ISCTM 2014 presentation
20 Years of Clinical Trials in AD: Some Lessons Learned

Pierre N. Tariot, MD

Director, Banner Alzheimer's Institute

Co-Director, Alzheimer's Prevention Initiative

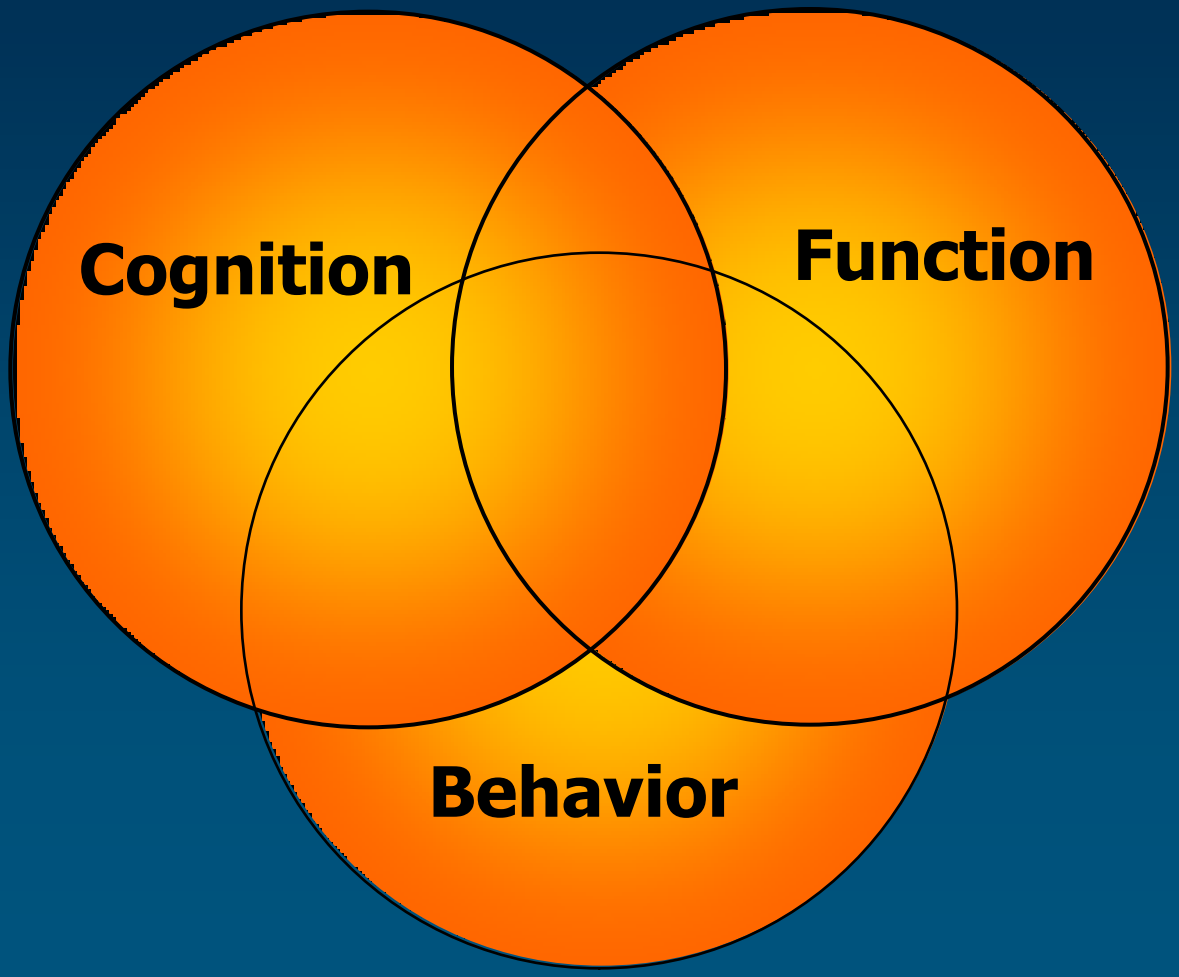
Research Professor of Psychiatry
University of Arizona

Pierre N. Tariot, MD
Disclosures pertinent for the last 2 years

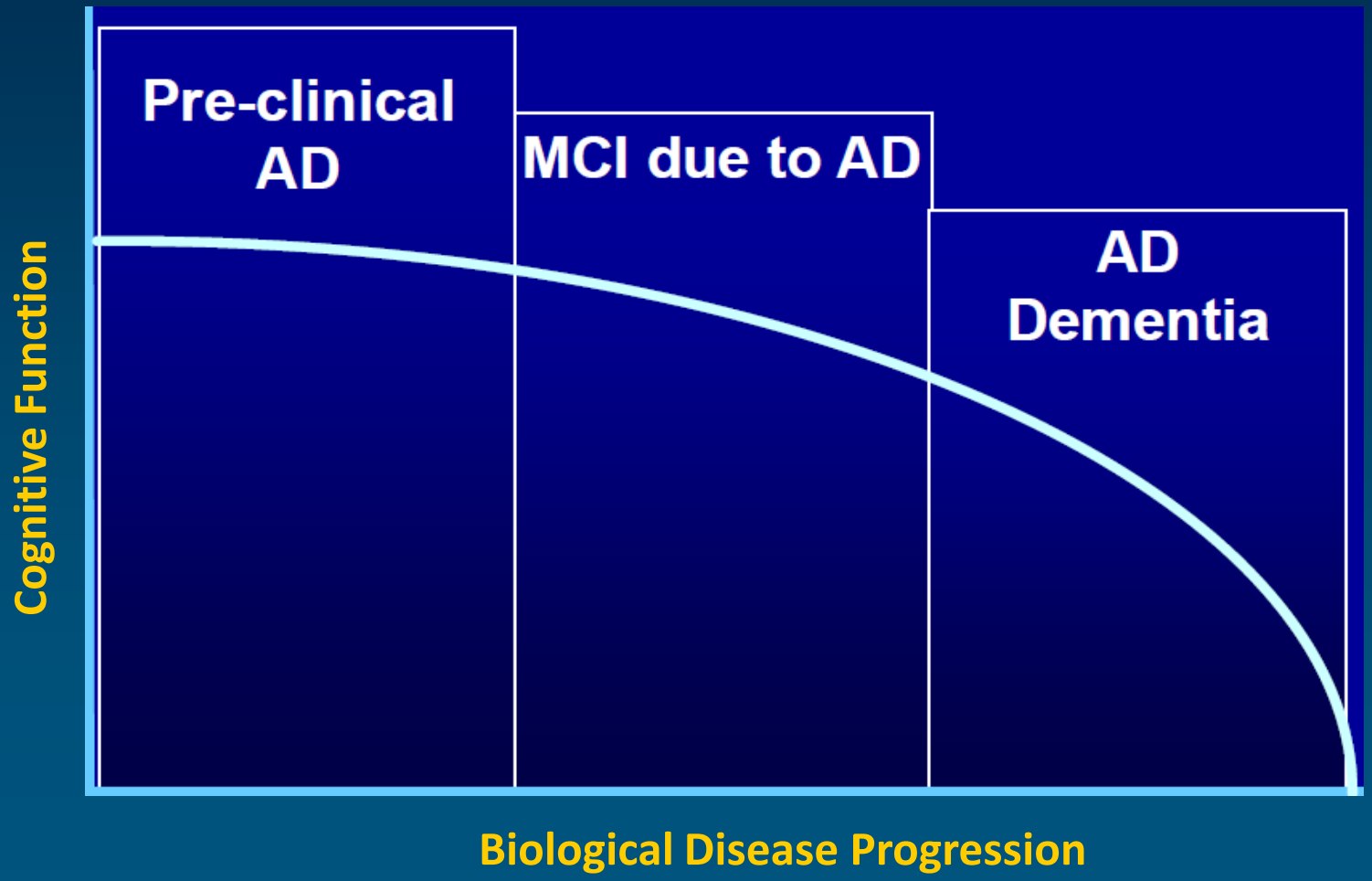
- **Consulting fees:** Abbott Laboratories, AbbVie, AC Immune, Adamas, Boehringer-Ingelheim, California Pacific Medical Center, Chase Pharmaceuticals, Chiesi, CME Inc., Elan, Medavante, Merz, Otsuka, Sanofi-Aventis.
- **Consulting fees and research support:** AstraZeneca, Avanir, Avid, Bristol Myers Squibb, Cognoptix, GlaxoSmithKline, Janssen, Eli Lilly, Medivation, Merck and Company, Roche.
- **Research support only:** Functional Neuromodulation (f(nm)), GE, Genentech, Pfizer, Targacept, Toyama.
- **Other research support:** NIA, Arizona Department of Health Services.
- **Investments:** Stock options in Adamas.
- **Patents:** listed as a contributor to a patent owned by the University of Rochester, “Biomarkers of Alzheimer’s Disease.”
- **Speakers’ bureaus:** NA.

