Advances for Alzheimer's in the Horizon

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Disclosure

I have no actual or potential conflict of interest in relation to presentation.

Advances for Alzheimer’s on the Horizon

Overview of Drug Development Process

Recent Advances in Therapeutics

Understanding the latest breakthroughs

How these changes impact patient care

Clinical Trials

Insights into current studies

Implications for future treatments

Biomarkers

The role of biomarkers in diagnosis and treatment

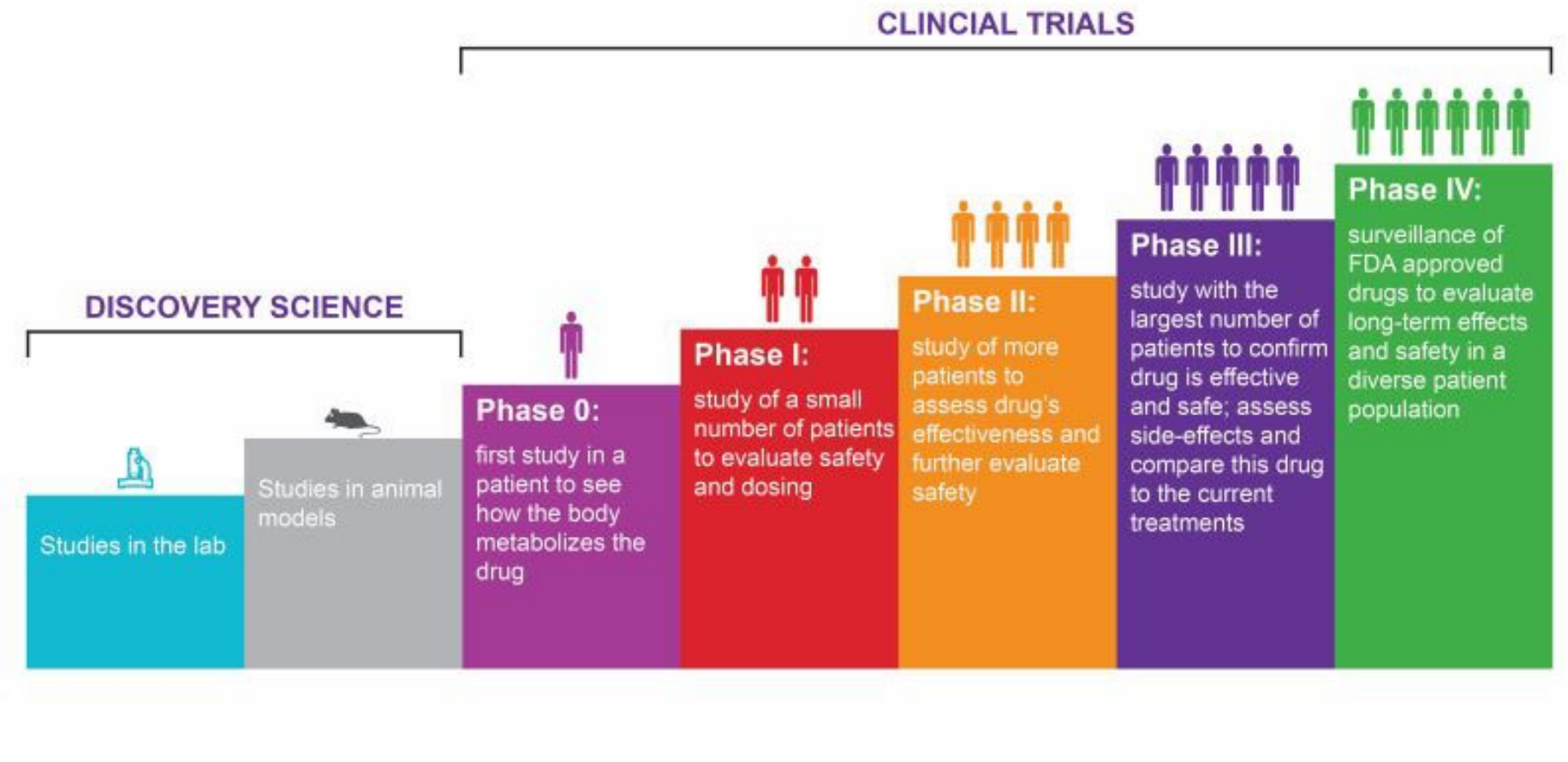
Emerging trends and their significance

Therapeutic Targets

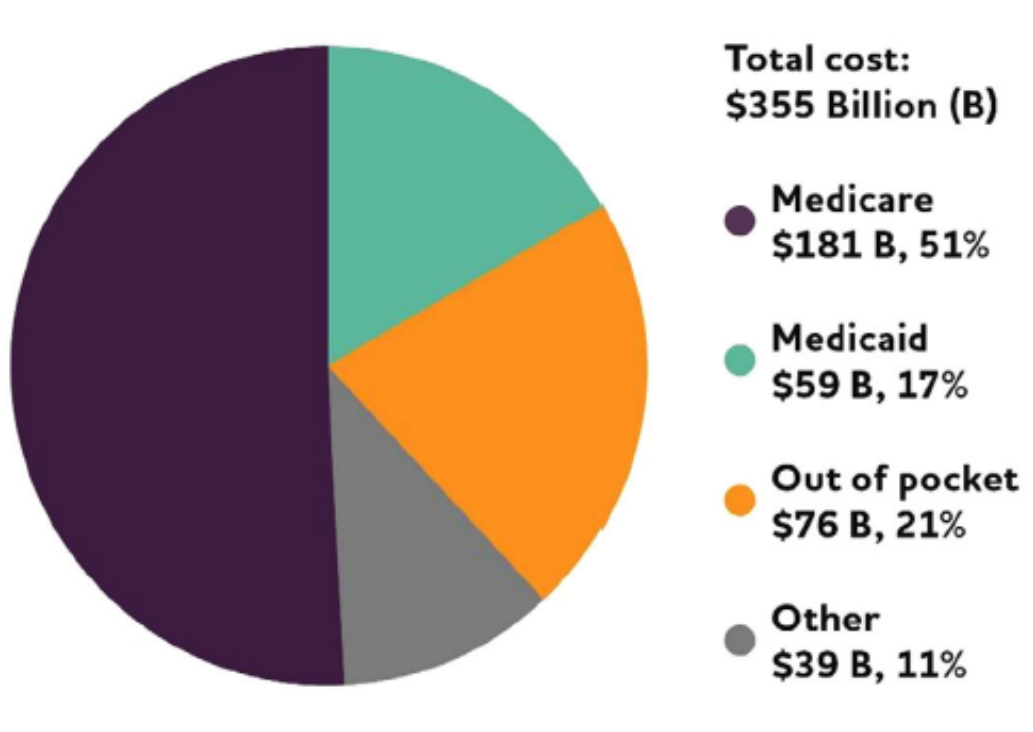
Identifying new targets for intervention

Strategies for personalized medicine

Challenges in Drug Development for Alzheimer's Disease



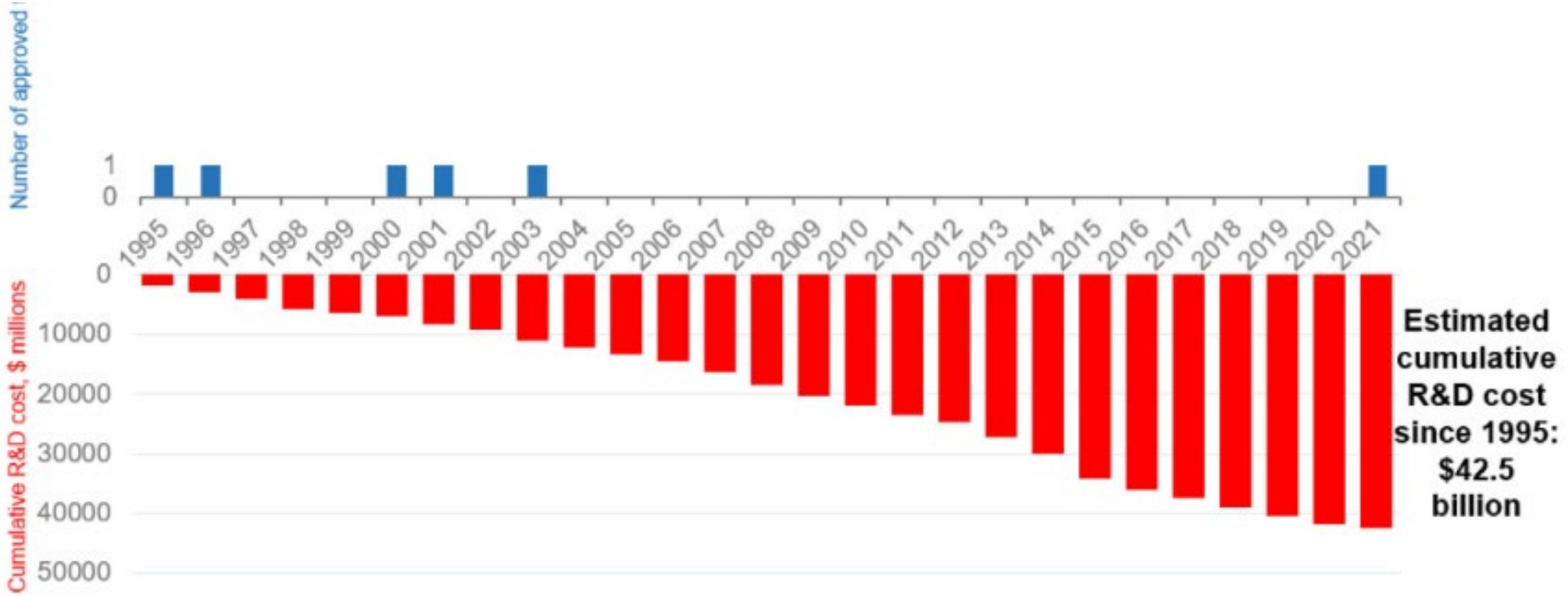
Rising Costs of Alzheimer's Disease



Payment Source	Beneficiaries with Alzheimer's or Other Dementias	Beneficiaries without Alzheimer's or Other Dementias
Medicare	$26,358	$8,102
Medicaid	9,178	391
Uncompensated	408	409
Health maintenance organization	1,351	1,655
Private insurance	2,414	1,524
Other payer	1,004	259
Out of pocket	11,571	2,503
Total*	52,481	14,976

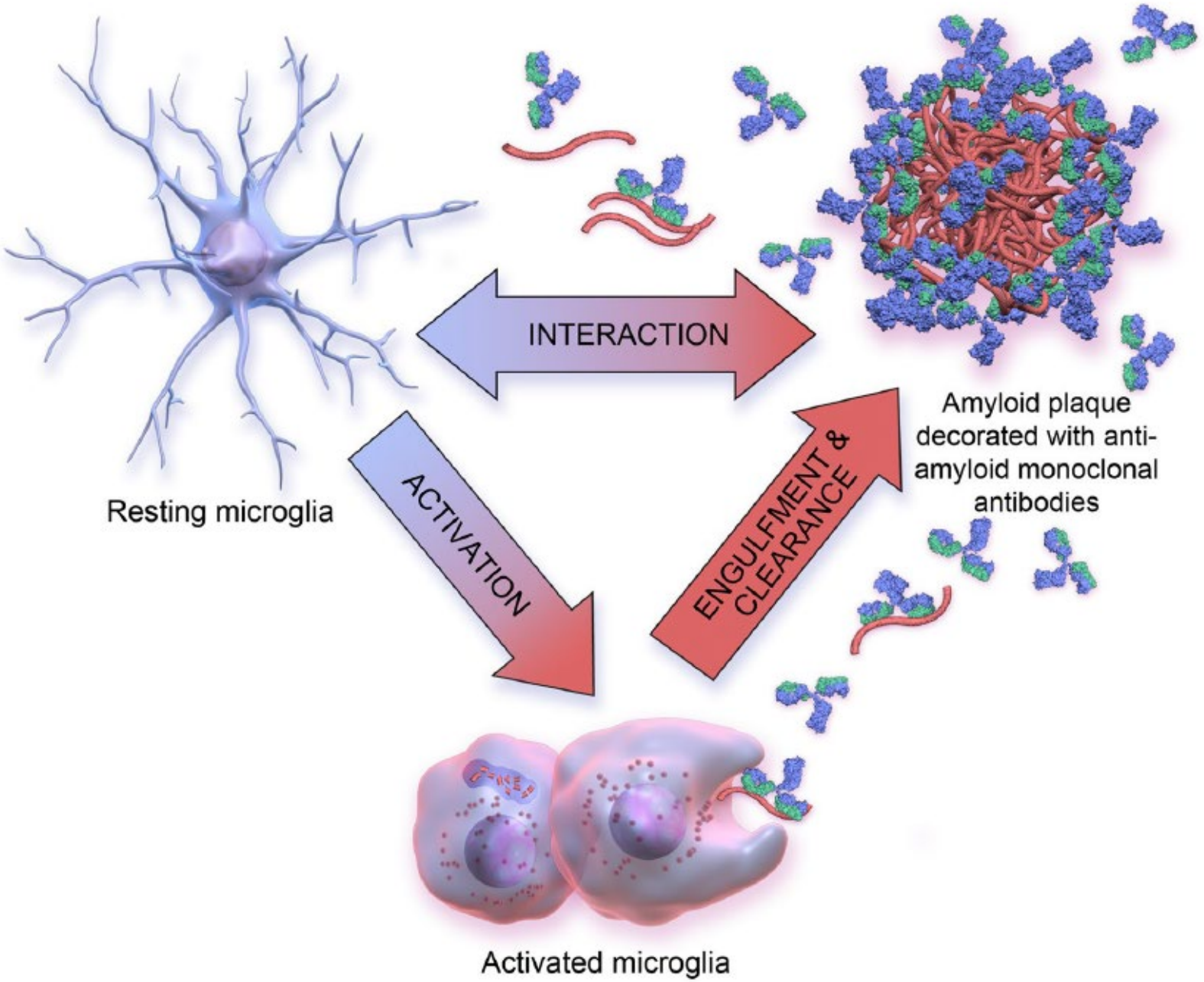
2021 Alzheimer's Disease Facts and Figures

The Price of Progress



J. L. Cummings et al.*Alzheimer's & Dementia* (2022)

Anti-Amyloid Monoclonal Antibodies



Mechanism of Action o Anti-Amyloid Monoclonal Antibodies

- Monoclonal antibodies (mAbs) bind to amyloid-beta
- They flag plaques for removal
- This action recruits microglia, the brain's immune cells, to marked plaques.
- Once there, microglia can engulf and clear amyloid-beta

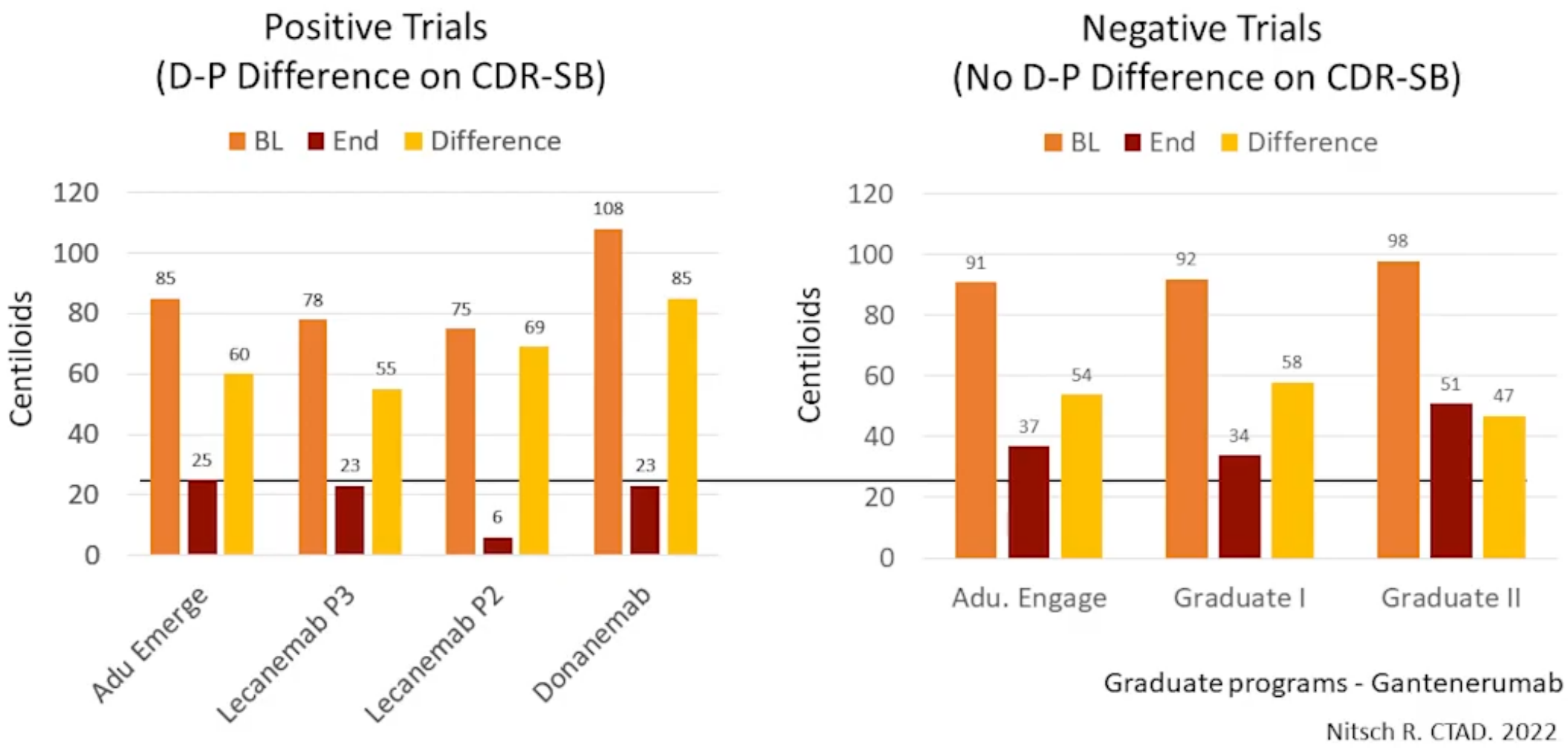
Anti-amyloid monoclonal antibodies

Lowers brain β-amyloid plaque and slowing of clinical decline as measured by the Clinical Dementia Rating–Sum of Boxes and other clinical and functional measures

Anti-amyloid monoclonal antibodies produce amyloid-related imaging abnormalities (ARIA) that are usually asymptomatic but may be severe and require anticipatory management

Slowing of clinical decline has been observed when the β-amyloid lowering reaches 15–25 centiloids, a common measure of β-amyloid abundance in the brain.

