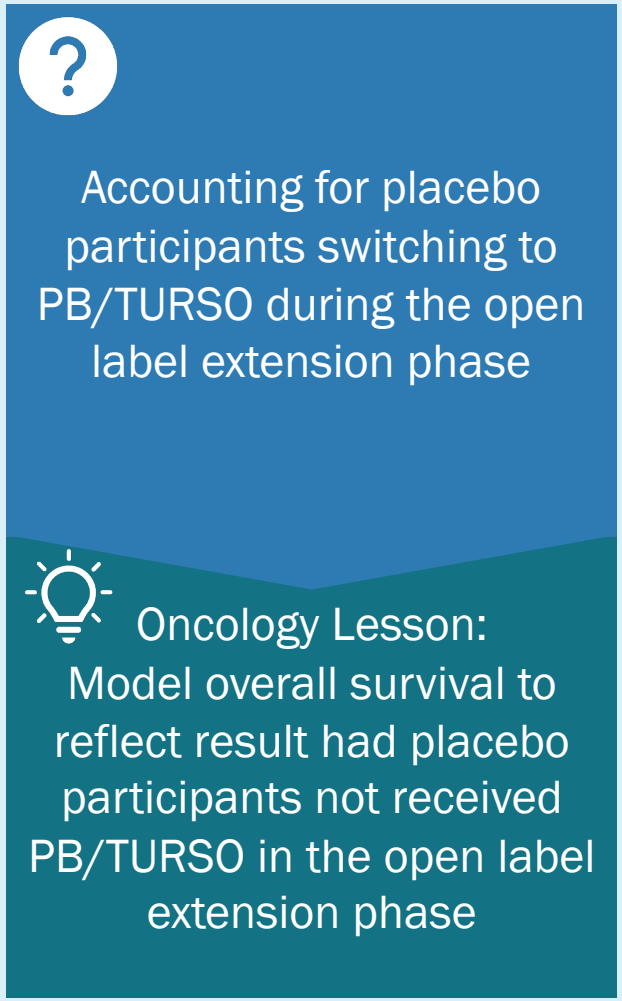


Paganoni S, et al. Muscle Nerve. 2020. https://doi.org/10.1002/mus.27091

Challenge 2



Lesson 2: Analysis Methods



Lesson #2: Adjusting Survival Analysis

- In oncology trials, participants in the placebo arm are frequently provided the option to receive experimental therapy either after disease progression or at study end[1]
- Treatment effect on overall survival may be **underestimated[1]**
  - Can impact both clinical decision-making and health economic assessments
- Statistical models are available to account for this crossover and to model the overall survival result in the absence of the placebo group switching over to receive active treatment[1]
  - Models are accepted by reimbursement agencies

Rank Preserving Structural Failure Time Model (RPSFTM) allows a direct comparison of randomization groups by adjusting the overall survival of participants who cross over so that it reflects the overall survival had they not received the investigational therapy[1]