Clinical Presentation of Dementia

Outcomes of Relevance in Trials May Vary by Dementia Type



Eventually the Field Reconceptualized AD disease as a Continuum; Criteria Are Evolving



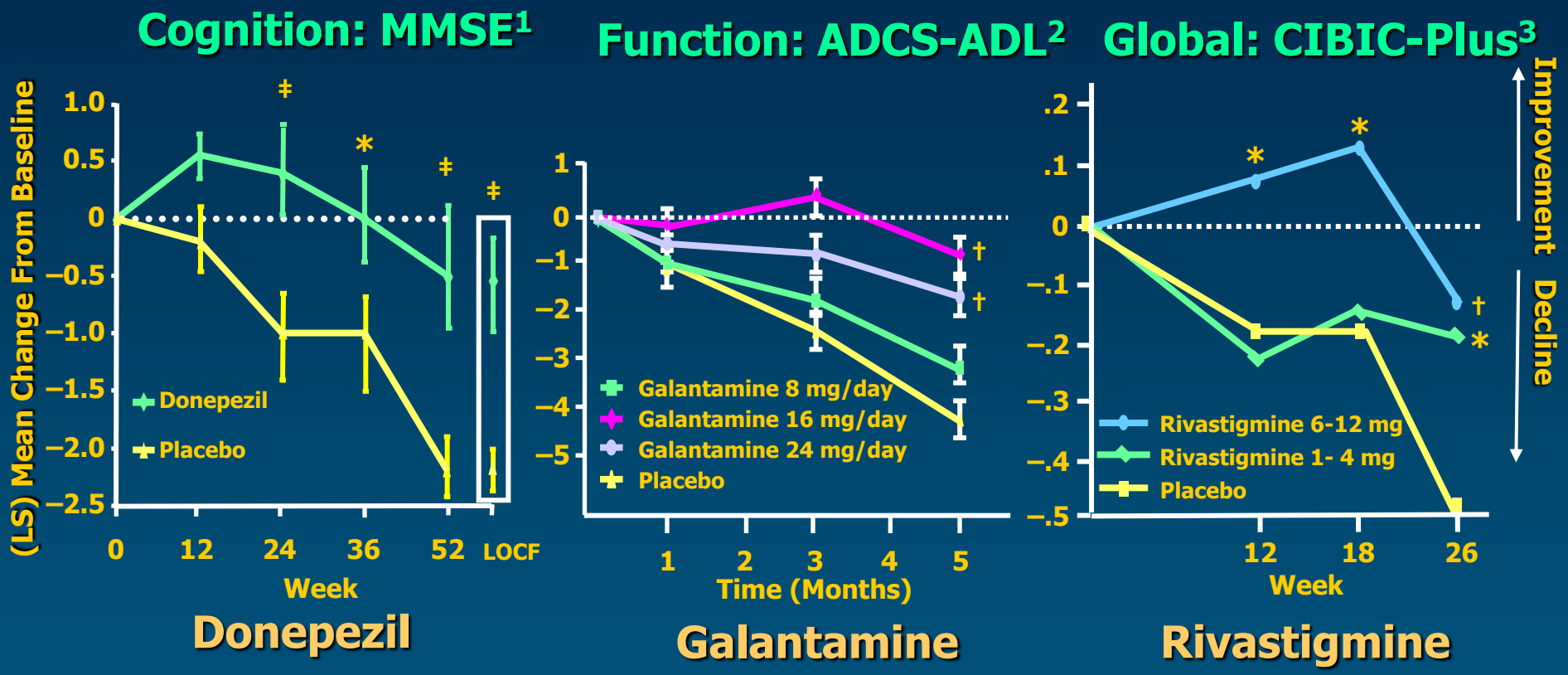
Initial Registration Trial Designs: "Symptomatic"

- Neurotransmitters as targets
- Assess effects over 3-6 months
- Rely on change scores for efficacy
- 2 co-primary outcomes
    - Cognition (FDA, EMA) (e.g., ADAScog)
    - Function (EMA)
    - Global status (FDA)
- Superiority over active comparator not required
- Gradual increased in use of stratification variables
    - Severity of dementia
    - *APOE e4* status
- The approach worked: 4 cholinesterase inhibitors and memantine approved
    - Beware of the canard: "these are not important"

Initial Registration Trial Designs

- Used diagnostic criteria from 1984; not updated until 2011
- Impact of inclusion of at least 20-30% subjects with non-AD dementia
- Mostly mild-moderate severity of dementia
    - Viewed as the salient clinical population, early success of tacrine
- Most cognitive measures also from 1980's
    - Incremental changes in measures (role of ADCS)
    - Relatively effort to optimize quality
- Why did we wait?
        - Conservatism? ("It is a safe path forward")
        - Sled dog phenomenon?
        - Could we have found better measures and methods, sooner?
- Mainly ignored background therapy
- Registration trials tend not to inform practice
    - Not their goal
    - Examples: what drug is most effective; how long to treat; what about other doses, combinations; long term safety

Examples of Efficaciy results with ChEI Monotherapy in Mild to Moderate AD

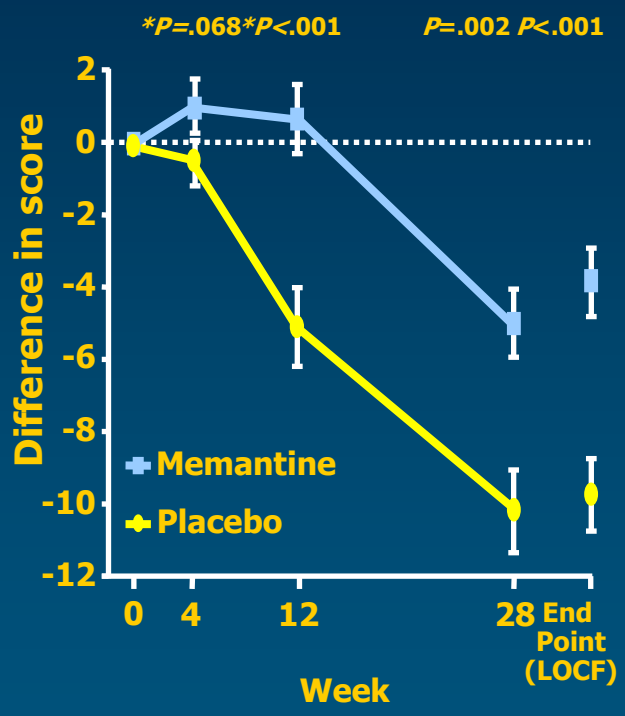


*$P<.05$; †$P<.01$; ‡$P\leq.001$.
CIBIC-Plus = Clinician's Interview-Based Impression of Change with caregiver input; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living inventory.

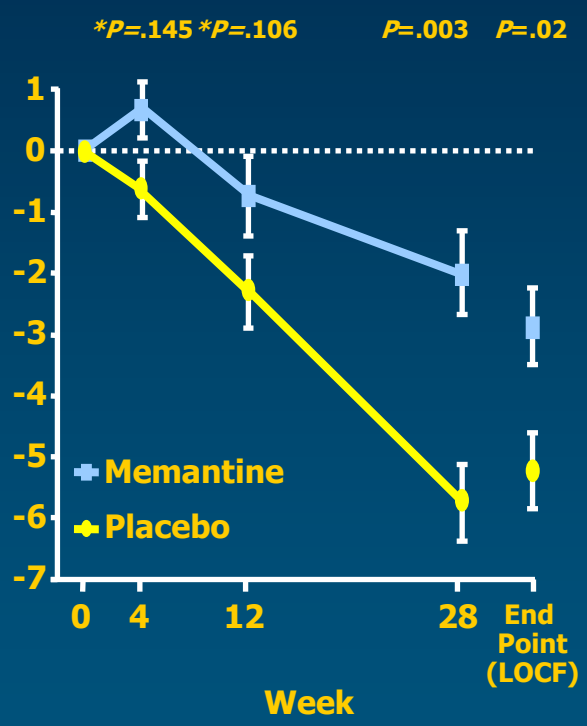
Sources: 1. Winblad B, et al. *Neurology*. 2001;57:489-495. (Data represent change in least squares [LS] mean)
2. Tariot PN, et al. *Neurology*. 2000;54:2269-2276.
3. Corey-Bloom J, et al. *Int J Geriatr Psychopharmacol*. 1998;1550:55-65.