Amyloid Lowering with Anti-Amyloid Monoclonal Antibodies Appears to Require Reducing Amyloid to at Least 25 Centiloids to have a Corresponding Clinical Benefit



Graduate programs - Gantenerumab

Nitsch R. CTAD. 2022

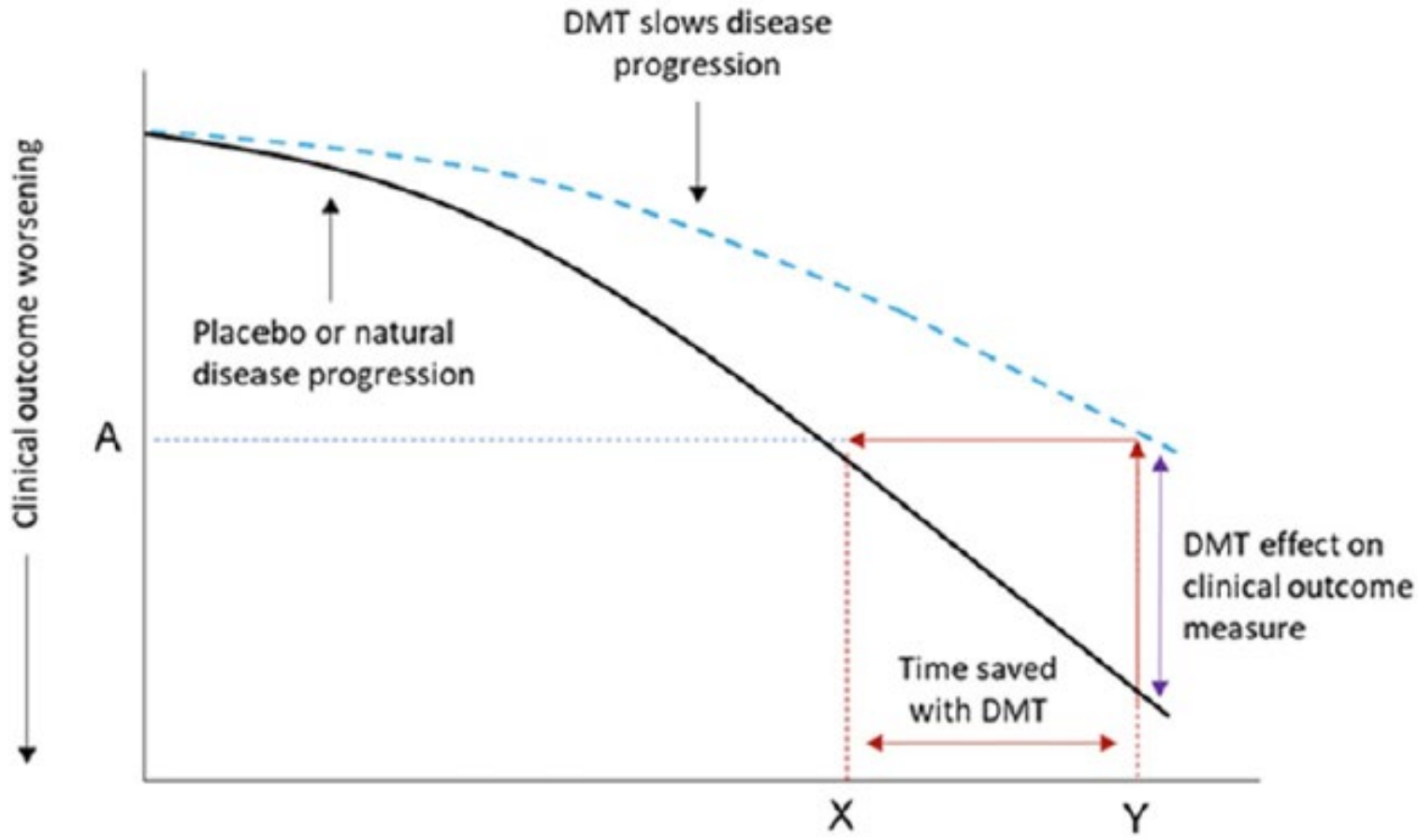
Cognitive Assessments

Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)	**Measures cognitive functions like memory, language, and praxis. Used to assess cognitive decline**
Clinical Dementia Rating - Sum of Boxes (CDR-SB)	**Assesses the severity of dementia across six cognitive and functional domains, providing a sum total score that reflects the level of impairment.**
Integrated Alzheimer's Disease Rating Scale (iADRS)	**Combines cognitive assessment (ADAS-Cog) with functional assessment to give a comprehensive overview of disease impact.**
Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory for Mild Cognitive Impairment (ADCS-MCI-ADL)	**Assesses the functional capabilities of individuals with mild cognitive impairment, focusing on the impact of cognitive changes on the ability to perform daily activities.**
Rapid Utility of Disease Lite (RUD-Lite)	**A brief assessment tool for evaluating the health economics of dementia by measuring resource use and costs associated with care.**
Quality of Life in Alzheimer's Disease (QOL-AD)	**Measures the quality of life from the perspective of both the patient with Alzheimer's disease and their primary caregiver.**
Mini-Mental State Examination (MMSE)	**A widely used test of cognitive function among the elderly that includes tests of orientation, attention, memory, language, and visual-spatial skills.**
Digit Symbol Substitution Test (DSST)	**Assesses attention, speed, and visuospatial processing by requiring the matching of symbols to numbers according to a key within a time limit.**

Example - Schedule of Assessments

Phase	Randomization																							
Period	Treatment																							
Visit[a]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Week	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35	37	39	41	43	45	47	49
Procedures/Assessments																									
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[c]	X						X							X						X					
Routine physical examination					X				X					X						X					
12-lead ECG					X				X					X						X					
Urine pregnancy test[d]							X							X						X					
Blood for laboratory tests[e]	X	X		X			X							X						X					
Urinalysis	X	X		X			X							X						X					
MMSE[f]							X							X						X					
CDR[f]							X							X						X					
ADAS-cog14[f]							X							X						X					
EQ-5D-5L[f,g]														X											
QOL-AD[f,g]														X											
ADCS MCI-ADL[f,g]														X											
Zarit Burden Interview[f,g]														X											
C-SSRS	X													X											
Safety MRI[h]					X		X							X											
Volumetric MRI (for PD)[i]					X		X							X											

Disease-Modifying Effect



S.P. Dickson, A.M. Wessels, S.A. Dowsett, et al. 'Time Saved' As a Demonstration of Clinical Meaningfulness and Illustrated Using the Donanemab TRAILBLAZER-ALZ Study Findings. J Prev Alz Dis 2023;3(10):595-599; http://dx.doi.org/10.14283/jpad.2023.50

Understanding differences in outcome measures

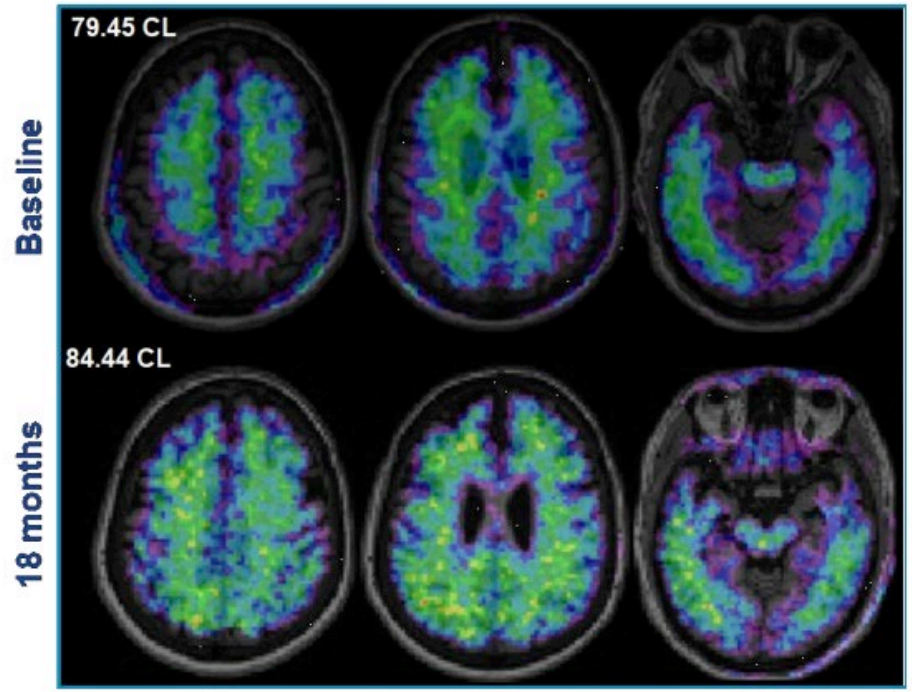
- **"Time Saved"**
  - Slowing progression
  - Prolonging independence
- **ADL**
  - Functional abilities
  - Quality of life
- **Memory**
  - Cognitive retention
  - Everyday recollection
- **Function**
  - Task execution
  - Self-sufficiency
- **Patient and caregiver reported outcomes**

Leqembi (lecanemab)

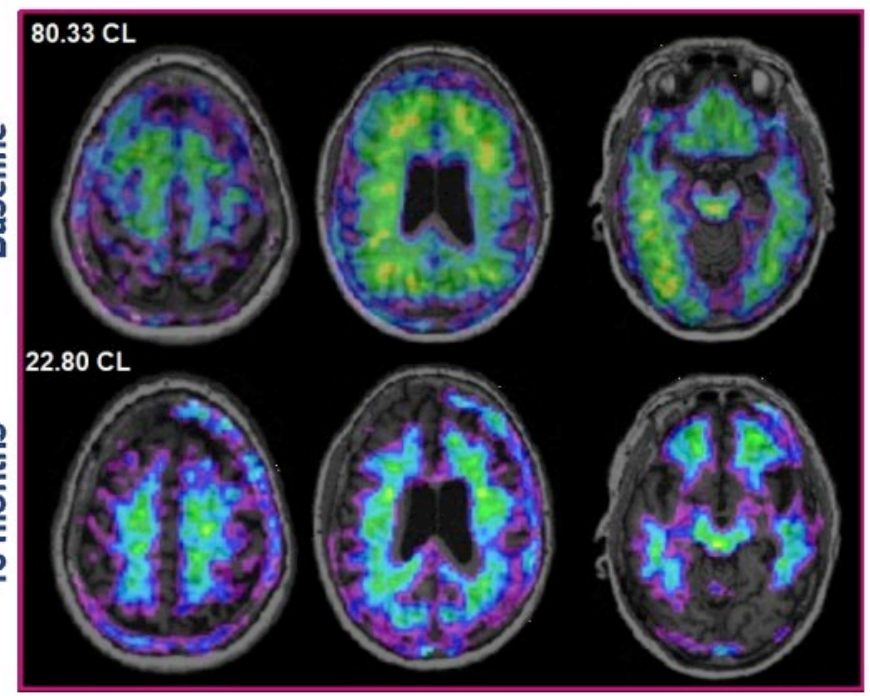
- January 2023 - Received accelerated approval from the FDA
- July 2023 – received full FDA approval

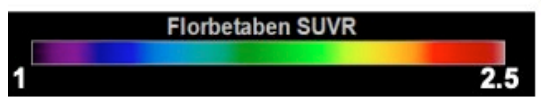
Swanson CJ, Zhang Y, Dhadda S, Wang J, Kaplow J, Lai RYK, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Alzheimer's Res Ther. 2021;13(1):80. 4. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early Alzheimer's disease. N Engl J Med. 2023;388(1):9–21