ORIGINAL ARTICLE

Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study

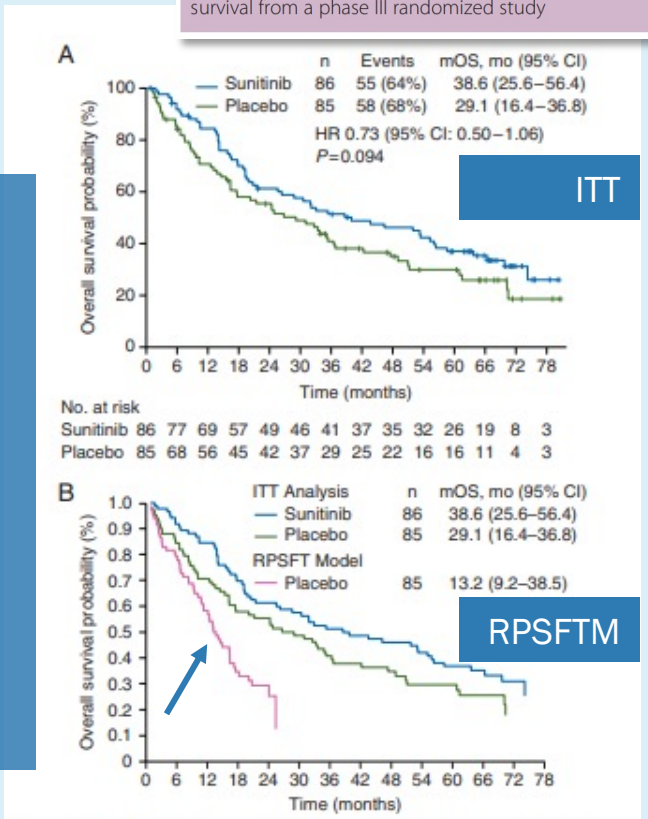


Figure 2 Kaplan–Meier estimates of overall survival in the intent-to-treat (ITT) population (A) without adjustment for crossover and (B) both with and without adjustment for crossover in the placebo arm. CI, confidence interval; HR, hazard ratio; mOS, median overall survival; RPSFT, rank-preserving structural failure time.

1 Jönsson L, et al. Analyzing overall survival in randomized controlled trials with crossover and implications for economic evaluation. Value Health. 2014 Sep;17(6):707-13. **2.** Faivre S, et al. Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study. Ann Oncol. 2017 Feb 1;28(2):339-343.