Memantine Monotherapy in Moderate to Severe AD: Efficacy

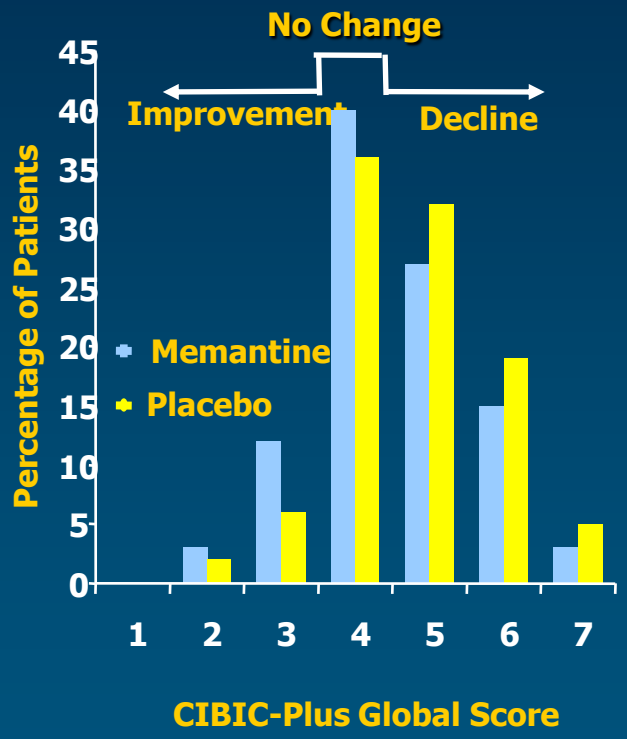
Cognition: SIB



Function: ADCS-ADL$_{19}$



Global: CIBIC-Plus



SIB = Severe Impairment Battery.

Source: Reisberg B,et al. *N Engl J Med*. 2003;348:1333-1341.

Evolving Registration Trial Designs

- General failure in “anti-dementia” trials to grapple with behavioral outcomes
- Gradually explored more severe and milder AD dementia
- Other dementias: VaD, DLB, PD; some FTD
  - But few “mixed” dementia studies
- Typically longer duration
- New regulatory and design questions
  - How long to treat?
  - How to measure change?
- Began to address other pathobiological targets
- Eventual MCI studies
  - A recognized condition?

Treating Behavioral Changes in Dementia: A Vexing Public Health Issue

- Cardinal features of dementia
  - Impact of specific dementia diagnosis
  - Major cause of morbidity, medical involvement
  - Driver of cost
  - Exaggerate functional/cognitive deficits
- Most trials show limited/no benefit
  - Disconnect between data showing limited/no efficacy and clinical practice
- No treatment is FDA approved
  - Disconnect between clinical indication and regulatory approval
- Overall, an example of inherent limitations of “evidence based medicine”
  - Blending different outcomes/goals/purposes

Finding Targets: A Proposed Temporal Progression Of AD

Genetic Factors
APP mutations
Presenilin 1,2 mutations
APOE4 alleles
Family history
APOE2 alleles protects
APP/BACE mutation protects

Environmental Factors
Head Injury
Toxins

Age

Endogenous Factors
Diet
Cardiovascular risk factors
Diabetes
Smoking
Education
Menopause
Physical/Mental Activity

Protective Factors
Estrogen?
Anti-inflammatory Drugs?

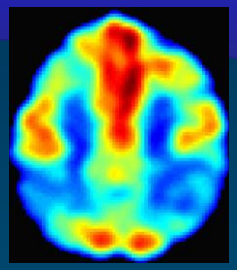
Net effect = stress and vulnerability to stress

Molecular Phenotype	*Neuropathology*	*Clinical Phenotype*
INITIAL STRESSORS Proximal Apoptosis APP dysregulation Impaired neurotrophic function Oxidative stress Excitotoxicity	Normal	Normal
FAILED STRESS RESPONSE Cell cycle dysregulation Kinase/phosphatase dysfunction Protein misfolding Altered DNA repair Vascular/membrane dysfunction	Normal	Normal
CELL INJURY Inflammation Cytoskeletal dysfunction Synaptic dysfunction Mitochondrial damage	Tangles, Plaques	Mild Cognitive Impairment
CELL DEATH Distal apoptosis Neurotransmitter failure	Tangles, Plaques Neurodegeneration	Dementia

The figure depicts apparently continuous processes, though they are likely to be asynchronous . Yaari and Tariot 2008

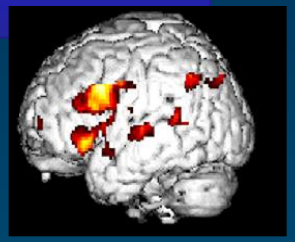
Using Information From Multiple Sources to Improve Diagnosis and Assess Treatment

Neuronal Activity
FDG PET



Fluid
Biomarkers

Cognitive Reserve
fMRI



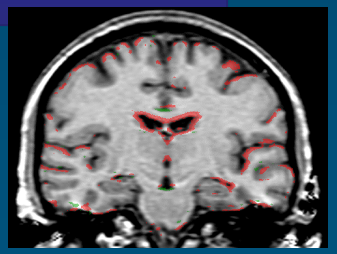
Diagnosis
Treatment

Plaque Load
Amyloid PET

Genetic Risk
Profile

Cognitive, Functional
Profile

Brain Atrophy
Structural MRI



How Might Promising Advances in AD Treatment Address Unmet Needs?

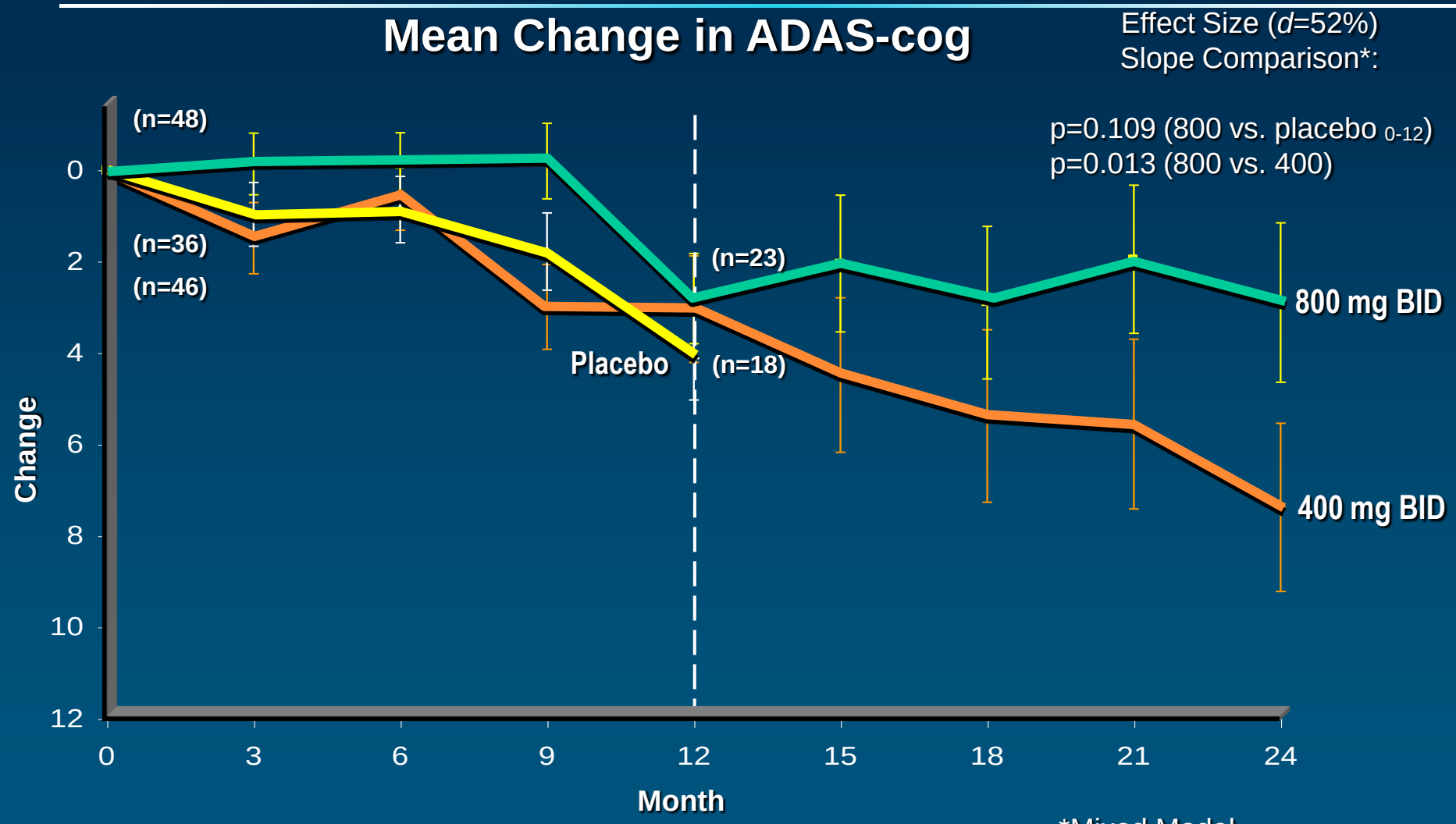
- **Symptomatic**
  - Improved efficacy
    - Cognition
    - Function
    - Behavior
    - Being pursued in several trials now
  - Enduring response
  - Fewer side effects
  - Simple to administer
  - Reduced number of treatment unresponsive patients
- **"Disease modification"**
  - Increase neuroprotection against pathology, e.g.:
    - Impact Aβ dysregulation
    - Impact processes leading to neurofibrillary tangles
  - Reverse existing neuronal damage?
  - Address other aspects of pathobiology
- **Slow, delay or even prevent disability**

Modified from Husain MM, et al. *Neuropsychiatr Dis Treat*. 2008;4(4):765–777.