Placebo

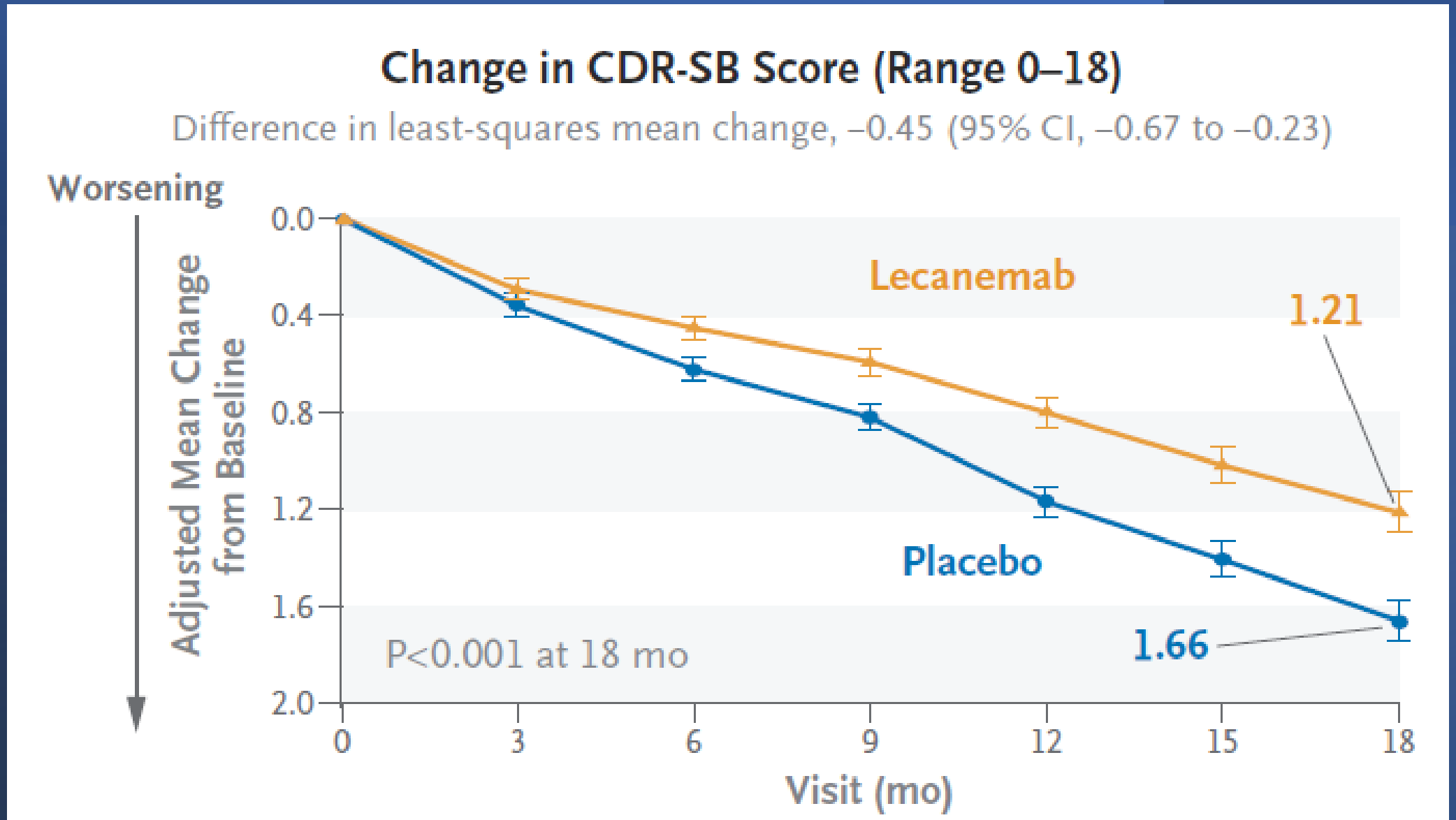


Lecanemab

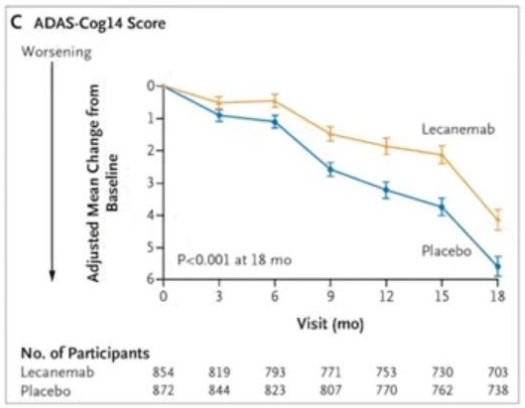


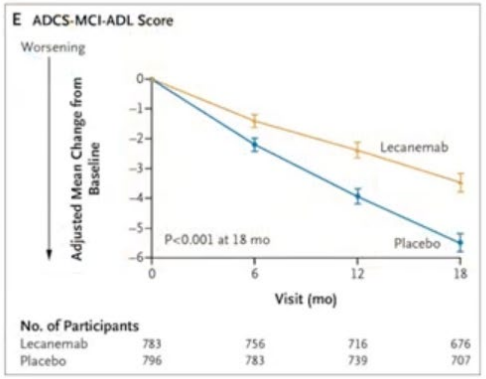


C. H. Van Dyck et al. New England Journal of Medicine (2023)

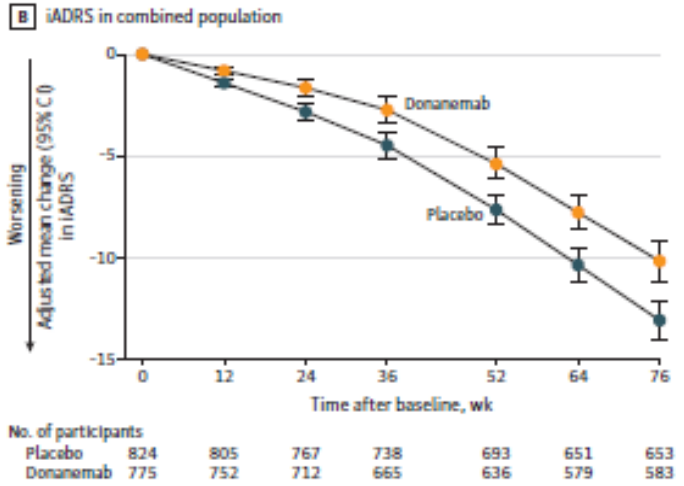


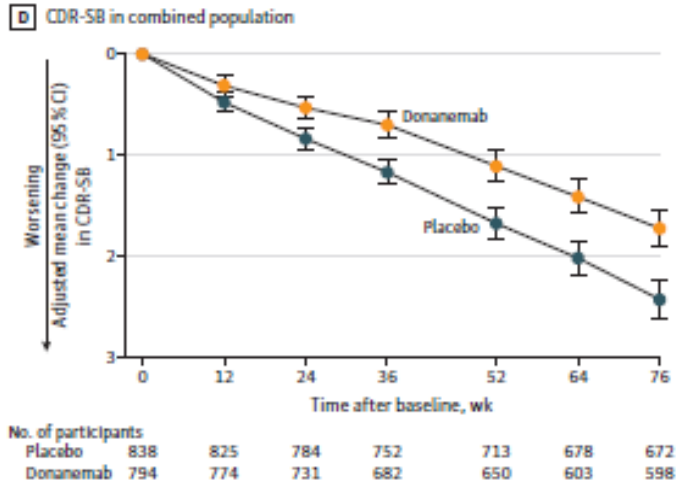
Lecanemab: Significant Slowing on Measures of Cognition and Function





van Dyck C, et al. New Engl J Med 2022; DOI: 10.1056/NEJMoa2212948





JAMA

QUESTION Does donanemab, a monoclonal antibody designed to clear brain amyloid plaque, provide clinical benefit in early symptomatic Alzheimer disease?

CONCLUSION Among patients with early symptomatic Alzheimer disease and amyloid and tau pathology, donanemab significantly slowed clinical progression at 76 weeks in low/medium tau and combined low/medium and high tau pathology populations.

POPULATION

996 Women
740 Men

Adults aged 60-85 years with symptomatic Alzheimer disease and amyloid and tau pathology

Mean age: 73 years

LOCATIONS

277
Medical sites
in 8 countries

INTERVENTION

1736 Patients randomized
1599 Patients analyzed

860
Donanemab
Administered intravenously every 4 weeks for up to 72 weeks

876
Placebo
Administered intravenously every 4 weeks for up to 72 weeks

PRIMARY OUTCOME

Least-squares mean change in integrated Alzheimer Disease Rating Scale (iADRS) score (range, 0-144; lower scores indicate greater impairment) from baseline to 76 weeks

FINDINGS

Least-squares mean change in iADRS

Donanemab

Low/medium tau population: −6.02
Combined population: −10.19

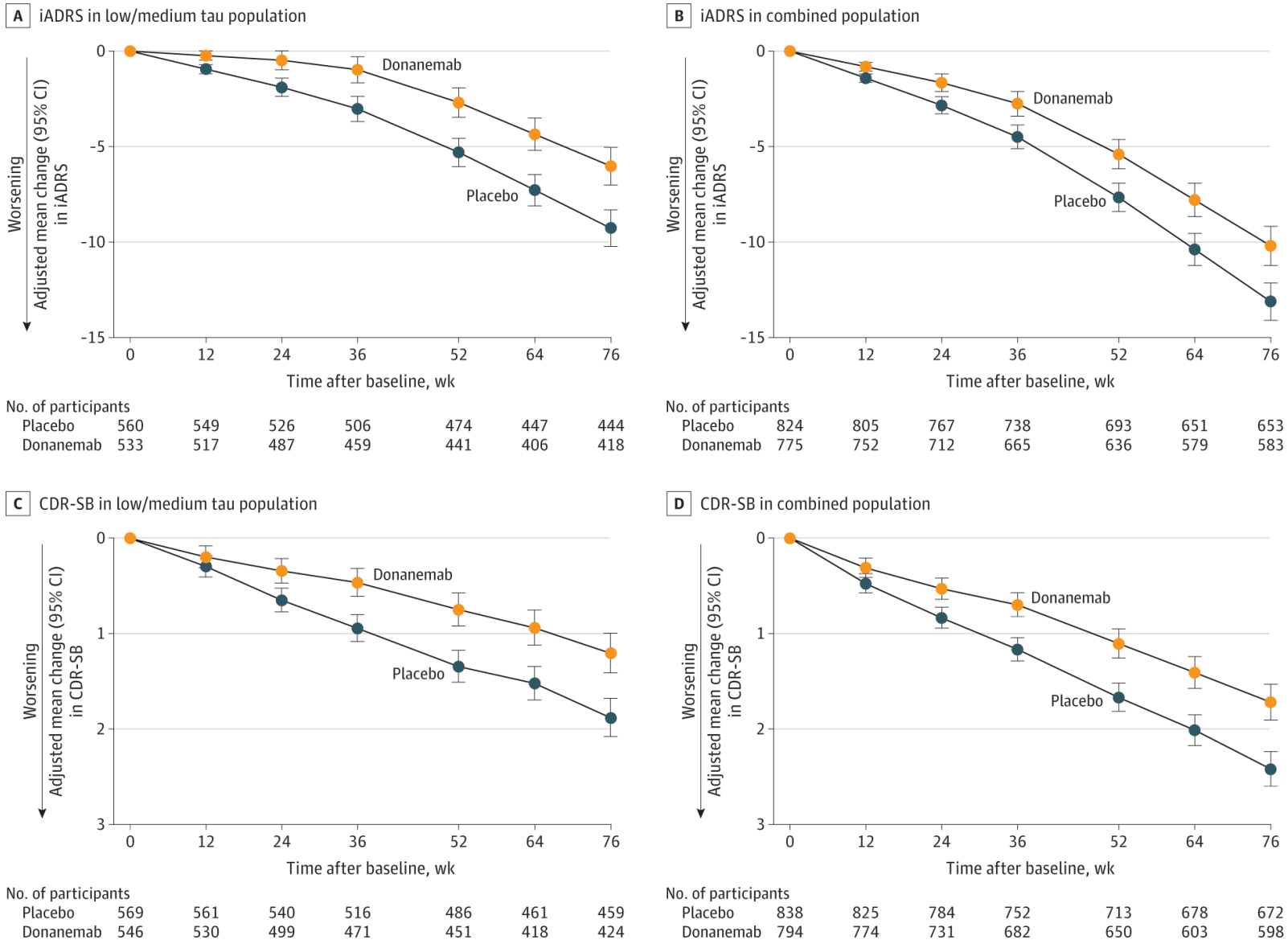
Placebo

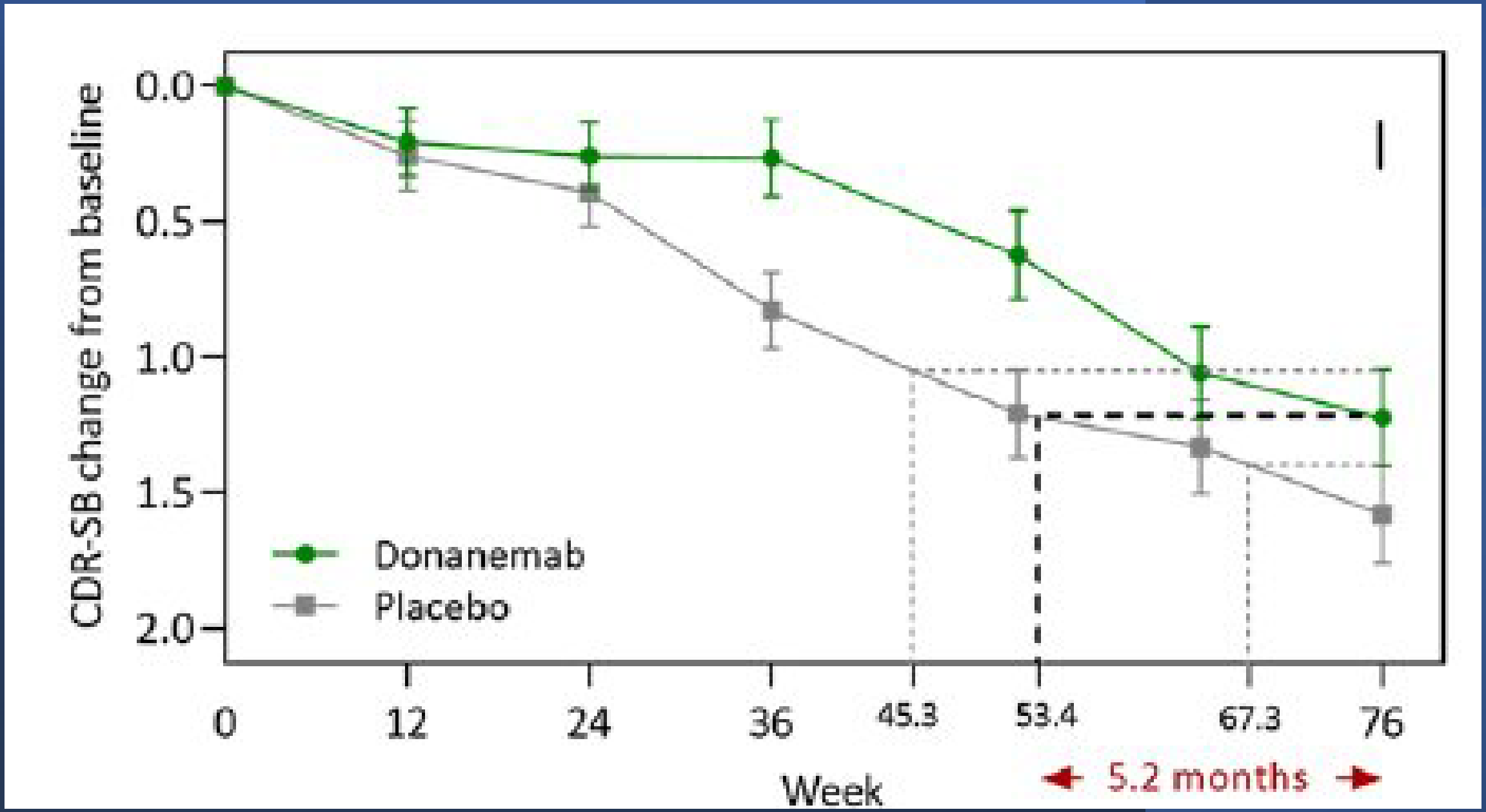
Low/medium tau population: −9.27
Combined population: −13.11

Differences were statistically significant:

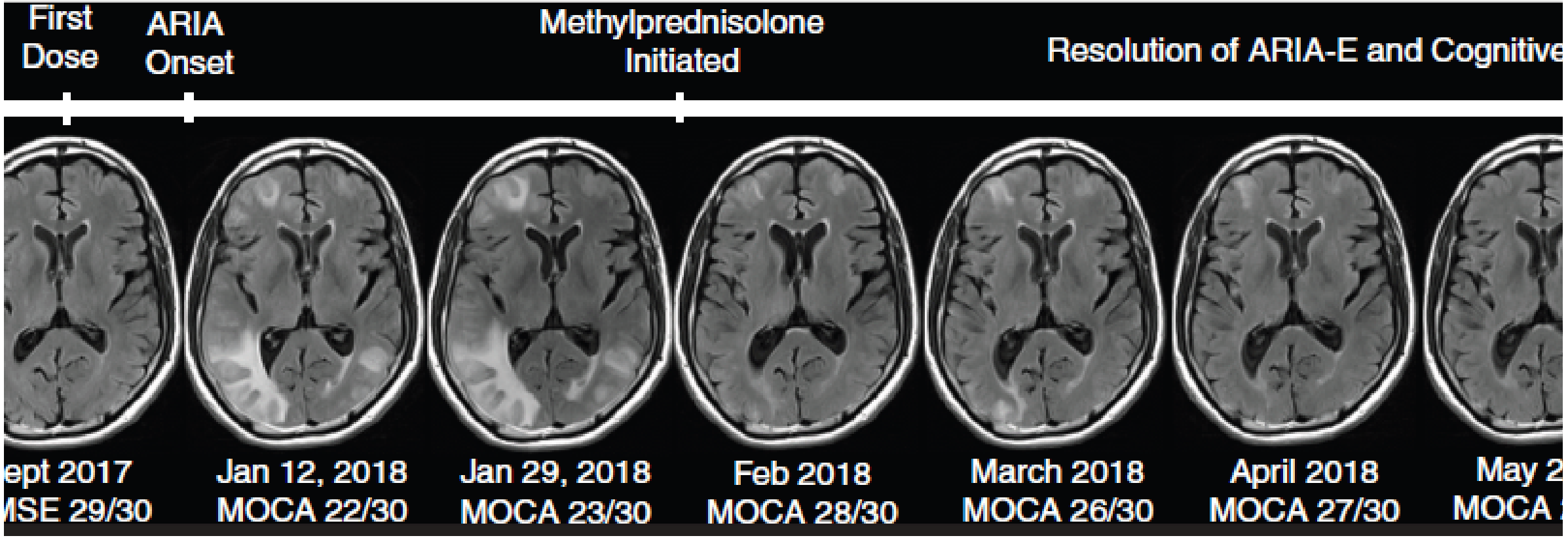
Low/medium tau: 3.25 (95% CI, 1.88-4.62); $P < .001$
Combined: 2.92 (95% CI, 1.51-4.33); $P < .001$

Sims JR, Zimmer JA, Evans CD, et al; TRAILBLAZER-ALZ 2 Investigators. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. Published online July 17, 2023. doi:10.1001/jama.2023.13239


A iADRS in low/medium tau population
Worsening
Adjusted mean change (95% CI) in iADRS
0
-5
-10
-15
Donanemab
Placebo
0 12 24 36 52 64 76
Time after baseline, wk
No. of participants
Placebo 560 549 526 506 474 447 444
Donanemab 533 517 487 459 441 406 418
B iADRS in combined population
Worsening
Adjusted mean change (95% CI) in iADRS
0
-5
-10
-15
Donanemab
Placebo
0 12 24 36 52 64 76
Time after baseline, wk
No. of participants
Placebo 824 805 767 738 693 651 653
Donanemab 775 752 712 665 636 579 583
C CDR-SB in low/medium tau population
Worsening
Adjusted mean change (95% CI) in CDR-SB
0
1
2
3
Donanemab
Placebo
0 12 24 36 52 64 76
Time after baseline, wk
No. of participants
Placebo 569 561 540 516 486 461 459
Donanemab 546 530 499 471 451 418 424
D CDR-SB in combined population
Worsening
Adjusted mean change (95% CI) in CDR-SB
0
1
2
3
Donanemab
Placebo
0 12 24 36 52 64 76
Time after baseline, wk
No. of participants
Placebo 838 825 784 752 713 678 672
Donanemab 794 774 731 682 650 603 598


CDR-SB change from baseline
0.0
0.5
1.0
1.5
2.0
Donanemab
Placebo
0
12
24
36
45.3
53.4
67.3
76
Week
5.2 months

Amyloid-Related Imaging Abnormalities (ARIA)



Monoclonal Antibodies in Early Alzheimer's Key Considerations

- **Target Audience**
  - For Mild Cognitive Impairment (MCI) or mild Alzheimer’s dementia with confirmed amyloid plaques.
- **ARIA Awareness**
  - Serious risk of Amyloid-Related Imaging Abnormalities (ARIA).
  - MRI scans required for monitoring.
- **Treatment Goals**
  - Aim: Slow cognitive decline, not symptom improvement.
  - Efficacy: 25-40% slowdown in progression, measurement-dependent.
- **Informed Use**
  - Vital to understand risks and benefits.
  - Communication essential for setting treatment expectations.
- **Outlook**
  - Future expansion subject to further research.
  - Complements symptomatic treatments.