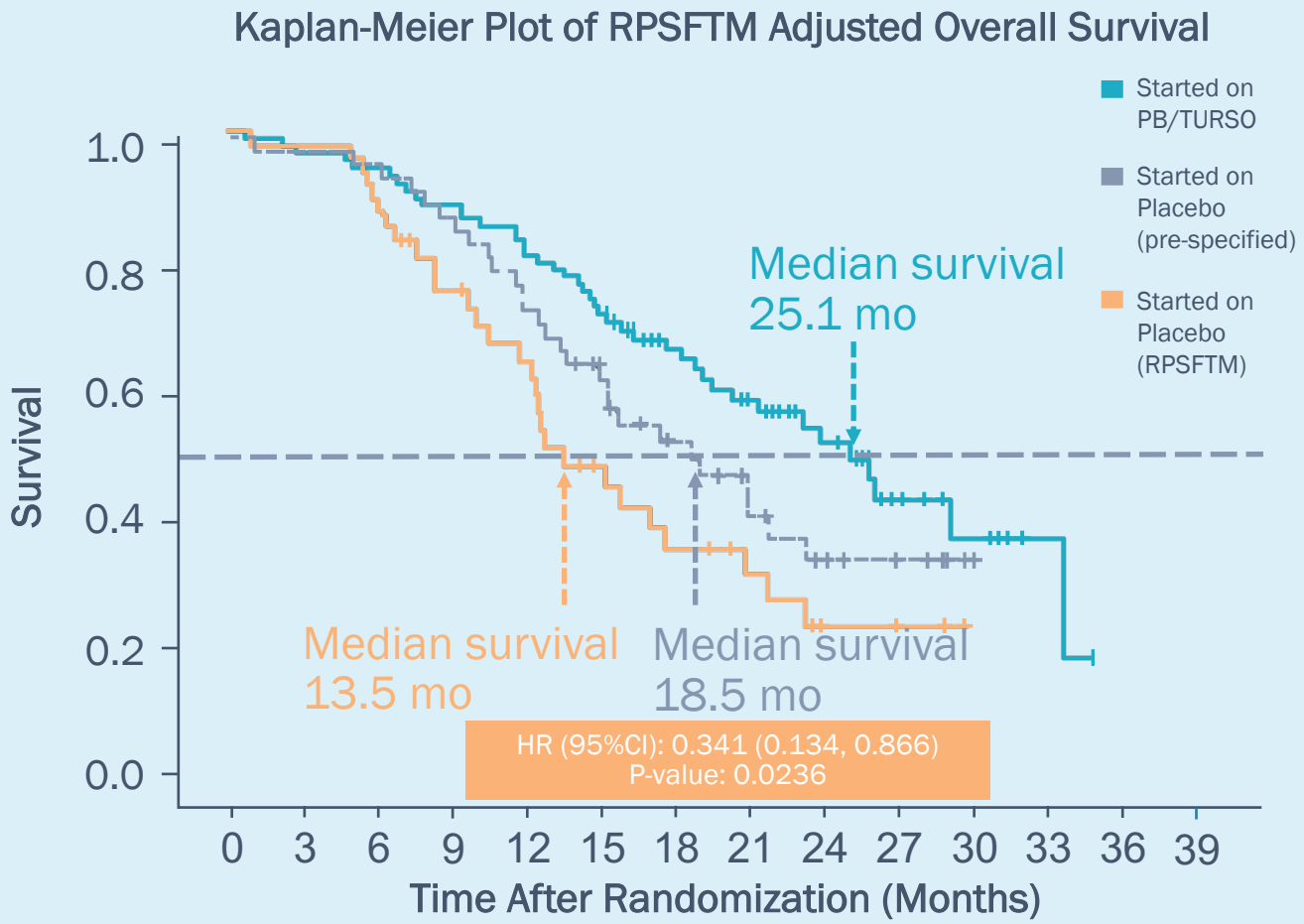
Methods

- Exploratory analysis used a RPSFTM on the randomized population (N=137)
  - Adjusted the overall survival of participants who started on placebo and then switched to PB/TURSO in the OLE phase to reflect their overall survival in the absence of receiving PB/TURSO

- Kaplan Meier curves were produced for the **observed survival** in the started on PB/TURSO arm and the **adjusted survival** in the started on placebo arm
  - Hazard ratios (HRs) were estimated using a Cox proportional hazards model with covariates of prebaseline ALSFRS-R slope, baseline ALSFRS-R, and age

Data on File. Amylyx Pharmaceuticals.

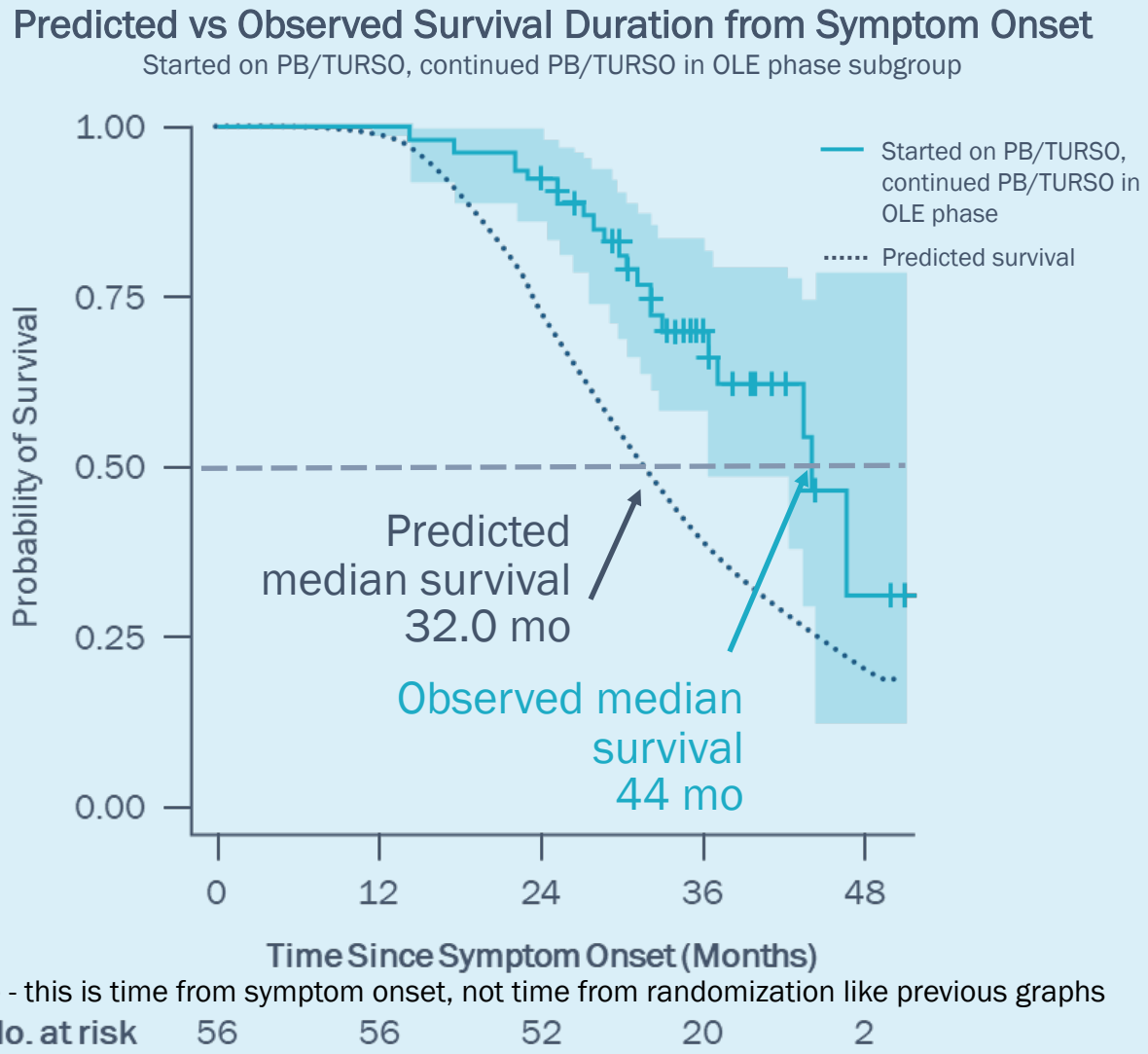
RPSFTM Analysis:
Increased Survival Benefit for Group Starting on PB/TURSO