Trial Designs for Emerging Therapies Aimed at Slowing Progression

- Phase 2 data become more important, but what to use as go signal?
  - Is there a translatable pharmacodynamic signal?
  - Are there interpretable effects on disease related or "downstream" biomarkers in humans?
  - Is there any clinical signal?
    - Or must we go to phase 3 to get answers?
  - Are dosing, safety and tolerability clarified?
- Phase 3 designs use clinical outcomes:
  - Assess treatment over extended time period, e.g., 12-36 months
  - Compare change scores? slope of performance over time?
  - Prior FDA design suggestion: staggered start or stop
  - Survival approaches?
- Biomarkers embedded in phase 2/3 to explore response to treatment, relationship with clinical outcomes, possible predictive utility
  - In some cases, used as outcomes

Phase 2 Clinical Results as Basis for Phase 3: Tarenflurbil (gamma secretase modulator) Cognition in Mildly Impaired AD Subjects

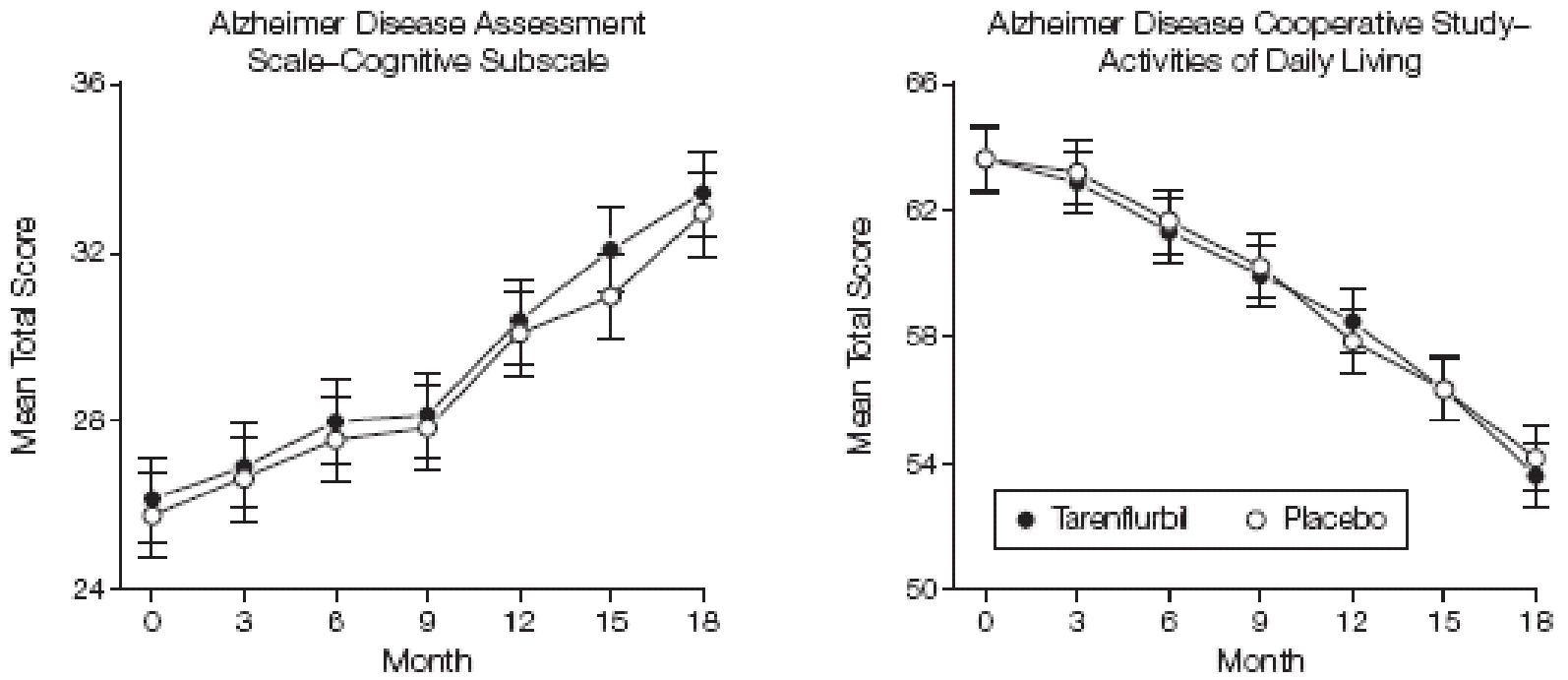


*Mixed Model

Wilcock et al. *Proceedings of ICAD*; 2006. (#O4-03-08).

Negative Tarenflurbil Phase 3 Results

Figure 2. Alzheimer Disease Assessment Cognitive Subscale and Alzheimer Disease Cooperative Studies–Activities of Daily Living Scale Scores by Visit



No.													
Tarenflurbil	837	772	778	779	779	780	789	803	756	770	774	774	774	783
Placebo	806	741	746	746	746	746	749	777	725	747	749	750	750	752

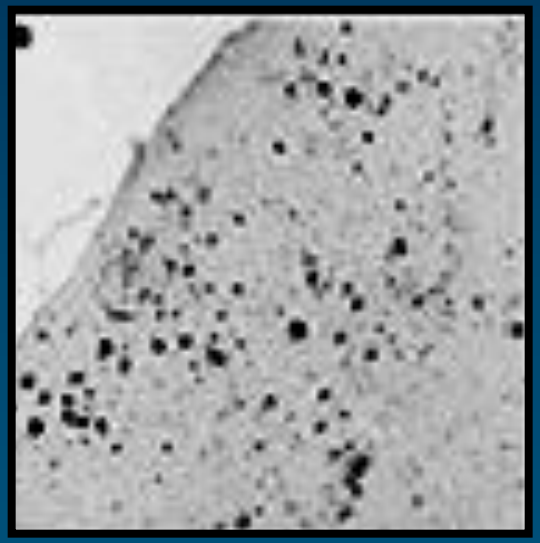
Values represent means using imputed last observation carried forward. Error bars represent 95% CIs.

Source: Green et al JAMA 2009

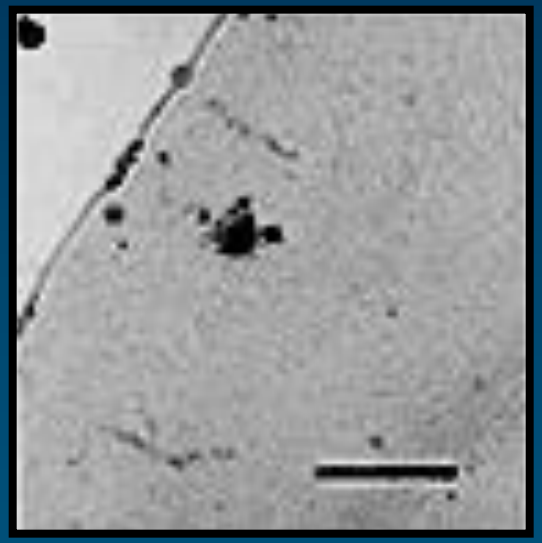
Anti-amyloid Immunotherapy AN 1792: Amyloid "Vaccine" Reduces Plaque Burden and Memory Loss in Transgenic Mouse Model of AD

Amyloid Stain (Mouse Brain)

Unvaccinated



Vaccinated



Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse

Dale Schenk, Robin Barbour, Whitney Dunn, Grace Gordon, Henry Grajeda, Teresa Guido, Kang Hu, Jiping Huang, Kelly Johnson-Wood, Karen Khan, Dora Kholodenko, Mike Lee, Zhenmei Liao, Ivan Lieberburg, Ruth Motter, Linda Mutter, Ferdie Soriano, George Shopp, Nicki Vasquez, Christopher Vandevert, Shannan Walker, Mark Wogulis, Ted Yednock, Dora Games & Peter Seubert

Elan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, California 94080, USA

NATURE | VOL 400 | 8 JULY 1999

Morgan et al. *Nature.* 2000;408:982-985.