Study Population Criteria

Inclusion Criteria Overview:

- Diagnosed with MCI or mild AD dementia.
- NIA-AA criteria for probable AD dementia.
- Specific CDR and Memory Box scores.
- Objective memory impairment on WMS-IV LMII.
- Positive brain amyloid pathology via PET or CSF.
- Age 50-90 years, BMI within 17-35.
- Stable AD medication dose for 12 weeks, if applicable.
- Identified and consenting study partner.
- Compliant with protocol requirements.

Exclusion Criteria Summary:

- Pregnant or breastfeeding females.
- Certain females not using effective contraception.
- Contributing neurological conditions beyond AD.
- Recent TIA, stroke, or seizures.
- Psychiatric symptoms interfering with the study.
- MRI contraindications or significant non-AD brain lesions.
- Uncontrolled immunologic or bleeding disorders.
- Certain malignancies within the last 3 years.
- Recent or significant history of substance abuse.
- Unstable or significant other medical conditions.
- Use of prohibited or investigational medications.
- Recent participation in certain other clinical studies.
- Any known exposure to BAN2401.
- Planned surgery during the study requiring general anesthesia.
- Severe sensory impairments affecting test performance.

APOE-Related Treatment Risks in AD Therapy

- **APOE genotyping is recommended prior to starting therapy.**
- **Risks of ARIA (E and H types) and symptomatic ARIA are elevated in individuals carrying the APOE4 allele.**
- **Possession of two copies of the APOE4 allele (homozygous status) substantially increases the risk for all ARIA forms.**
- **Genotyping enables precise risk discussions and tailored patient care.**
- **Study demographics: 53% of the trial's participants had one copy of the APOE4 allele (heterozygotes), 15% had two copies (homozygotes), and 68% overall were APOE4 carriers.**

APOE Status	ARIA-E Incidence	ARIA-E with Symptoms	ARIA-H Incidence
Noncarriers	5.4%	1.4%	11.9%
APOE4 Carriers	15.8%	3.4%	19.7%
Heterozygotes	10.9%	1.7%	14.0%
Homozygotes	32.6%	9.2%	39.0%

Management of ARIA

Table 3: Management of ARIA-E

	ARIA-E Severity at MRI		
Clinical Severity of ARIA-E	Mild	Moderate	Severe
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing; once imaging findings resolve, resume dose	Suspend dosing; once imaging findings resolve, resume dose
Mild, moderate, severe, serious ("other medically important event" only)	Suspend dosing; once ARIA-E resolves, same dose treatment can resume	Suspend dosing; once ARIA-E resolves, same dose treatment can resume	Suspend dosing; once ARIA-E resolves, same dose treatment can resume
Serious, except for "other medically important event"	Discontinue dosing	Discontinue dosing	Discontinue dosing

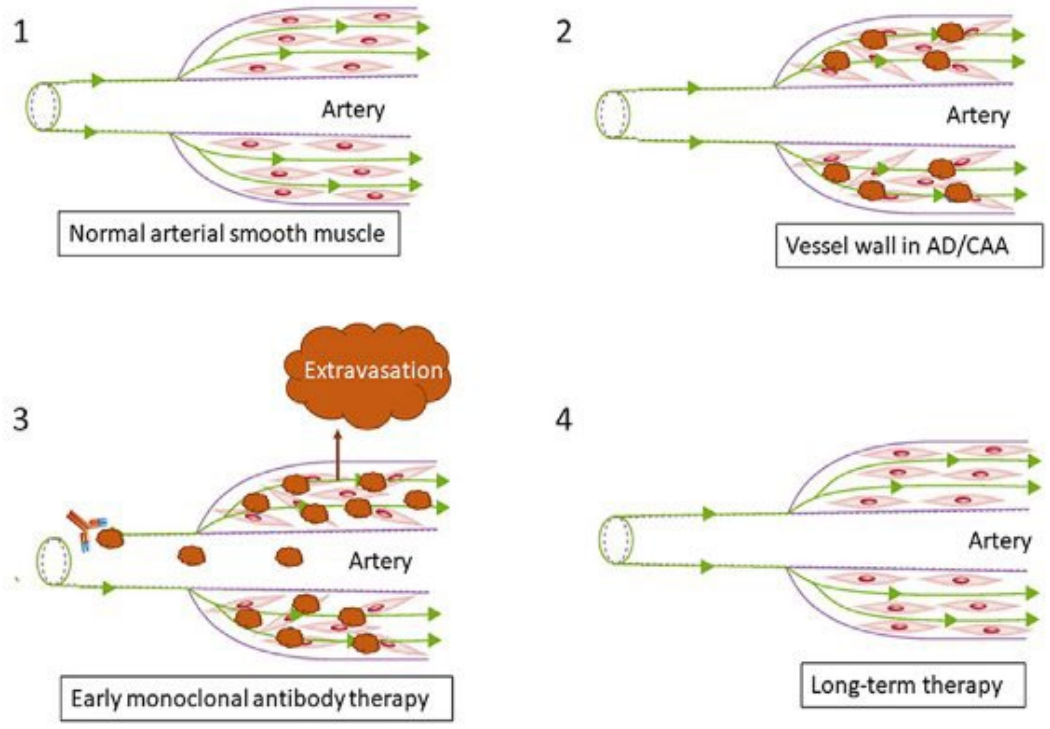
Source.—Reference 48.

Table 4: Management of ARIA-H

	ARIA-H Severity at MRI		
Clinical Severity of ARIA-H	Mild	Moderate	Severe
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing; once imaging findings resolve, resume dose	Discontinue
Mild, moderate, severe, serious ("other medically important event" only)	Suspend dosing; once ARIA-H resolves, same dose treatment can resume	Suspend dosing; once ARIA-H resolves, same dose treatment can resume	Suspend dosing; once ARIA-H resolves, same dose treatment can resume
Serious, except for "other medically important event"	Discontinue dosing	Discontinue dosing	Discontinue dosing

Source.—Reference 48.

LEQEMBI (lecanemab). Prescribing information. LEQEMBI. https:// www.leqembi.com/-/media/Files/Leqembi/Prescribing-Information.pdf. Accessed July 26, 2023.



Anti-Amyloid Antibody Treatments

Current Approvals:

- **Lecanemab**: Granted both accelerated and standard approvals.
- **Aducanumab**: Received accelerated approval status.

Clinical Trial Updates:

- **Imminent Phase 3 Results**:
  - Donanemab: Anticipating standard outcomes with ongoing FDA review, expected in 2023.
- **On the Horizon - Phase 3**:
  - Remternetug (LY3372993): Results expected in 2025.

Ongoing Developmental Stages:

- **Phase 2 Investigations**:
  - Trontinemab (Gantenerumab shuttle): In active development.
- **Early Phase 1 Exploration**:
  - ACU193, SHR-1701, PROX12, PMN310: Currently in preliminary testing stages.

OPEN TO ENROLLMENT– ADC-061-BENFO

- Phase 2A-2B randomized, randomized double-blind, placebo-controlled trial to evaluate the safety and efficacy of Benfotiamine in patients with early Alzheimer's disease
- Mechanism of action raises blood thiamine levels. In AD, it addresses and treats a well characterized tissue thiamine deficiency and related changes in glucose metabolism as well as post-translational modifications that are linked to thiamine dependent processes including neuroinflammation, abnormalities of advanced glycation end products, plaques and tangles, and downstream neurodegeneration

ADCS
Alzheimer's Disease Cooperative Study

NIH

OPEN TO ENROLLMENT– ADC-061-BENFO

- 72 week treatment duration
- Will randomize 406 total participants to a 1:1:1 ratio of oral medication (1200 mg/day, 600 mg/day, or placebo)
- Currently, there is not an Open-label portion, but this may change in the future
- Key inclusion – 50-89 years old, MMSE of 20-30, MoCA of <26, positive plasma AD biomarker signature
- Sara Boarman, BS, is the Lead Coordinator for this study – you can reach her at sboarman93@siumed.edu or 217.545.6829.

ADCS
Alzheimer's Disease Cooperative Study

NIH

Health-Care Integration

Healthcare System Challenges

- Unprecedented demands on global healthcare delivery.
- The evolving landscape of drug reimbursement and access.

Contrast in Progress and Delivery

- Advances in neuroscience vs. practical healthcare integration.
- Ensuring accessibility and benefit to those in need.

The Approval-Use Paradox

- Celebrating breakthroughs while navigating the complexity of clinical application.
- Focus on both innovative drugs and systemic assimilation into patient care.

Forward Momentum

- Adapting healthcare systems to match the pace of scientific innovation.

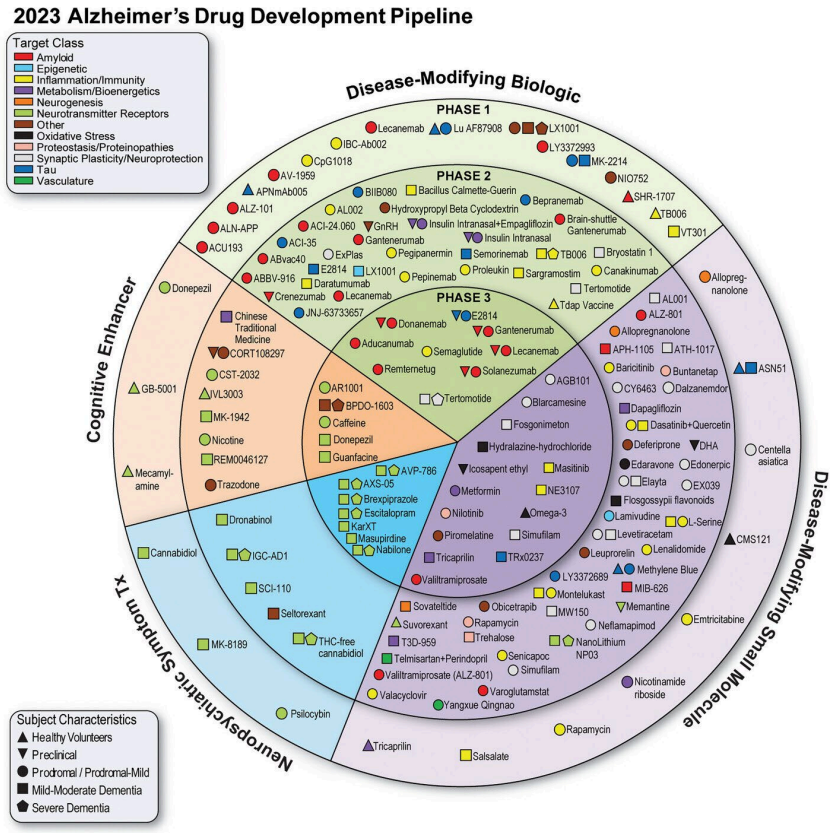
The dual goal: dynamic healthcare and enhanced patient outcomes.

A Call to Action

The need for a broad dialogue on making therapies accessible and affordable.

Commitment to equitable patient benefit as the driving force.