- Model shows an up to **11.6 month** longer median survival in the group starting on PB/TURSO
  - Compared to a 6.5 month difference in pre-specified analysis

Data on File. Amylyx Pharmaceuticals.

Predictive Model Analysis: Increased (and consistent) Survival Benefit for Group Starting on PB/TURSO



- ENCALS survival prediction model
  - Exploratory analysis applied model to CENTAUR population
  - Comparison of **predicted** survival to **observed** survival

- In the subgroup of participants originally randomized to PB/TURSO who continued into the OLE phase (n=56), median observed survival duration exceeded predicted survival duration by **12 months**

Data on File. Amylyx Pharmaceuticals.

Take Home Points

- Robust survival data can be collected while implementing patient-centric trial design
  - Short (6-month) randomized phase + open label extension phase

- Incorporate novel methods
  - Participant locating service
  - RPSFTM and prediction modeling

Thank you!

177 participants screened
137 participants in CENTAUR

Swedish
OHSU
Hennepin Healthcare
University of Michigan Medical School
UMass Medical School
Healey Center
Mount Sinai Beth Israel
Penn Medicine
School of Medicine Temple University
University of Iowa Hospitals & Clinics
Sutter Health CPMC
Neurology Associates, P.C.
The Ohio State University Wexner Medical Center
Johns Hopkins Medicine
Washington University in St. Louis School of Medicine
University of Kentucky College of Medicine
UC Irvine Health
Wake Forest School of Medicine
Barrow Neurological Institute
Emory University School of Medicine
Texas Neurology
UT Health San Antonio
Ochsner Health System
UFHealth University of Florida Health
USF Health Morsani College of Medicine

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

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ALS Association

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NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

Overall Survival Analysis
- Suzanne Hendrix, PhD
- Janet Wittes, PhD

Pentara

wcg Statistics•Collaborative

RPSFTM analysis: Claire Watkins, MSc

MAPLE HEALTH GROUP

ENCALS analysis: Ruben van Eijk, MD, PhD

TRICALS The highway towards a cure

ENCALS Survival Prediction Model

NCRI Neurological Clinical Research Institute

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