AN 1792 Vaccination in Humans: Reversal of AD Neuropathology, But New Toxicity, No Clinical Benefit

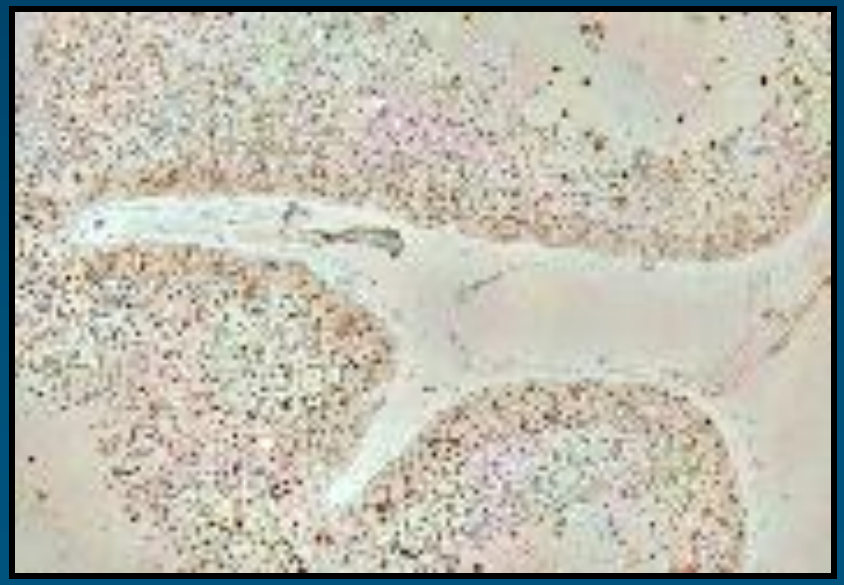
ARTICLES

Neuropathology of human Alzheimer disease after immunization with amyloid-β peptide: a case report

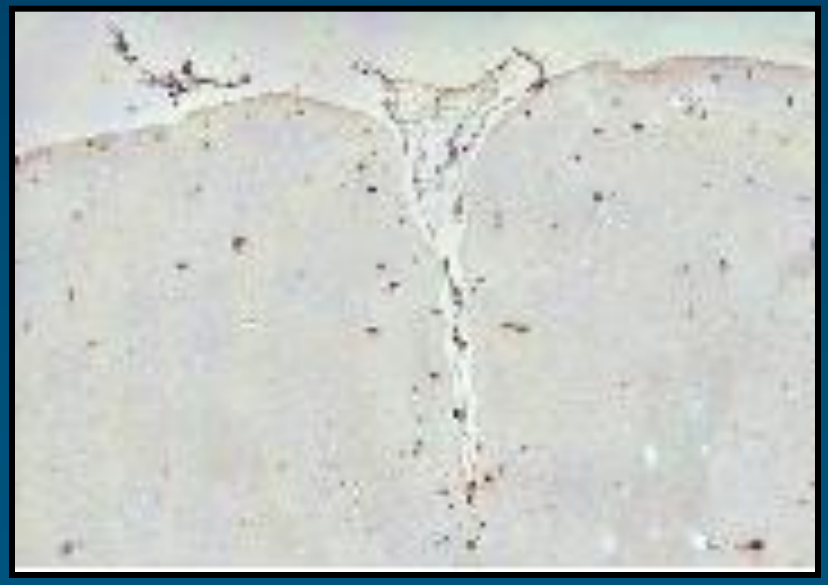
James A.R. Nicoll[1,2], David Wilkinson[1,3], Clive Holmes[1,3], Phil Steart[2], Hannah Markham[1,2] & Roy O. Weller[1,2]

NATURE MEDICINE • VOLUME 9 • NUMBER 4 • APRIL 2003

Parietal neocortex, non-immunized patient at comparable stage of AD



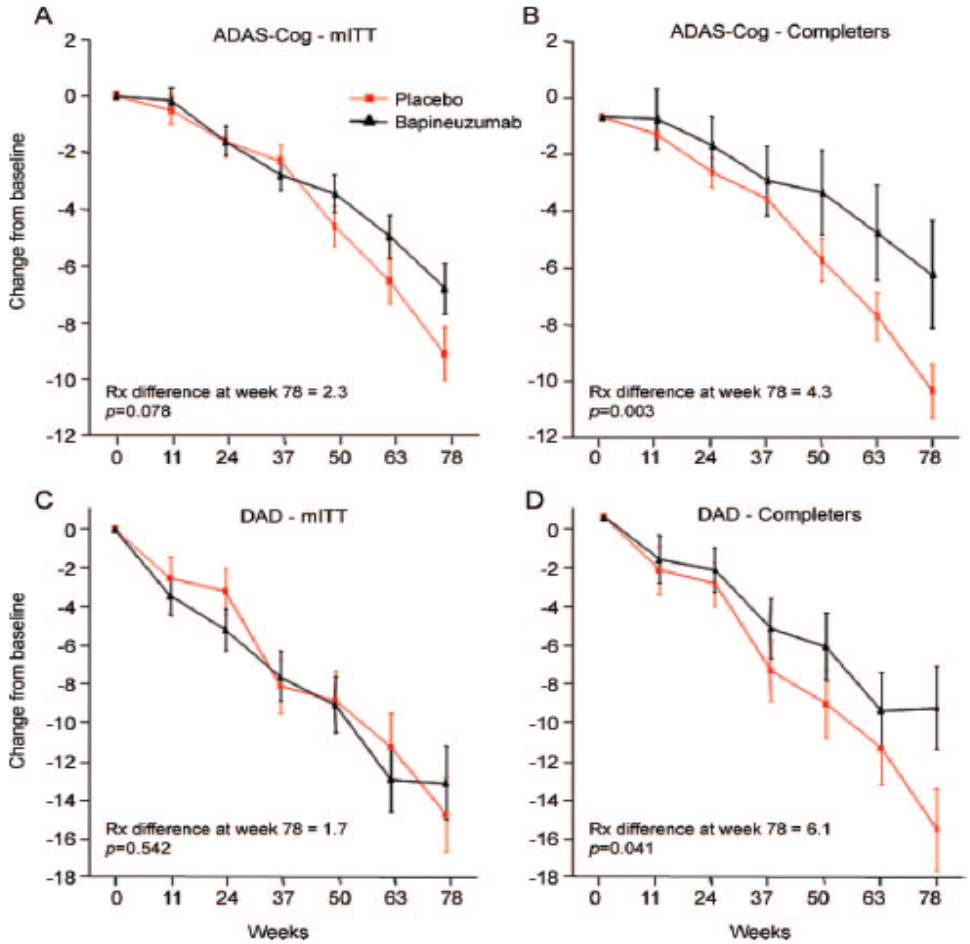
Parietal neocortex, immunized AD patient in Elan AN-1792 Trial



Nicoll et al. *Nat Med*. 2003;9:448-452.

Bapineuzumab Phase 2 Clinical Outcomes as Partial Basis for Phase 3 (Salloway et al 2009)

Figure 2 Estimated mean change from baseline over time on Alzheimer's Disease Assessment Scale- Cognitive subscale (ADAS-Cog) and Disability Assessment for Dementia (DAD) for the 4 combined dose cohorts in the modified intent-to-treat (mITT) and completer populations



Bapineuzumab Phase 2 PIB-PET Data
(Rinne et al 2010)