Drug Development Pipeline

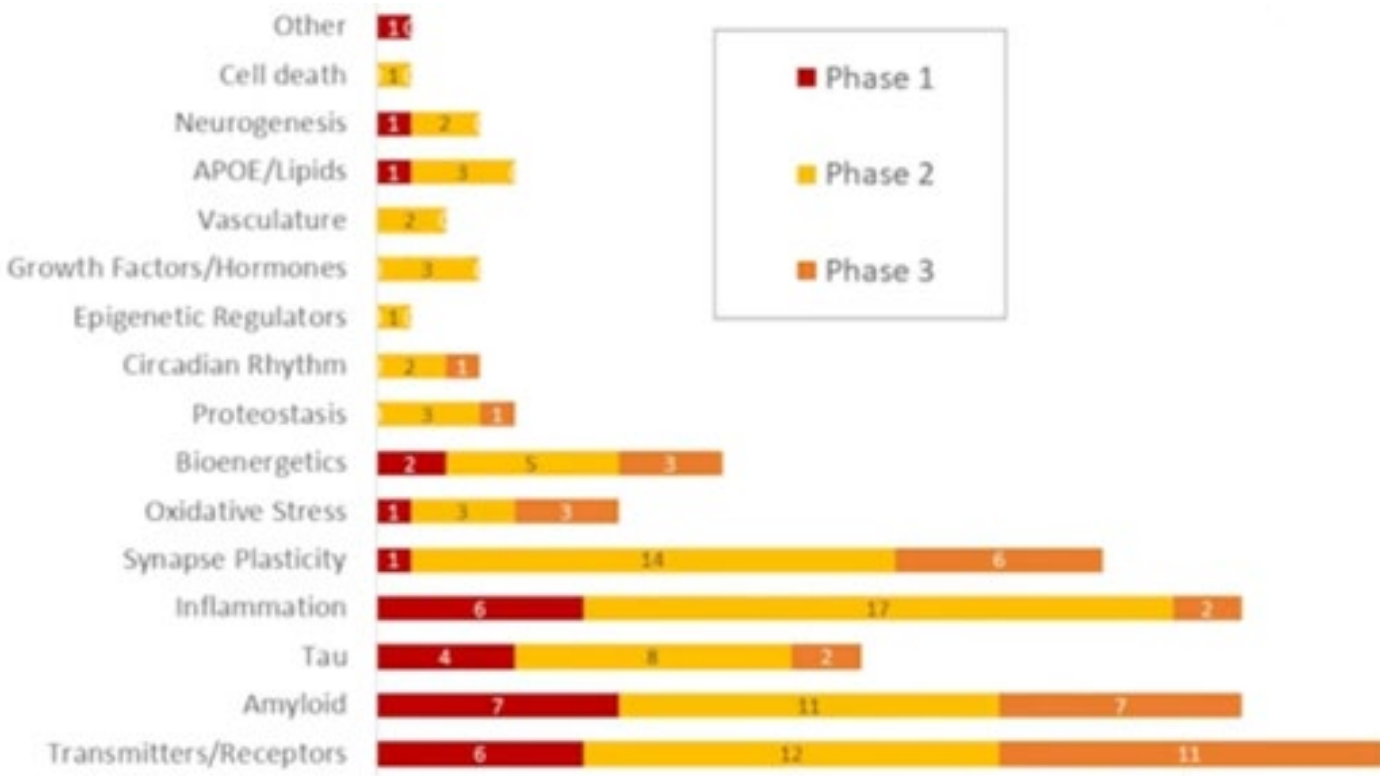


Cummings J, et al. Alz&Dem, 2023

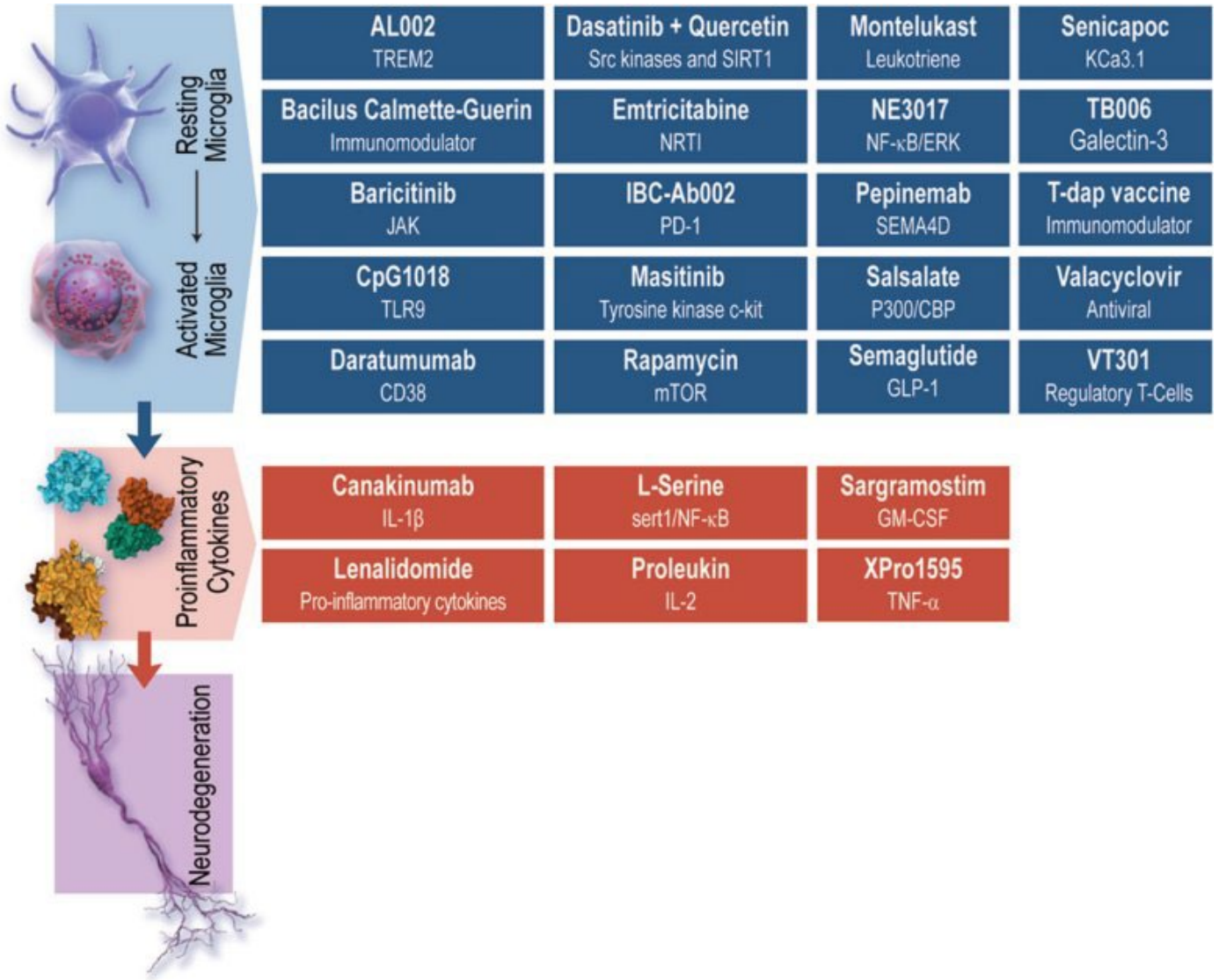
- 141 unique drugs
- 78% disease modifying treatments
  - 35% biologics
    - Notable Phase 1
  - 44% DMT small molecules
- 11% cognitive enhancers
- 11% drugs for behavioral symptoms
  - Notable Phase 3 activity
- 28% repurposed agents

CADRO Targets

- Diverse pipeline
- CADRO categories describe drug targets
- 4 targets account for 71% of pipeline drugs
- Transmitter targets include symptomatic agents
- 18% of the agents target amyloid
- 10% of agents target tau
- Inflammation is the 2nd most common target for pipeline agents (18% of agents)



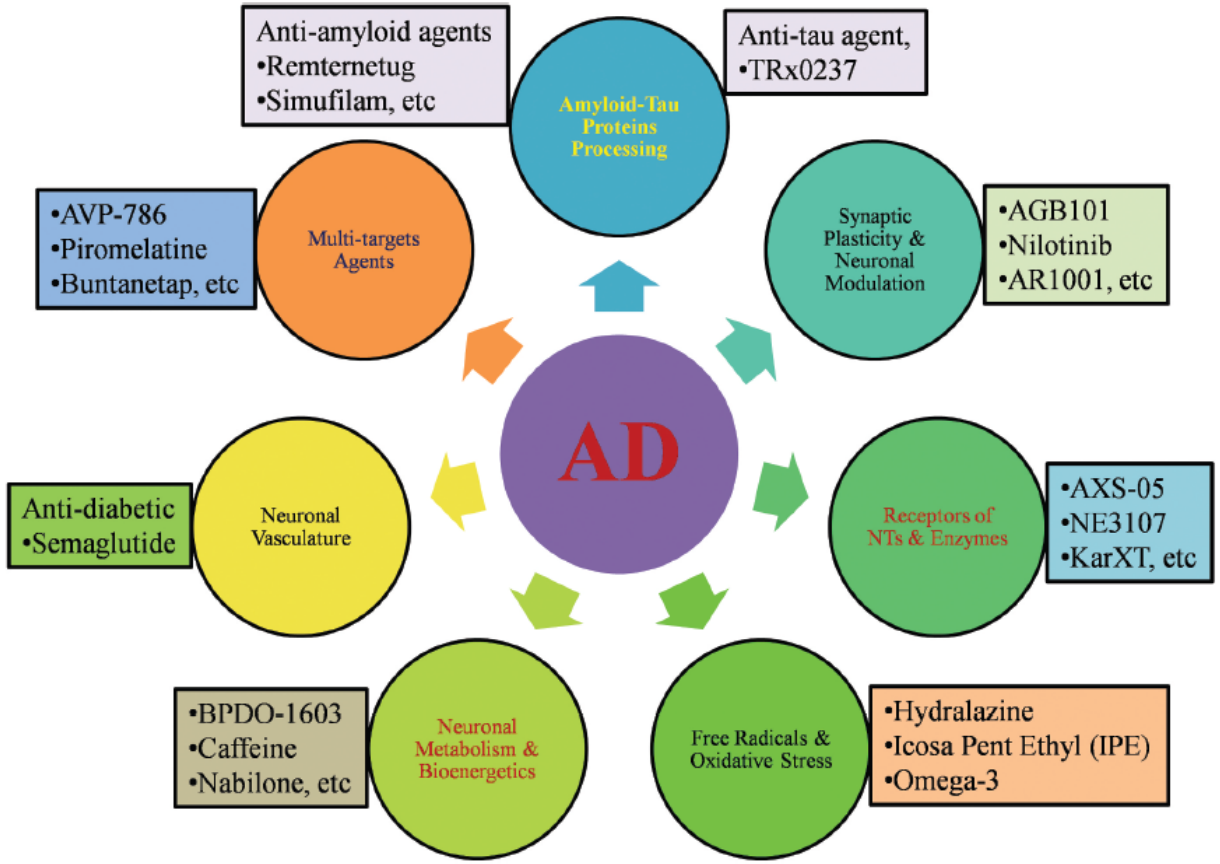
Cummings J, et al. Alz&Dem: TRCI 2023 9(2)e12385. doi: 10.1002/trc2.12385



Inflammation

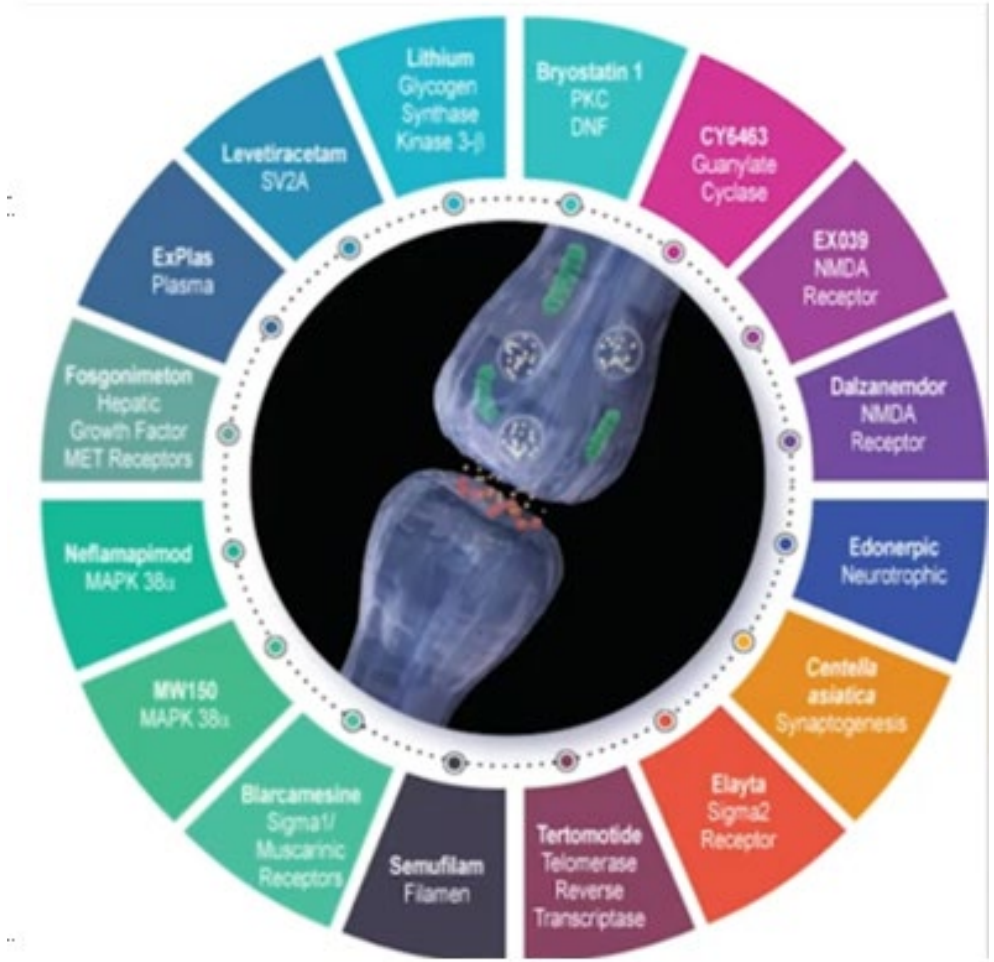
Cummings J, et al. Alz&Dem, 2023

Phase-3 trial's anti-Alzheimer's disease (AD) drugs against their targeting-pathways



J. Alam et al. Neurological Research (2024)

Synaptic Plasticity



Synaptic Plasticity & Neuronal Modulation in AD

Early Synaptic Malfunction: Critical in Alzheimer's Disease (AD) progression.

Preservation of Cognitive Functions: Targeting synaptic dysfunction to halt disease progression and maintain cognitive abilities.

Underlying Challenges:

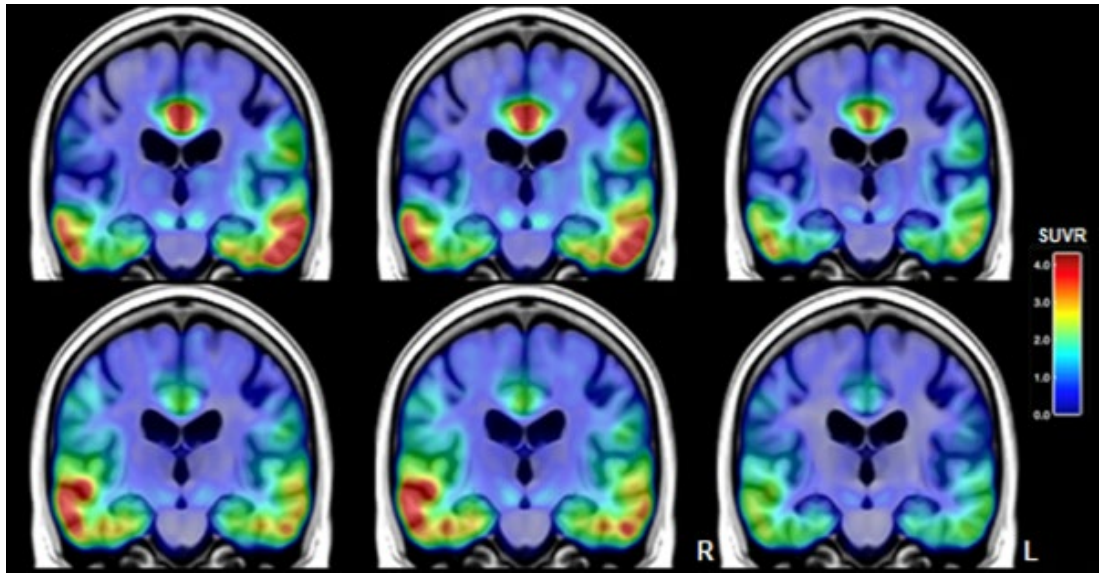
- Synaptic loss precedes neuronal death.
- Largest pathological marker of cognitive decline.

Therapeutic Approaches:

- Protective therapies to prevent synaptic malfunction.
- Novel drug molecules in phase-3 clinical trials aiming at enhancing synaptic health.

BIIB080

- **BIIB080 Overview**:
  - Investigates BIIB080, a tau-targeting antisense oligonucleotide (ASO), in mild Alzheimer's disease.
  - Phase 1b trial focusing on safety, pharmacokinetics, and effect on tau protein levels.
- **Trial Design & Participants**:
  - Randomized, double-blind, placebo-controlled study.
  - Enrolled 46 patients with mild Alzheimer's, treated with BIIB080 or placebo via intrathecal administration.
- **Key Findings**:
  - **Safety Profile**: BIIB080 was generally well-tolerated; adverse events were mild or moderate with no serious adverse events reported in treated patients.
  - **Efficacy**: Significant, dose-dependent reduction in cerebrospinal fluid (CSF) total-tau concentration, with over 50% reduction observed in higher dose groups.
  - **Exploratory Outcomes**: Indications of sustained reduction in tau protein levels, offering potential for modifying disease progression.
- **Conclusion & Future Directions**:
  - BIIB080 demonstrates a promising safety profile and a significant impact on tau protein levels.
  - These results warrant further exploration in larger clinical trials to evaluate the potential disease-modifying effects of BIIB080 in Alzheimer's disease.



Mummery, C.J., Börjesson-Hanson, A., Blackburn, D.J. *et al.* Tau-targeting antisense oligonucleotide MAPTRx in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial. *Nat Med* **29**, 1437–1447 (2023). https://doi.org/10.1038/s41591-023-02326-3

Neuronal Vasculature

Vital Role of Brain Vasculature:

Essential for delivering nutrients and oxygen, removing waste, and maintaining cognitive functions.

Disruptions in cerebral blood flow (CBF) and blood-brain barrier (BBB) integrity are early markers of Alzheimer's disease (AD).

Link to Neurodegeneration:

Compromised blood supply and BBB dysfunction contribute to neurodegeneration and cognitive decline in AD.

Hypothesized connection between vascular system disruptions and the progression of neurodegenerative diseases.

Therapeutic Focus:

Strategies aimed at improving vascular health as a means to counteract AD progression.

Importance of maintaining adequate blood supply and vascular integrity for brain health.

Emerging Therapies in Development:

Semaglutide: Examined for its potential to enhance neurovascular health, showcasing the therapeutic value of targeting vascular factors in AD.