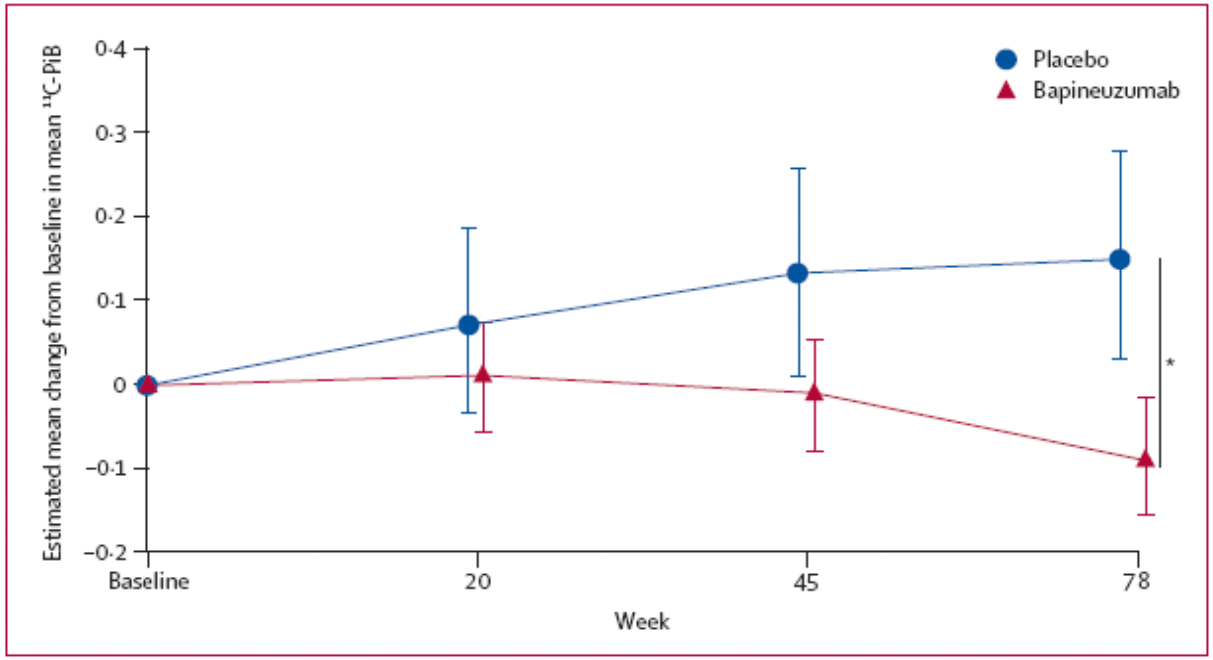


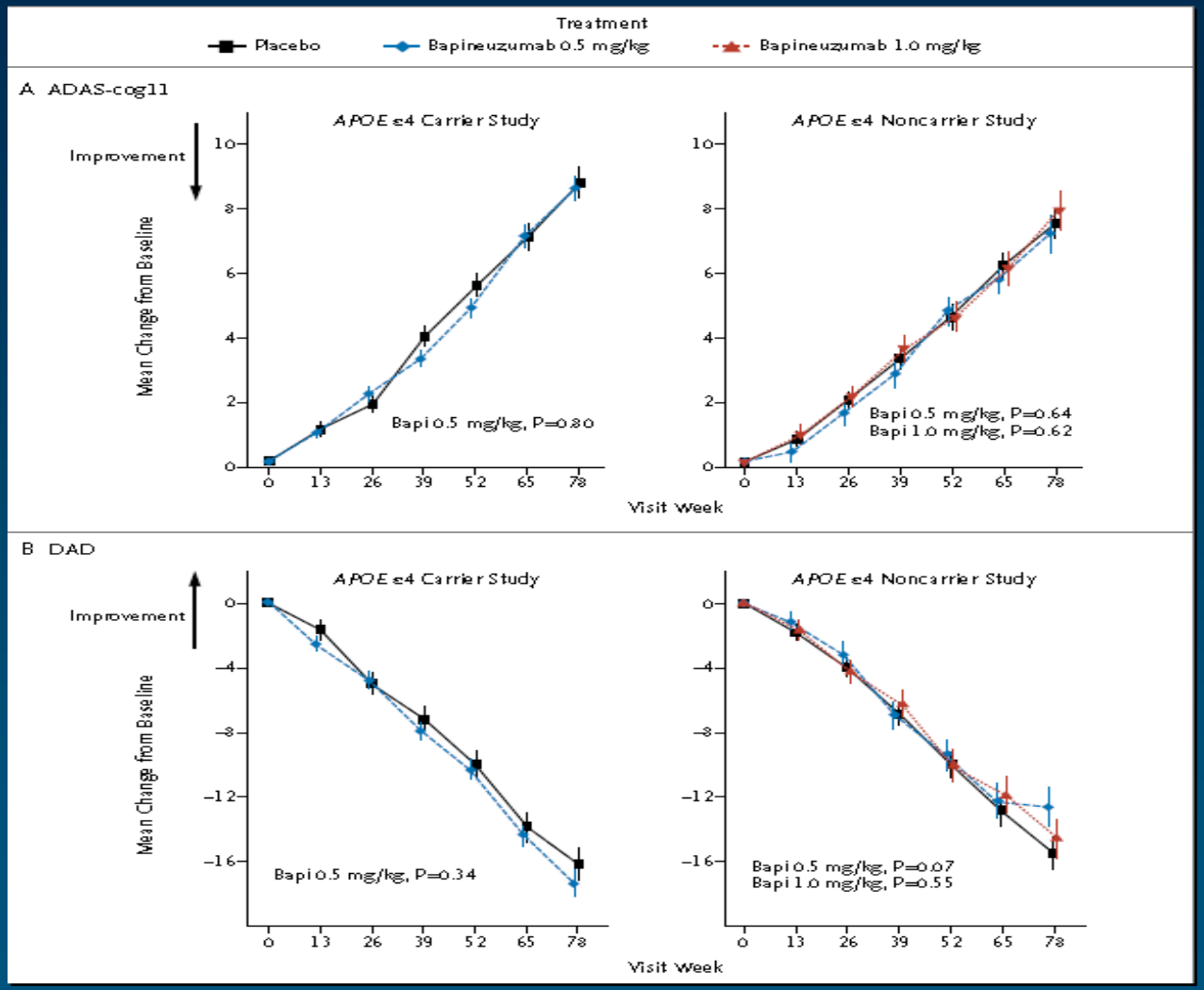
***Figure 2*: Estimated change from baseline over time in mean ^{11}C-PiB PET**
Data are least squares means and 95% CIs. * Difference between patients in the placebo group and those in the bapineuzumab group at week 78=−0·24 (p=0·003). PiB=Pittsburgh compound B.

Bapineuzumab Phase 2 Safety: Vasogenic Edema (ARIA-E)

- 12/124 (9.7%) patients on bapi (vs 0 on placebo) developed vasogenic edema (VE)
  - Most frequently detected by MRI, with few or no clinical symptoms in most cases, and resolved in weeks to months

Salloway S, et al. *Neurology.* 2009.

Negative Bapineuzumab Phase 3 Results



n engl j med 370;4 nejm.org january 23, 2014

Solanezumab Phase 2: Safety and Pharmacodynamic Data as Basis for Phase 3

- Safety, tolerability and biomarker effects in AD patients and controls1
  - AD patients: 12 weekly infusions, 4 doses vs placebo
  - Controls: 1 single dose-100 mg solanezumab
- Total (bound + unbound) plasma $A\beta_{1-40}$ and $A\beta_{1-42}$ increased, dose-dependent manner
- Total CSF $A\beta_{1-40}$ and $A\beta_{1-42}$ increased
  - Viewed as proof of concept
  - Peripheral sink hypothesis
- Well tolerated

1. Siemers ER, et al. "Safety, tolerability and biomarker effects of an Abeta monoclonal antibody administered to patients with Alzheimer's disease" *ICAD 2008*; Poster P4-346.

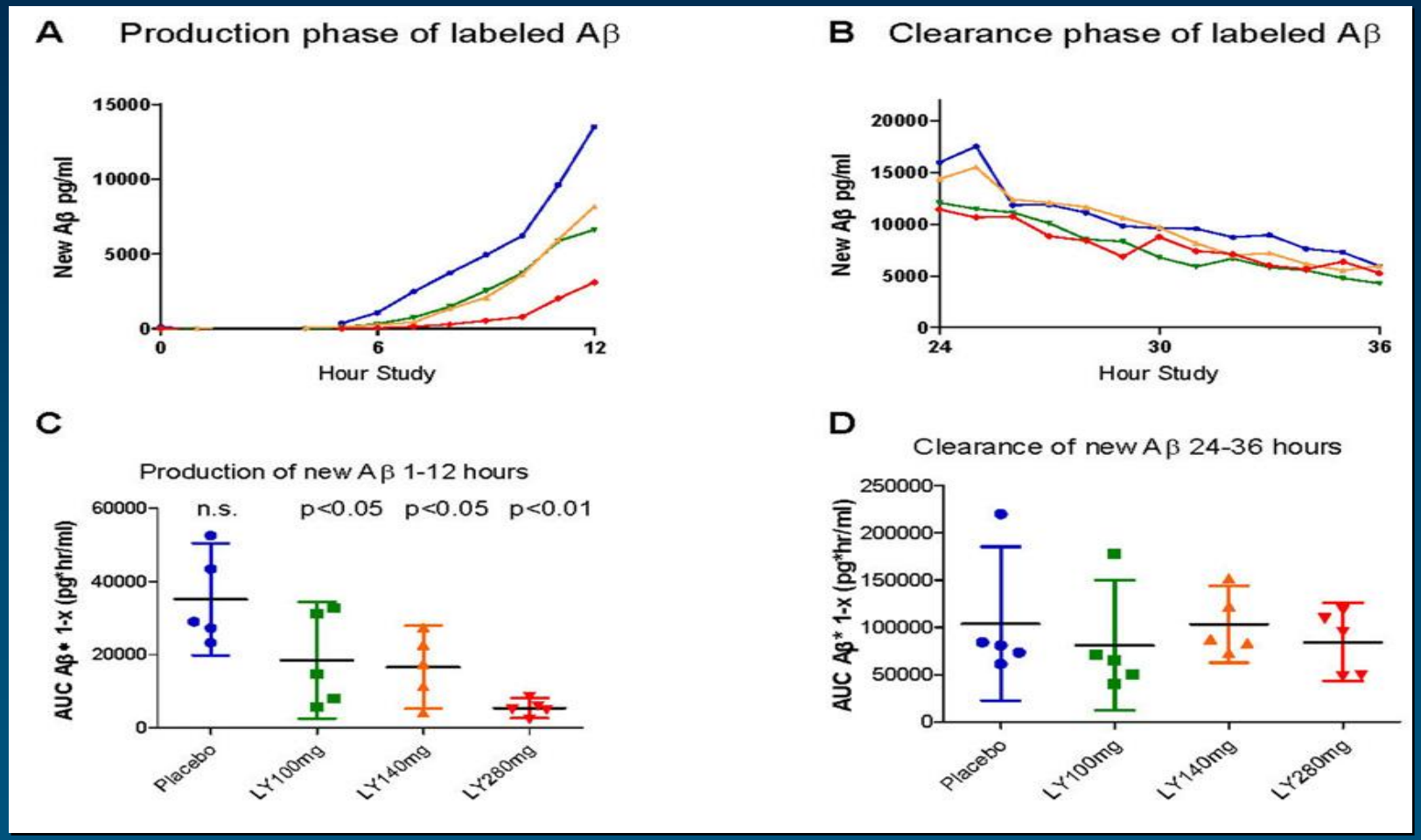
"Negative" Solanezumab Phase 3 Results*

Table 2. Primary and Secondary Outcomes in EXPEDITION 1, Intention-to-Treat Population.*

Variable	Mean Change from Baseline to Wk 80 (95% CI)		Mean Difference (95% CI)	P Value
	Placebo	Solanezumab		
ADAS-cog11 score†	4.5 (3.3 to 5.8)	3.8 (2.5 to 5.0)	-0.8 (-2.1 to 0.5)	0.24
ADAS-cog14 score‡	5.8 (4.3 to 7.3)	4.5 (2.9 to 6.0)	-1.4 (-2.9 to 0.2)	0.09
ADCS-ADL score†	-8.7 (-10.4 to -7.0)	-9.1 (-10.9 to -7.4)	-0.4 (-2.3 to 1.4)	0.64
CDR-SB score§	1.8 (1.3 to 2.3)	2.0 (1.5 to 2.4)	0.1 (-0.3 to 0.6)	0.51
NPI score¶	0.6 (-1.5 to 2.6)	-0.3 (-2.4 to 1.7)	-0.9 (-2.6 to 0.8)	0.29
MMSE score	-2.0 (-2.8 to -1.2)	-1.4 (-2.2 to -0.6)	0.6 (0.0 to 1.2)	0.06
Free $A\beta_{40}$ in CSF — pg/ml	80.9 (-2100.5 to 2262.3)	-1127.3 (-3272.4 to 1017.9)	-1208.2 (-2132.4 to -283.9)	0.01
Free $A\beta_{42}$ in CSF — pg/ml	-28.5 (-160.0 to 102.9)	-54.4 (-186.7 to 77.9)	-25.8 (-88.3 to 36.6)	0.41
Total $A\beta_{40}$ in CSF — pg/ml	-1902.1 (-6660.1 to 2855.8)	1325.4 (-3162.0 to 5812.9)	3227.6 (1253.6 to 5201.5)	0.002
Total $A\beta_{42}$ in CSF — pg/ml	-242.3 (-1144.4 to 659.7)	471.4 (-436.0 to 1378.8)	713.7 (309.1 to 1118.4)	<0.001

N ENGL J MED 370;4 NEJM.ORG JANUARY 23, 2014

Phase 2 Biomarker Data as Basis for Phase 3: Semagacestat Decreased CNS Aβ Production in Normals (Phase 3 showed no clinical benefit, and mild cognitive (and other) toxicity)



Bateman et al Ann Neurology 2009

Some Lessons From More Recent Trials

- Most now using updated AD diagnostic criteria
  - For AD dementia, MCI, and “preclinical” AD
- Will more refined cognitive (and functional, global, behavioral) measures and methods work better?
  - Empirically derived cognitive composite measures
  - Centralized expert raters
  - Computerized testing
  - Home based, telephonic, internet based assessments
- Translation of animal data to human, e.g., transgenics, remains problematic
- Phase 2 design/decision making still challenging
- New approaches to enrollment needed, including minorities
  - Alzheimer’s Association TrialMatch

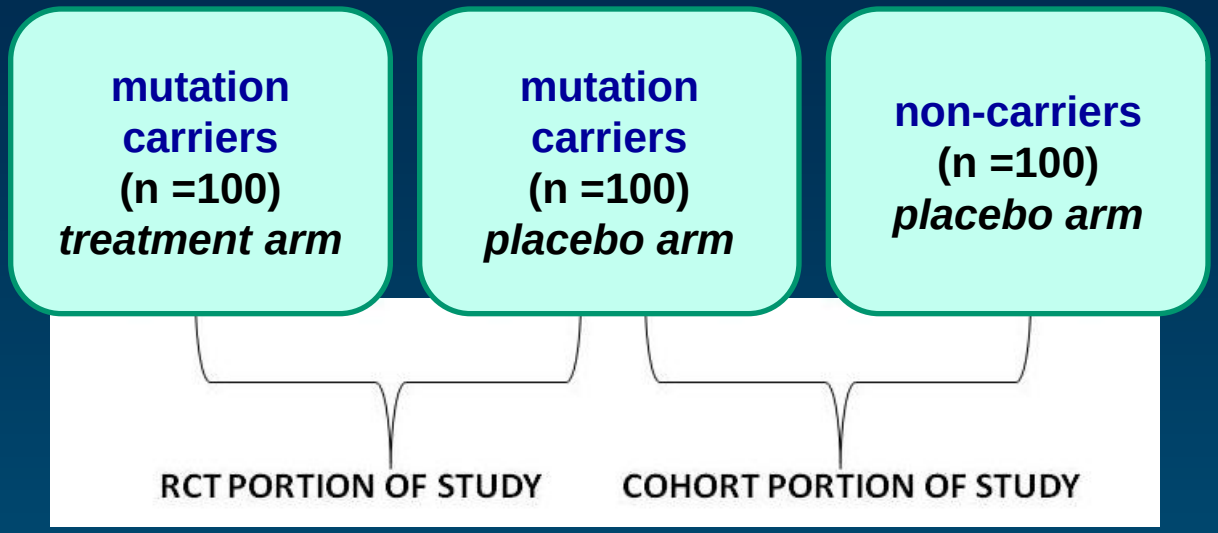
Role of Biomarkers Evolving: Humility Needed

- **Diagnostic:**
  - CSF, fDG PET, amyloid PET can have a role in improving *diagnostic* accuracy
  - e.g., about 35% of amyloid (-) APOE4 noncarriers in bapi, sola
  - suggests utility of enrolling amyloid (+) patients in anti-Aβ trials
  - But emerging information about “indeterminate” amyloid PET results (27%, K. Johnson, 2013 CTAD)
- **Prognostic:**
  - e.g., more rapid decline in amyloid (+) subjects; offers rationale for trial inclusion criterion
- **Pharmacodynamic:**
  - Fluid biomarkers offer PD signals for some drug development decisions, e.g., BACE inhibitors show lowering of CSF AB; fluid antibody levels increase with passive immunization
  - Utility of amyloid PET for PD uncertain
- **Predictive and theragnostic potential:** unknown

“Prevention” Research

- Lack of clinical impact of anti-Aβ therapies so far may reflect weak and/or off-target effects
  - and/or lack of potential for effect once brain is ravaged
- A preclinical stage of AD exists during which silent pathobiological and neuropathological changes occur
- Earlier treatment *may* slow the progression of AD in this silent phase
- Prior trials using survival to dementia failed to show benefit
  - Gingko biloba, NSAID’s, HRT
- New prevention trials are already underway or planned
  - Different approaches to enrichment, outcomes
  - “Coalition for Alzheimer’s Prevention”
- New FDA guidance
  - Possibly change in cognitive performance alone
  - Role of biomarkers TBD

API Preclinical ADAD Trial



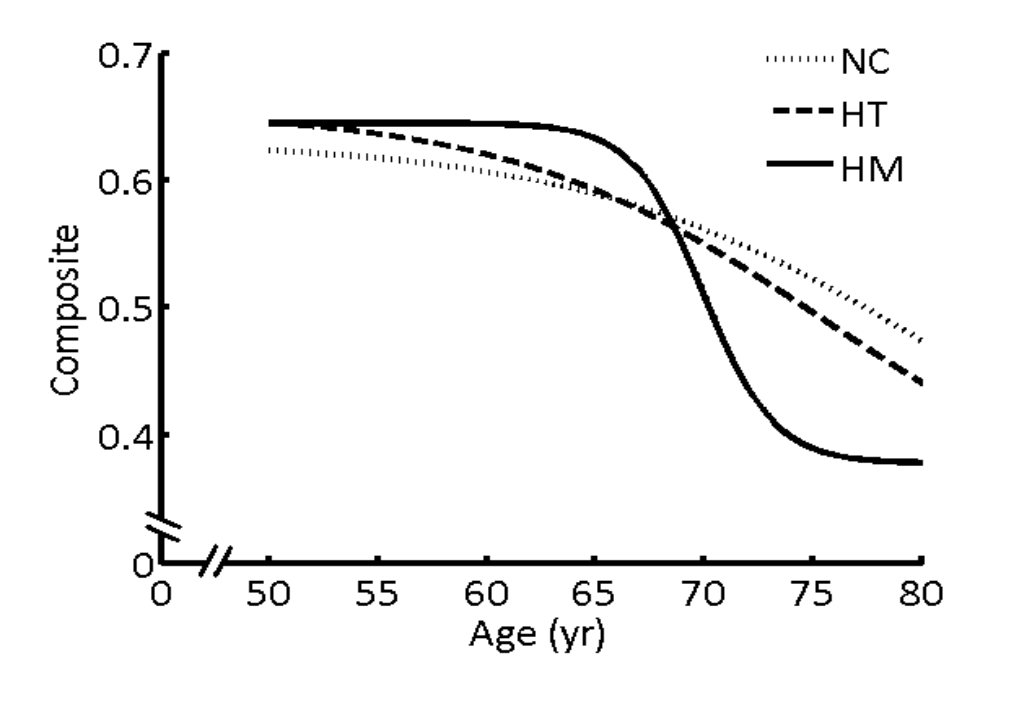
Double-blind, placebo-controlled 5 year trial
crenezumab 300 mg SC every 2 weeks