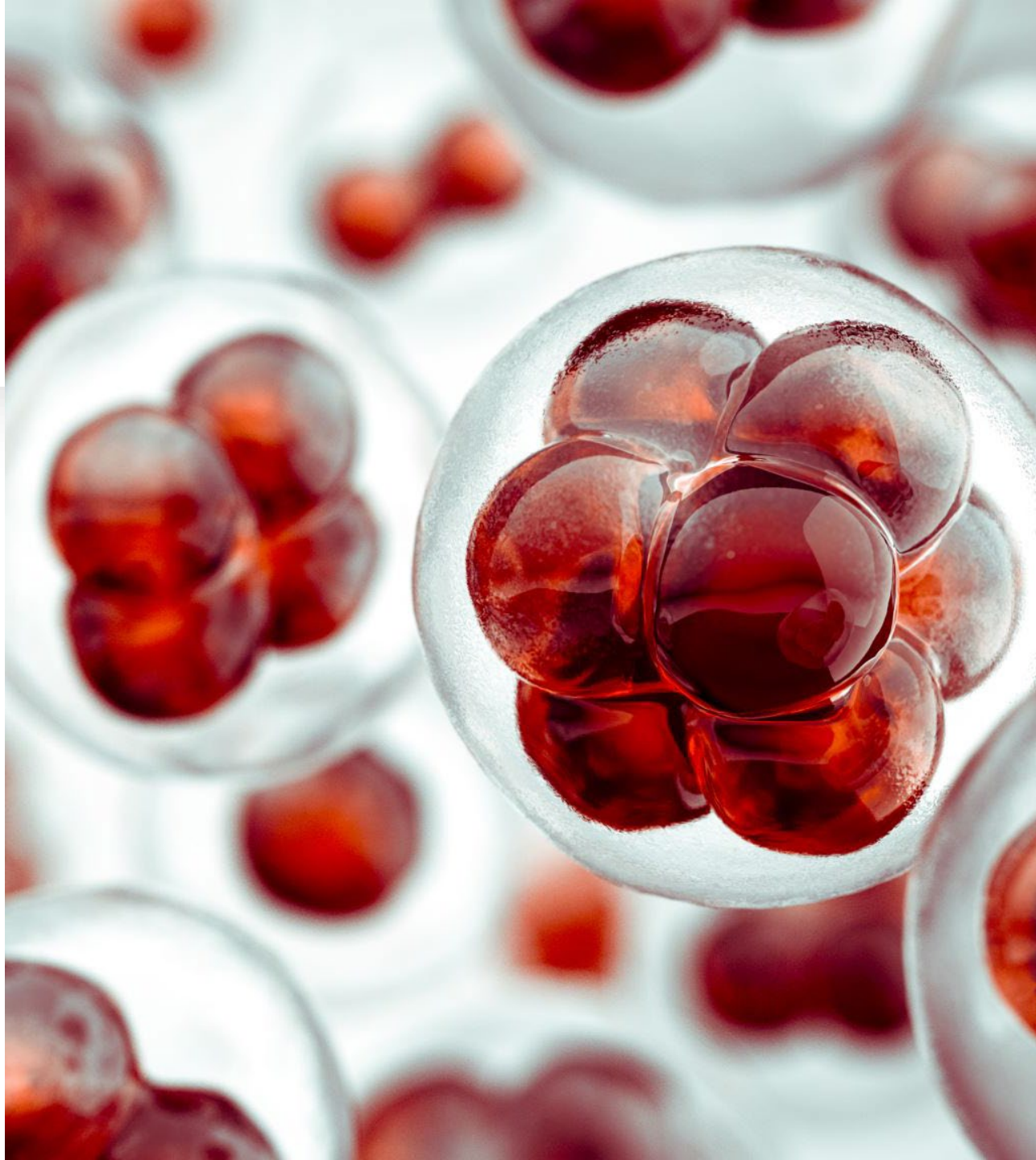
Innovative Research Directions:

Exploration of interventions that address vascular abnormalities to slow or prevent AD progression.

Potential for multi-target strategies that include vascular health as a key component.

Receptors of Neurotransmitters & Enzymes in AD

- **Cognitive Impairment & Neurotransmitters**: Linking alterations in neurotransmitter receptors to cognitive decline in AD.
- **Receptor Modulation**: Exploring the potential of modulating neurotransmitter receptors as a therapeutic strategy.
- **Current Therapeutic Strategies**:
  - Focus on enhancing neurotransmission.
  - Targeting specific neurotransmitter systems for improved cognitive functions.
- **Phase-3 Clinical Trials**:
  - Investigating novel agents that modulate neurotransmitter receptors.
  - Aimed at addressing cognitive impairment through receptor modulation.



Free Radicals & Oxidative Stress in AD

Oxidative Stress in AD: Identifies oxidative stress as a primary driver of Alzheimer's disease, contributing to neuronal damage and progression.

Role of Free Radicals:

- Produced by normal cellular metabolism but exacerbated in AD.
- Damage cellular components, leading to neuron dysfunction and death.

Antioxidants as Therapeutic Agents:

- Neutralize free radicals, reducing oxidative stress.
- Potential to protect neurons and slow AD progression.

Innovative Therapies in Development:

- Phase-3 trials exploring antioxidants and free radical scavengers.
- Aim: To manage AD pathology by reducing oxidative damage.

Highlighted Clinical Trials:

- **Hydralazine**: Free radical scavenger, potentially reducing oxidative stress.
- **Icosapent Ethyl**: Derived from omega-3 fatty acid, aimed at synaptic function improvement and inflammation reduction.
- **Omega-3 (DHA+EPA)**: Antioxidants, supporting brain health by combating oxidative stress.

Neuronal Metabolism & Bioenergetics in Alzheimer's Disease

Neuronal Energy Demands:

- The brain's high energy requirements and the critical role of efficient metabolism in maintaining cognitive functions.
- AD characterized by disrupted glucose metabolism and mitochondrial dysfunction.

Impact on AD Progression:

- Disruption in energy supply leads to synaptic loss, neurodegeneration, and cognitive decline.
- Mitochondrial dysfunction as a key contributor to AD pathophysiology.

Therapeutic Opportunities:

- Targeting metabolic pathways and mitochondrial function as novel strategies for AD intervention.
- Potential of dietary and metabolic interventions to enhance cerebral bioenergetics and prevent neurodegeneration.

Innovations in Phase-3 Trials:

- **BPDO-1603**: Aims at enhancing neuronal regeneration and reducing apoptosis.
- **Caffeine**: Explored for its potential to improve neurotransmission by antagonizing adenosine receptors.
- **Metformin**: Investigated for its insulin-sensitizing effects to improve central nervous system (CNS) glucose metabolism.
- **Nabilone**: A synthetic cannabinoid, acting through CB-1 receptor type as an agonist to modulate neuronal energy use.
- **Tricaprilin**: Induces ketosis to improve mitochondrial and neuronal function, targeting bioenergetic deficits in AD.

Brexpiprazole for Agitation

Agitation in Alzheimer's Disease (AD)

- Prevalence: Affects up to 90% of AD patients
- Impact: Accelerates cognitive decline, increases long-term care needs

Brexpiprazole: A Milestone in Treatment

- FDA-approved for AD-related agitation
- Offers a new pharmacological strategy for managing neuropsychiatric symptoms

Clinical Trial Insights

- Design: 12-week, randomized, placebo-controlled study
- Efficacy: Significant improvement in agitation scores (Cohen d 0.35)
- Safety: Well tolerated, with a cautious note on mortality risk

Clinical Practice Recommendations

- Indicated for severe agitation and aggression post nonpharmacological attempts
- Emphasis on judicious use and ongoing monitoring

Black Box Warning

- Psychosis in dementia

Conclusion

- Brexpiprazole represents a promising advancement in Alzheimer's care
- Highlights the importance of innovative treatments in addressing complex neuropsychiatric symptoms

Ballard, C. (2023). Brexpiprazole for the treatment of agitation and aggression in Alzheimer disease. *JAMA neurology*, *80*(12), 1272-1273.

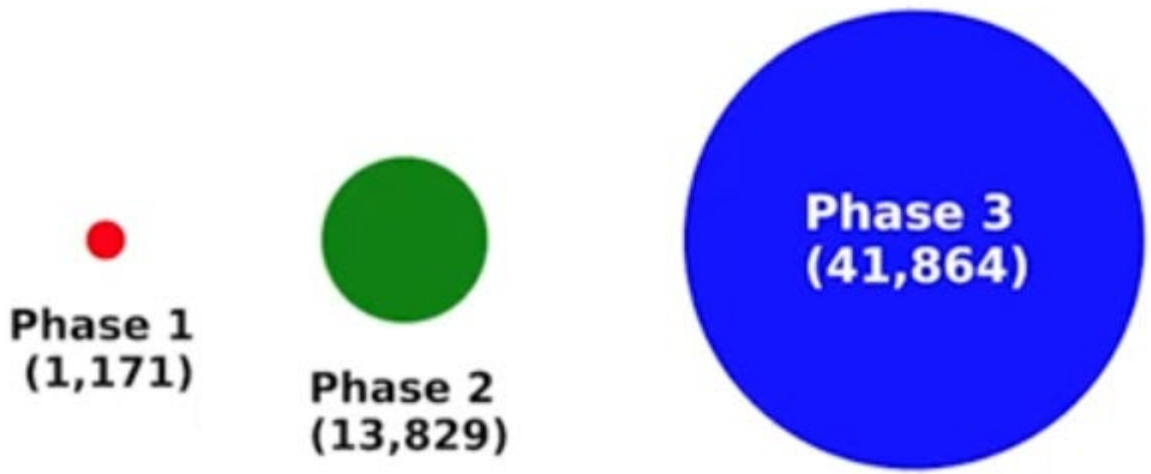
What's Coming

- Biologics rule
  - More monoclonal antibodies (amyloid, tau, inflammatory targets)
  - RNA therapeutics (ASOs and related)
  - Vaccines
  - Gene therapy (*APOE*, *APP*, etc)
  - Stem cell therapies
- Mechanisms for getting drugs/antibodies across the blood brain barrier (e.g., trontinemab; RO7126209)
- Psychotropics for psychosis, depression, apathy in Alzheimer's disease

Currently Active Trials Require 57,465 Participants

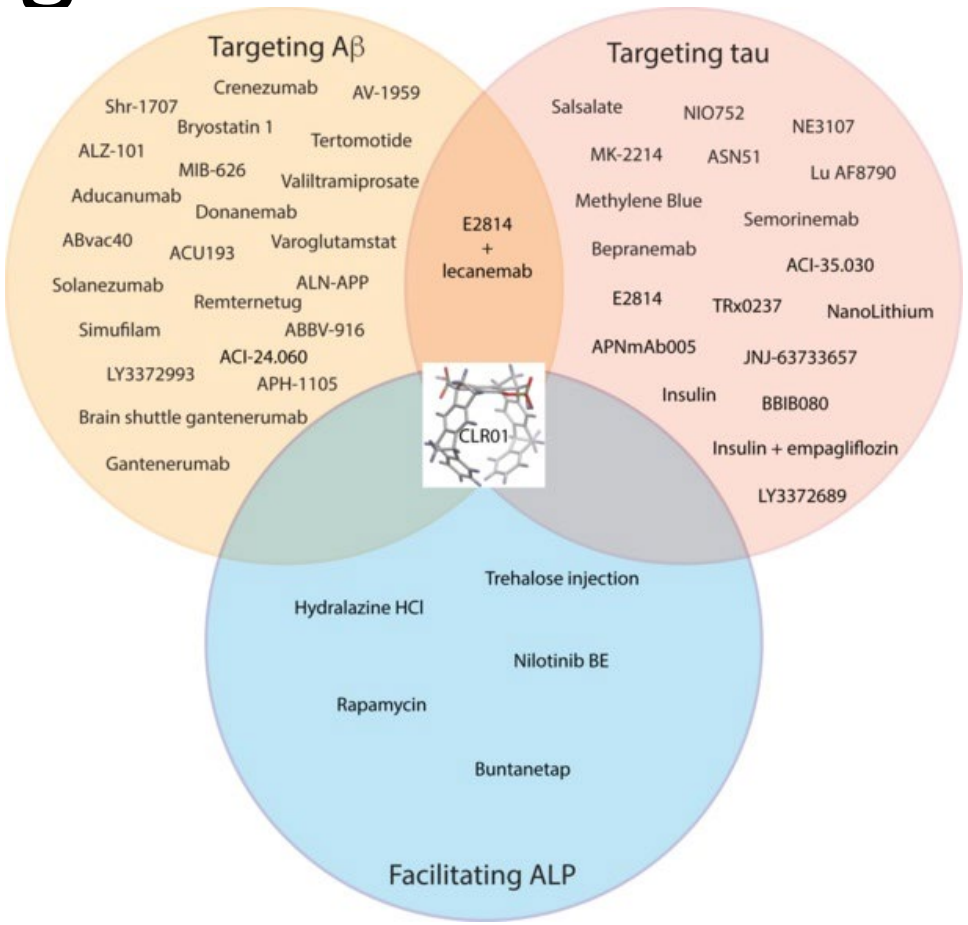
Participants Need for Currently Active Trials (Phase 1, 2, 3)

- Not enough good sites
- Slow recruitment
- Globalization required for large (Phase 3) trials



Cummings J, et al. Alz&Dem: TRCI 2023 9(2)e12385. doi: 10.1002/trc2.12385

Drug candidates targeting Aβ and/or tau or facilitating degradation via the ALP



Neural Regeneration Research19(9):1877-1878, September 2024.

Universe of Drugs in the 2023 and 2024 Alzheimer's Drug Development Pipelines

	2023	2024
Trials	187	171
Drugs	141	134
DMTs	78%	77%
DMT biologics	35%	34%
DMT small Mol	44%	43%
Cog enhancers	11%	12%
NPS sx	11%	12%
Repurposed	40 (28%)	53 (40%)

Cummings J, et al. Alz&Dem: TRCI 2023 9(2):e12385. doi: 10.1002/trc2.12385; NCEs – New Chemical Entities
2024 data being QC'd

Alzheimer's Prevention Trials

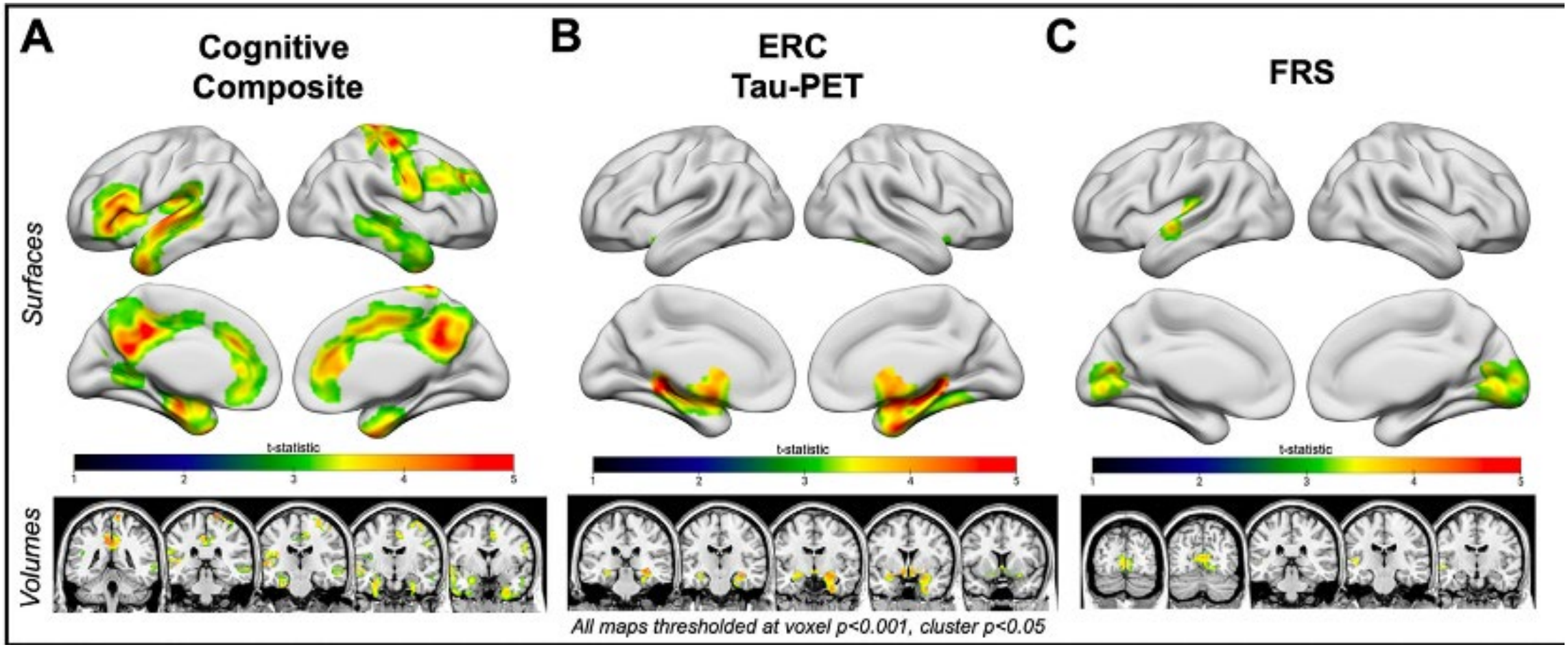
- **Objective**: Aiming to postpone the start of cognitive decline.
- **Leading Trials**:
  - AHEAD study with Lecanemab.
  - TRAILBLAZER 3 with Donanemab.
- **Trial Participants**:
  - Individuals without cognitive symptoms but with brain scans indicating early Alzheimer's changes.
- **Current Status**:
  - Enrollment completed; outcomes pending.
- **Trial Focus**:
  - Secondary prevention strategies under evaluation.
  - Primary prevention trials have not yet commenced.
- **Research Goals**:
  - Exploring whether memory impairment onset can be delayed.
  - Anticipating results by 2027.

Nonpharmacologic trials

FINGERS

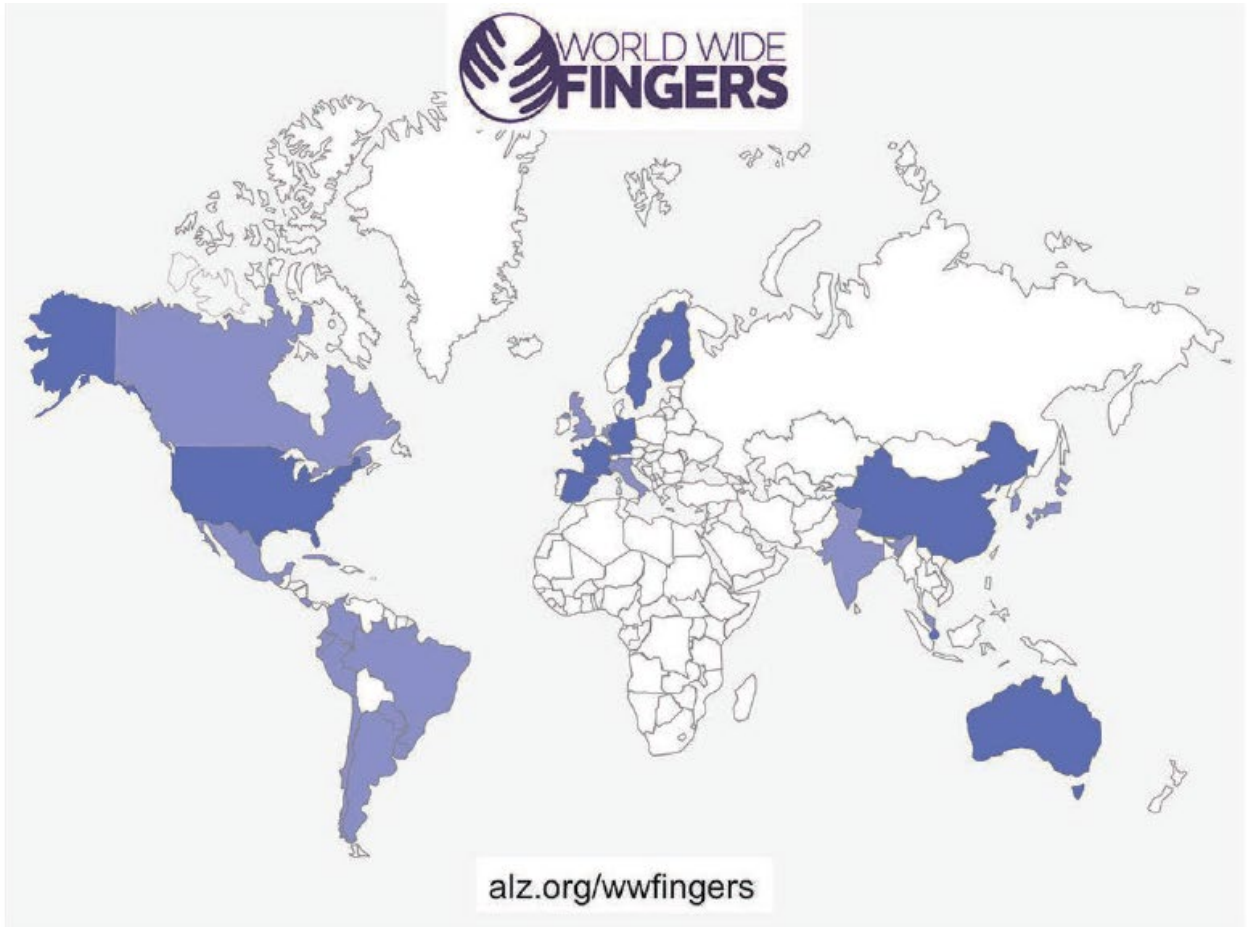
POINTERS

U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. POINTER)



The impact of Alzheimer's disease pathology and cardiovascular risk factors on cross-sectional brain structure in the U.S. POINTER Imaging study
Theresa M. Harrison, Tyler J. Ward, Samuel N. Lockhart, Prashanthi Vemuri, Laura Lovato, Heather M Snyder, Laura D Baker, Robert A. Koeppe, Charles Decarli … See all authors
25 December 2023. https://doi.org/10.1002/alz.079145

Finnish Geriatric Intervention Study (FINGERS)

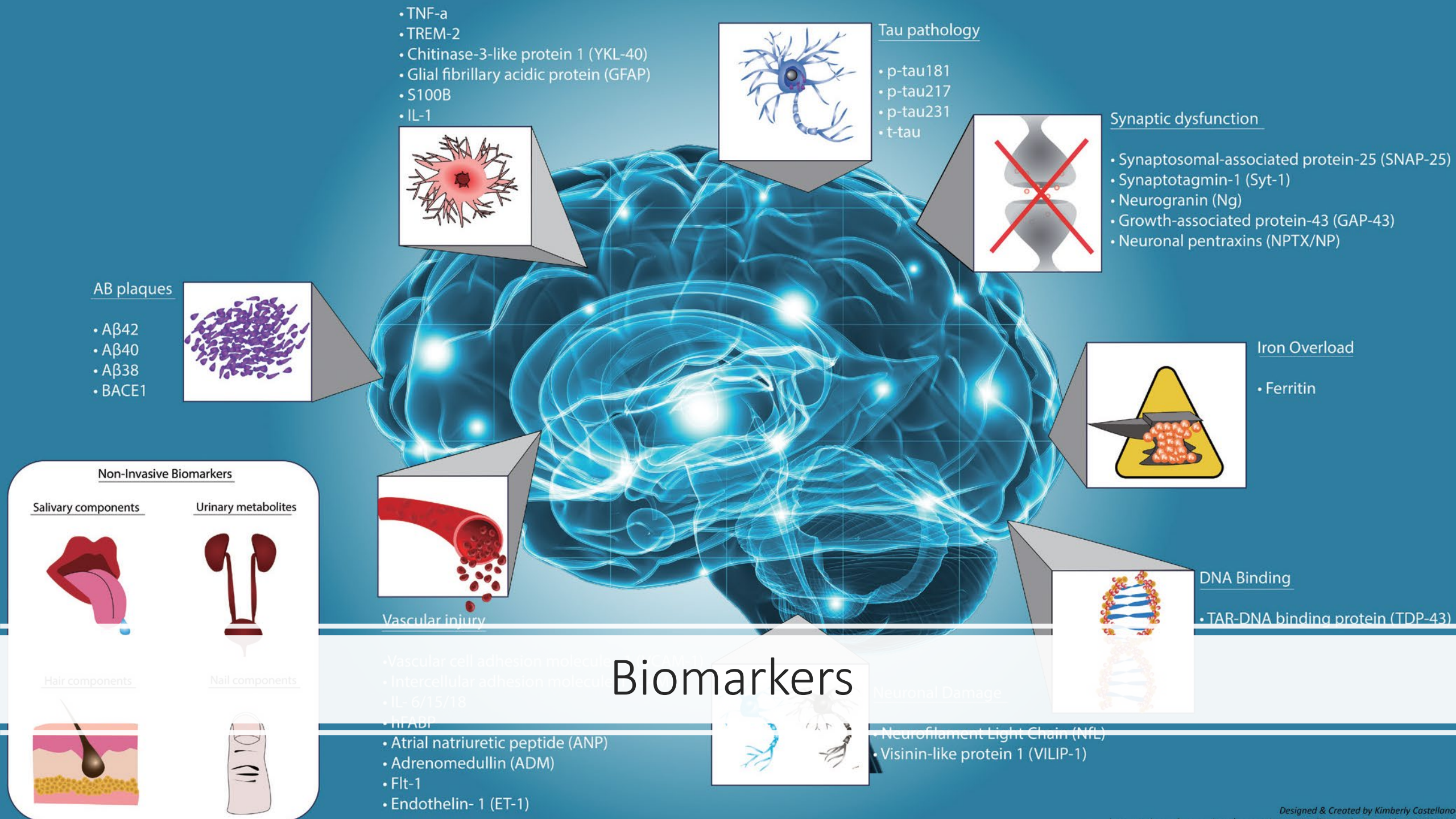


Rosenberg, A., Mangialasche, F., Ngandu, T. *et al.* Multidomain Interventions to Prevent Cognitive Impairment, Alzheimer's Disease, and Dementia: From FINGER to World-Wide FINGERS. *J Prev Alzheimers Dis* **7**, 29–36 (2020). https://doi.org/10.14283/jpad.2019.41

OPEN TO ENROLLMENT– CAREGIVER STUDY

- Caregiver characteristics that may be associated with the optimal care of patients with AD – investigates characteristics that may predict changes in caregiving over the course of 3 years
- Investigator initiated – no treatment
- We hope to enroll 217 couples – patients and their spouse or partner (not children)
- Couples will have a one-time visit in the clinic, questionnaires mailed to them every 6 months, phone call interview every 2 months
- Key inclusion – MMSE of <24, patient and spouse at least 70 years old, patient must live at home, not in a care facility
- Stephanie Kohlrus, is the contact for this study – and can be reached at skohlrus@siumed.edu or 217.545.3013.

Biomarkers


• TNF-a
• TREM-2
• Chitinase-3-like protein 1 (YKL-40)
• Glial fibrillary acidic protein (GFAP)
• S100B
• IL-1
Tau pathology
• p-tau181
• p-tau217
• p-tau231
• t-tau
Synaptic dysfunction
• Synaptosomal-associated protein-25 (SNAP-25)
• Synaptotagmin-1 (Syt-1)
• Neurogranin (Ng)
• Growth-associated protein-43 (GAP-43)
• Neuronal pentraxins (NPTX/NP)
AB plaques
• Aβ42
• Aβ40
• Aβ38
• BACE1
Iron Overload
• Ferritin
Non-Invasive Biomarkers
Salivary components
Urinary metabolites
Hair components
Nail components
Vascular injury
DNA Binding
• TAR-DNA binding protein (TDP-43)
• Atrial natriuretic peptide (ANP)
• Adrenomedullin (ADM)
• Flt-1
• Endothelin- 1 (ET-1)
• Visinin-like protein 1 (VILIP-1)
Designed & Created by Kimberly Castellano

Biomarkers Used in Clinical Trials have a Defined Context of Use (CoU)

Context of Use	Biomarker
Risk	APOE genotyping; tau PET
Diagnosis	Amyloid PET; CSF A$\mathcal{B}$ 42/40; ADAD mutation
Prognosis	Tau PET; p-tau 181, 217; GFAP
Pharmacodynamic; target engagement	SILK; CSF A$\mathcal{B}$; drug mechanism-related
Pharmacodynamic; disease modification	ATX(N)
Monitoring	p-tau 181, 217; GFAP
Predictive	Amyloid reduction on PET (accelerated approval); APOE4 predicts ARIA risk
Safety	MRI for ARIA

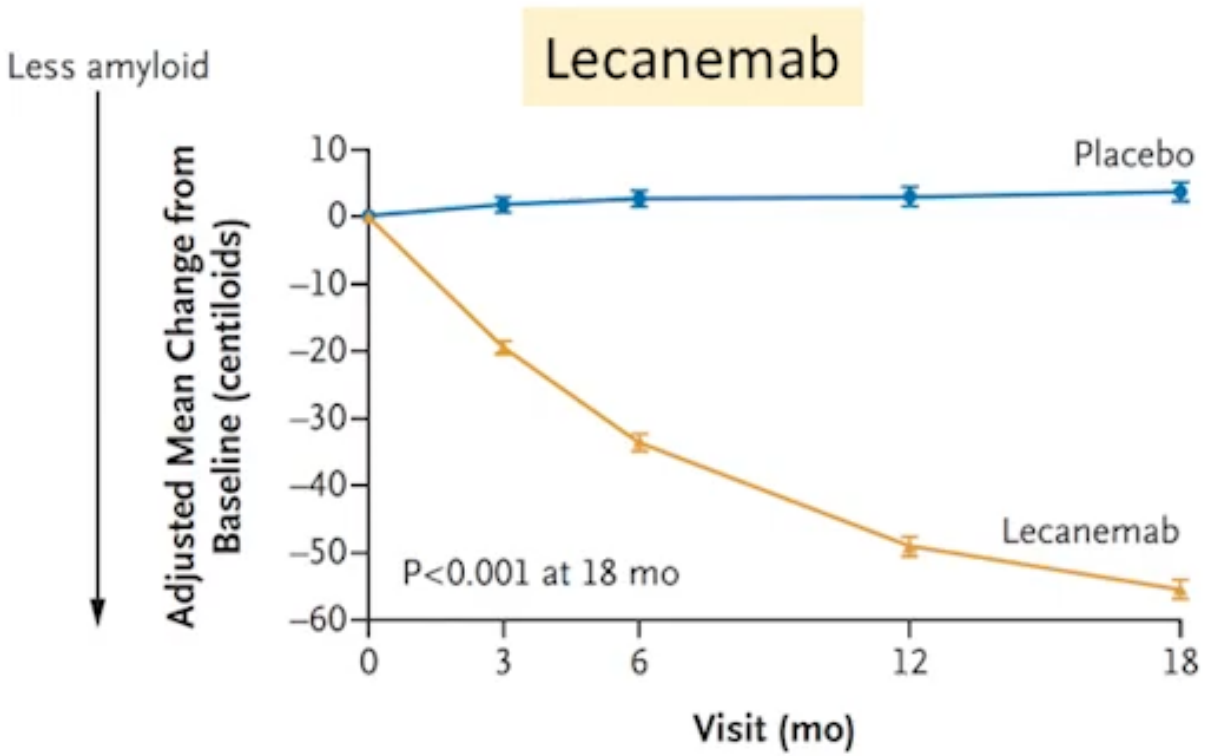
A$\mathcal{B}$ - amyloid beta protein; ADAD – autosomal dominant Alzheimer's disease; APOE – apolipoprotein E; ARIA – amyloid related imaging abnormalities; ATX(N) – amyloid, tau, "other", neurodegeneration; CSF – cerebrospinal fluid; GFAP – glial fibrillary acidic protein; PET – positron emission tomography; p-tau – phosphorylated tau; SILK – stable isotope labeled kinetics

FDA-NIH Biomarkers Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource, 2021

Biomarkers

Question	Biomarker Information
Who is in the trial?	Diagnostic biomarkers
How much will the placebo group decline?	Prognostic biomarker
Is my drug doing what I want?	Pharmacodynamic biomarker; target engagement
What effect is my drug having during the trial?	Monitoring biomarkers
Is my drug altering the disease biology?	Pharmacodynamic biomarker; disease modification
Do the biomarker changes imply clinical benefit?	Predictive biomarkers
Is my drug safe?	Safety biomarkers

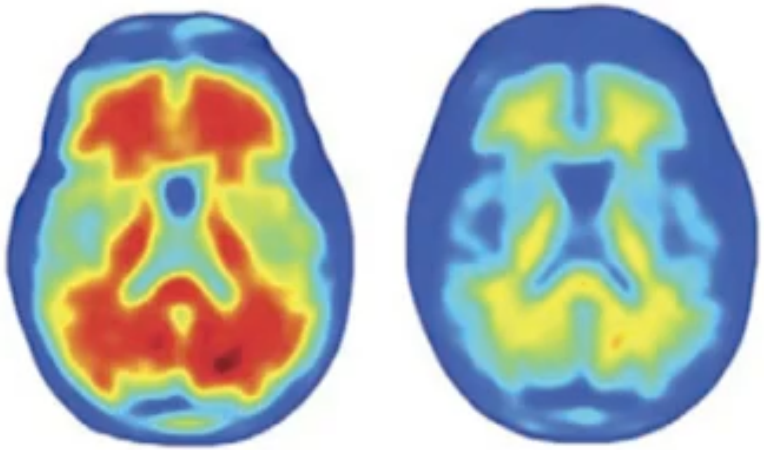
Amyloid PET: Diagnostic, Pharmacodynamic, and Predictive Biomarker in Anti-Amyloid Monoclonal Antibody Trials