Primary endpoint: change in the API composite cognitive score
24-mo interim analysis: florbetapir PET, FDG PET, MRI, CSF & cognitive/clinical endpoints

300 *PSEN1 E280A* kindred participants from Colombia

Launched 2013

Associations between the UDS Composite Cognitive Test Score and Age in Cognitively Normal APOE4 Homozygotes, Heterozygotes, and Noncarriers



The optimal ages to track preclinical AD cognitive decline: 60-75 in homozygotes; 70-80 in heterozygotes

Ayutyanont et al, *AAIC Abstr* 2013

API APOE4 Trial

- 650 participants
  - All *APOE4* homozygotes
  - Will disclose genetic status and monitor impact of disclosure
- 5 year trial to study efficacy of a TBD treatment by comparing change in cognition (& biomarkers)

Interested individuals who either know APOE4 status or willing are willing to undergo genetic testing and disclosure

↓ ↓

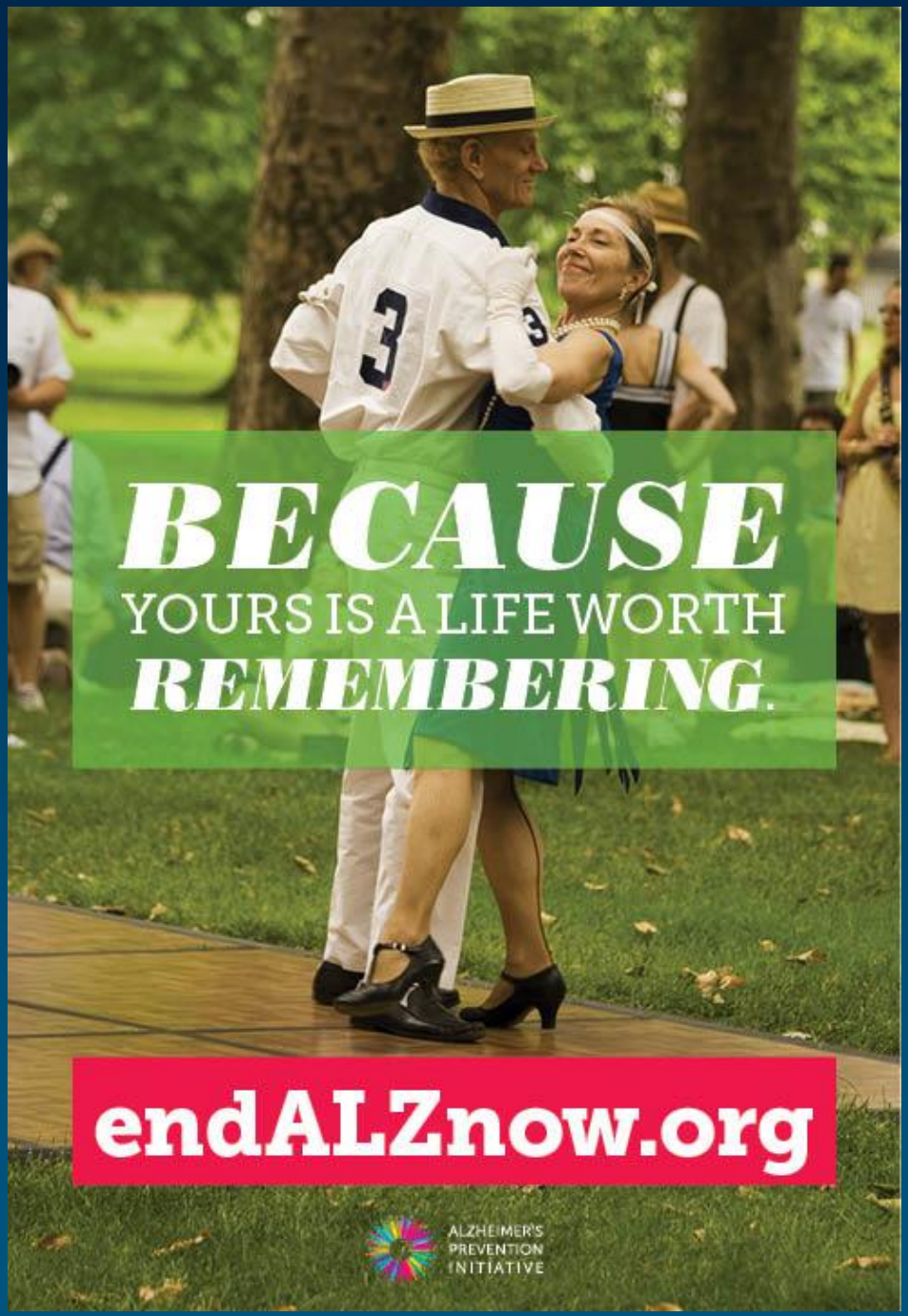
325
TREATMENT ARM

325
PLACEBO ARM

Trial estimated to begin 2015

Other New Prevention Studies

- **TOMMOROW**
  - Examine genetic profile as predictor of risk for developing MCI due to AD in cognitively unimpaired people
    - APOE, TOMM40, Age (65-83)
  - Test safety and effectiveness of low dose pioglitazone in delaying the onset of MCI
    - n>5000
    - about 5 years' duration of treatment (survival approach)
- **ADCS A4**
  - Test safety and effectiveness of solanezumab in cognitively unimpaired people with amyloid positive PET scan
    - about 1100 (400 amyloid (-) /100 amyloid indeterminate will be followed); age 65-85
  - Cognitive outcome, 3 years treatment
- **DIAN**
  - Test solanezumab & gantenerumab in people with different ADAD mutations
  - Small n
  - Biomarker outcome, 1-2 years treatment



- **Alzheimer's Prevention Registry**
  - **www.endALZnow.org**
  - **1-888-STOP-ALZ**
  - **info@endALZnow.org**

Some Lessons Learned

- Early AD drug development "worked"
  - Drugs undervalued
- Relying on outdated diagnostic criteria
- Slow to deal with pathological heterogeneity
- Using outdated clinical tools
- Slow adoption of:
  - "modern" QI methods
  - novel outcomes
  - novel designs
- Failing our patients with neuropsychiatric symptoms
- How best to inform practice?
- Many new targets
  - e.g., AlzForum Therapeutics Home Page
  - Will we move beyond "pathology focus?"
  - Non-drug interventions
- Evolution of biomarkers, understanding their use in drug development
- Phase 2 decision making remains treacherous

Some New Themes and Questions

- Ethical issues: disclosing genetic or biomarker risk; possible changes in community standards for disclosure
- Data and sample sharing: NIH requirement
- Assuring that all stakeholders are involved
- Precompetitive collaboration
  - Sharing placebo data, discovery/development, methods
- New approaches to enrollment
  - Including prospective cohort studies?
- New approaches to funding
  - Private/private
  - Public/private
  - Impact of philanthropy
- Potential for adaptive designs
  - Other designs: e.g., run-in?
- Non-drug interventions; or targeting nonpathological factors?
- Incorporating new data gathering technologies?
- Risk-based monitoring?
- Enrichment strategies: biomarker, genetic (DTC), DBS, TBI

Acknowledgements

National Institute on Aging

RF1 AG041705, 1UF1AG046150, R01 AG031581, P30 AG19610

Industry

Genentech, Avid/Eli Lilly

Foundations

Banner Alzheimer's Foundation, Anonymous Foundation, Nomis Foundation, Forget Me Not Initiative, Geoffrey Beene Foundation; Colciencias 1115-408-20512, 1115-408-20543

State of Arizona

Arizona Alzheimer's Consortium

Colleagues (esp. Eric Reiman, Jessica Langbaum, Francisco Lopera) collaborators (esp. at Genentech)

Advisors

Most of all our research participants