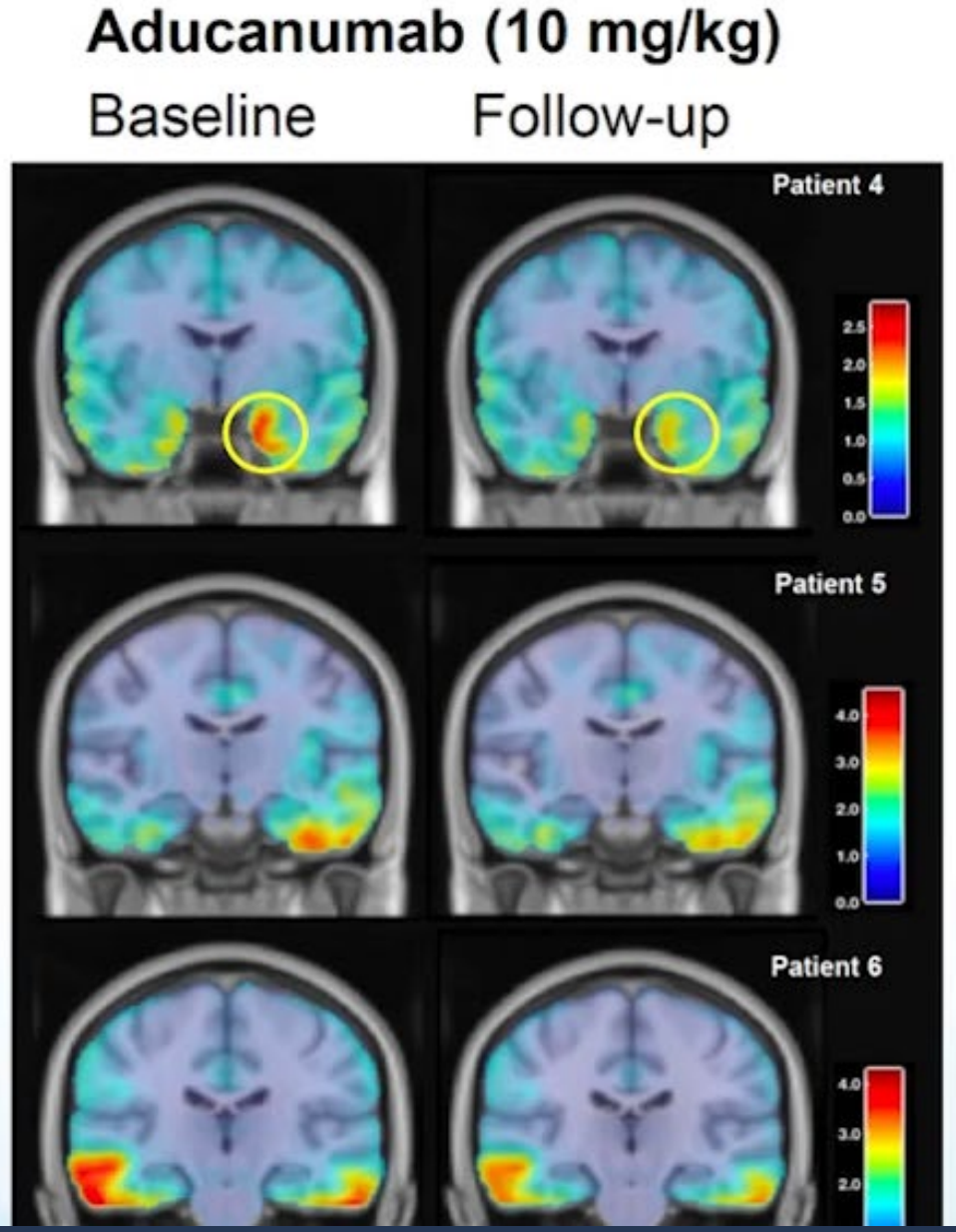
Amyloid PET

- Diagnostic: Positive at baseline
- Pharmacodynamic: Reduction at end of trial and a few interim points
- Predictive: reductions to 15-25 centiloid range are associated with slowing of clinical decline

Aducanumab: 10 mg/kg x 12 mo



van Dyck C, et al. New Engl J Med 2022; DOI: 10.1056/NEJMoa2212948;
images from [1]Sevigny J, et al. Nature 2016; 537; 50-56.



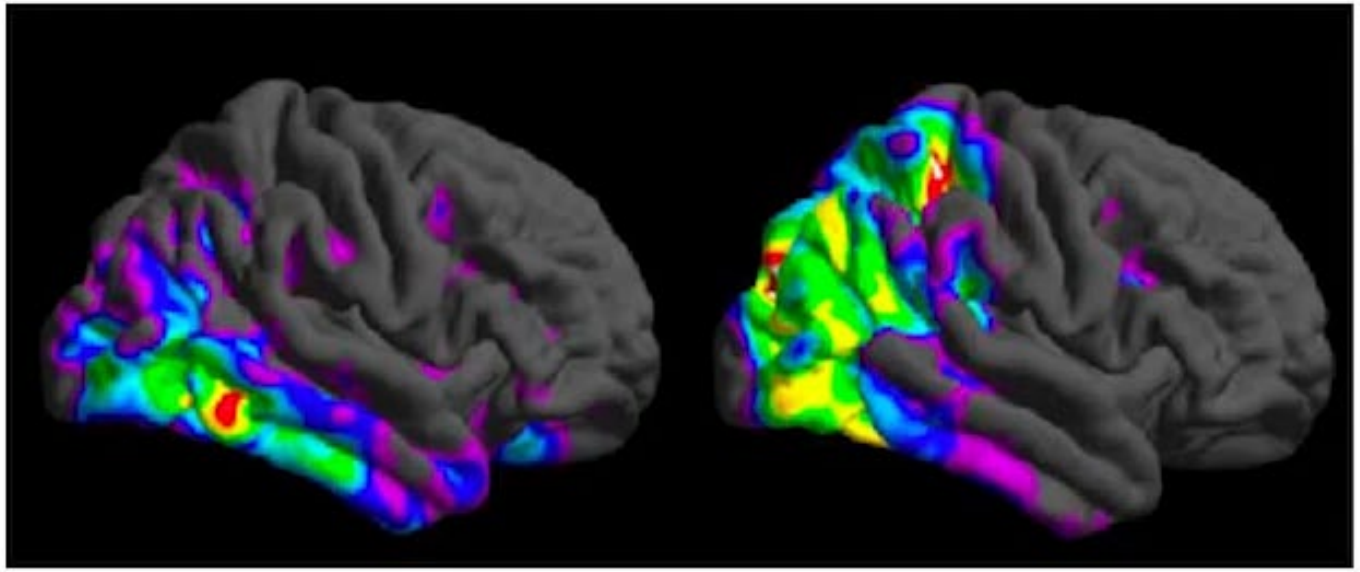
Tau PET: Pharmacodynamic Biomarkers in EMERGE and ENGAGE Trials of Aducanumab

- Decreased medial temporal neurofibrillary tangle ligand signal following aducanumab therapy

Neurofibrillary tangle signal reduction on tau PET

Budd Haeberlein S, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alzheimers

Tau PET: Prognostic Biomarker in the Donanemab TrailblazerALZ Trial



Intermediate tau levels required

- Ensure decline
- Patients with high levels might not respond

Mintun MA, et al. Donanemab in Early Alzheimer's Disease. N Engl J Med. 2021 May 6;384(18):1691-1704. doi: 10.1056/NEJMoa2100708.

pTau-217 & Plasma Assays

Plasma pTau-217 as a Promising Biomarker

Innovative Immunoassay Development

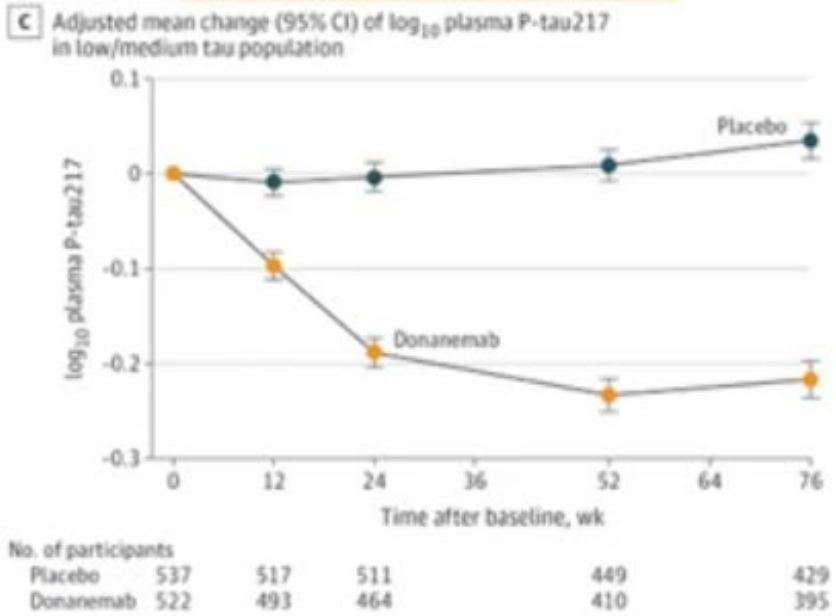
Diagnostic and Prognostic Value

Implications for Clinical Practice and Research

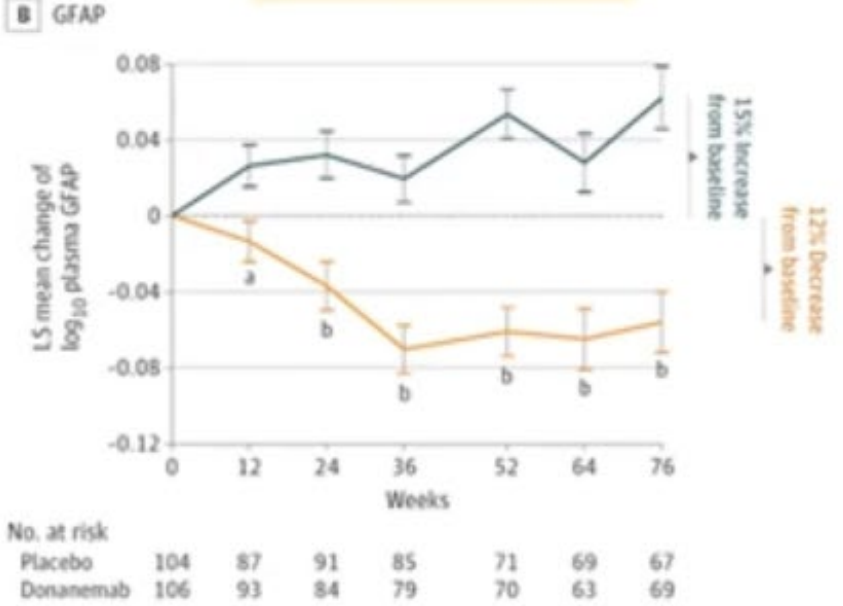
Future Directions

P-tau 217 and GFAP: Monitoring and Pharmacodynamic Biomarkers in the Donanemab Trailblazer Trials

P-tau 217; TrailblazerALZ-2

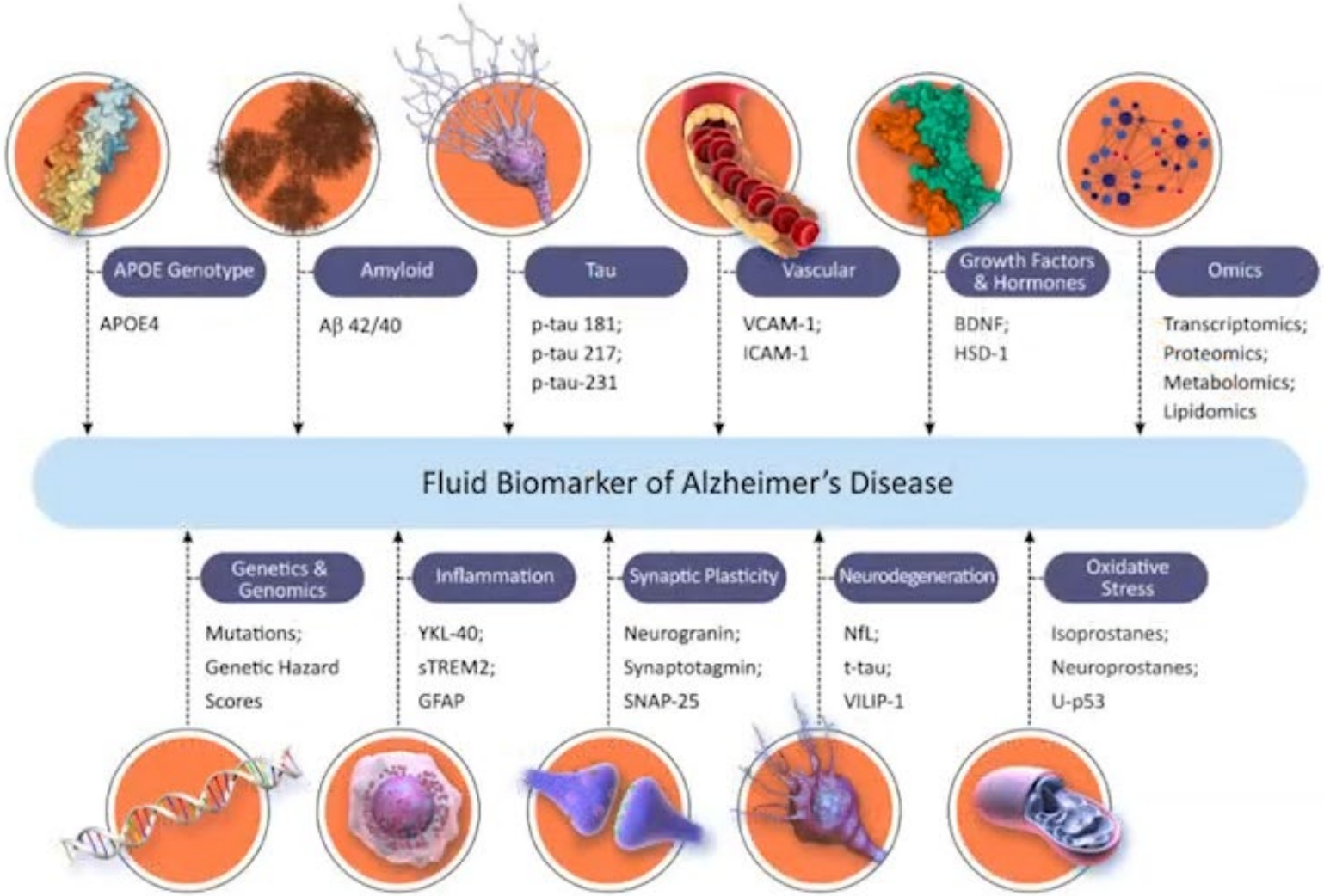


GFAP; TrailblazerALZ



Sims JR, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023; 330:512-527. doi: 10.1001/jama.2023.13239; Pontecorvo MJ, et al. Association of Donanemab Treatment With Exploratory Plasma Biomarkers in Early Symptomatic Alzheimer Disease: A Secondary Analysis of the TRAILBLAZER-ALZ Randomized Clinical Trial. JAMA Neurol. 2022; 79:1250-1259. doi: 10.1001/jamaneurol.2022.3392..

"X" of ATX(N) Will Add Additional Information



Cummings J, Kinney J. *Medicina* 2022; 58: 952-973; M de la Flor, PhD, illustrator; ©J Cummings

Hampel H, Cummings J, Blennow K, Gao P, Jack CR Jr, Vergallo A. Developing the ATX(N) classification for use across the Alzheimer disease continuum. Nat Rev Neurol. 2021;17:580-589

Emerging Trends in Alzheimer's Drug Development

Milestone Achievements:

Celebrating the first approved therapies that modify Alzheimer's disease progression.

Journey Ahead:

Newly approved treatments mark the first steps towards effectively arresting AD.

Focus on Modification:

The majority of the drug pipeline is dedicated to altering the disease process.

Diverse Drug Targets:

A broad array of targets and agents is currently being investigated.

The Scale of Trials:

An estimated 60,000 participants are engaged in ongoing Alzheimer's trials.

The Role of Biomarkers:

Biomarkers are enhancing the efficiency of clinical trials and aiding drug development.

Each biomarker has its specific utility within clinical trial settings.

ALZHEIMER'S NEUROLOGY CLINICAL RESEARCH TEAM

- Jennifer Arnold, MD, PhD – Principal Investigator
- Tom Ala, MD – Principal Investigator/Sub-Investigator
- Cindy Womack, DNP – Sub-Investigator
- Amber Fifer, PharmD, ACRP-CP – Research Assistant Professor of Neurology and Psychiatry
- Andre Catalano, PharmD, MBA – Research Assistant Professor of Neurology
- Stephanie Kohlrus, BA, CCRP – Senior Clinical Research Coordinator
- Ann Jirmasek, BS, MA, LPC, NCC – Rater
- Amy Richey, LPN – Rater
- Sara Boarman, BS – Clinical Research Coordinator
- Rylee Manka, BA – Clinical Research Specialist
- Mary (Missy) Cartwright, RN, BSN – Research Nurse
- Megan Meinke, MD – Post-Doctoral Fellow

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