Hitting the target: the first Alzheimer's-specific treatments are approved

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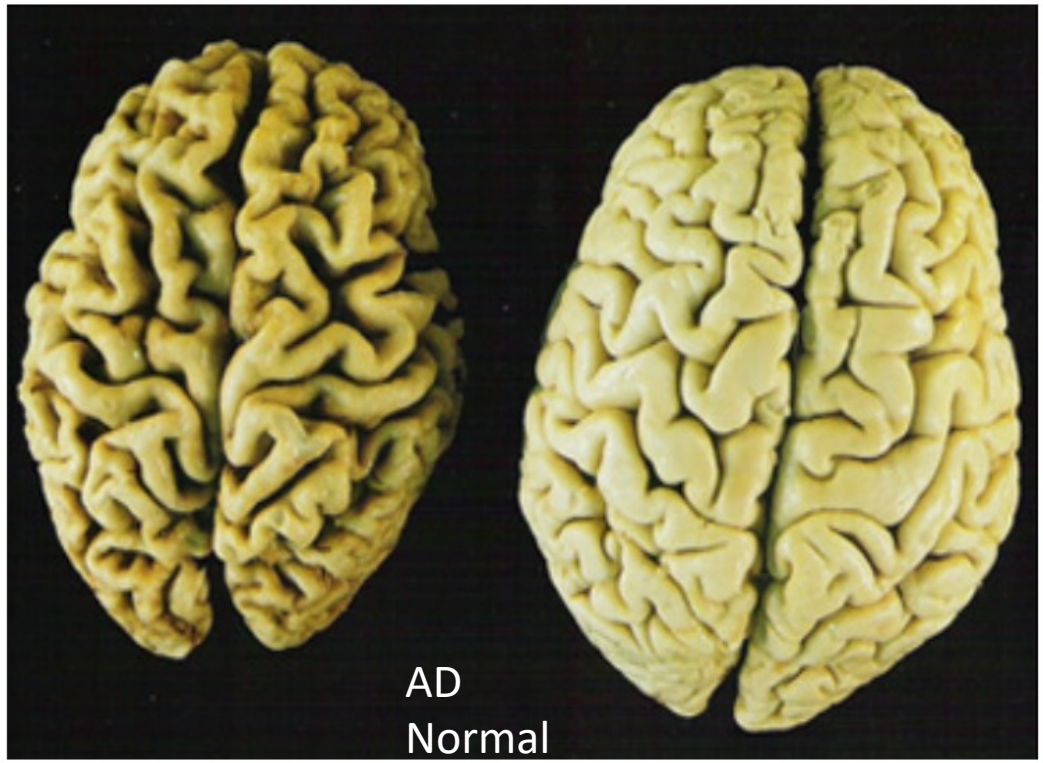
Disclosures/Conflict of Interest

- I am site-principal investigator for Alzheimer's disease clinical trials sponsored by Alector, Cognition Therapeutics, Eisai, Eli Lilly, Vivoryon, and the National Institute on Aging.

Hallmarks of Alzheimer's Disease

- With the naked eye: shrinkage of the brain *(cerebral atrophy)*
- Under the microscope: amyloid plaques and neurofibrillary tangles



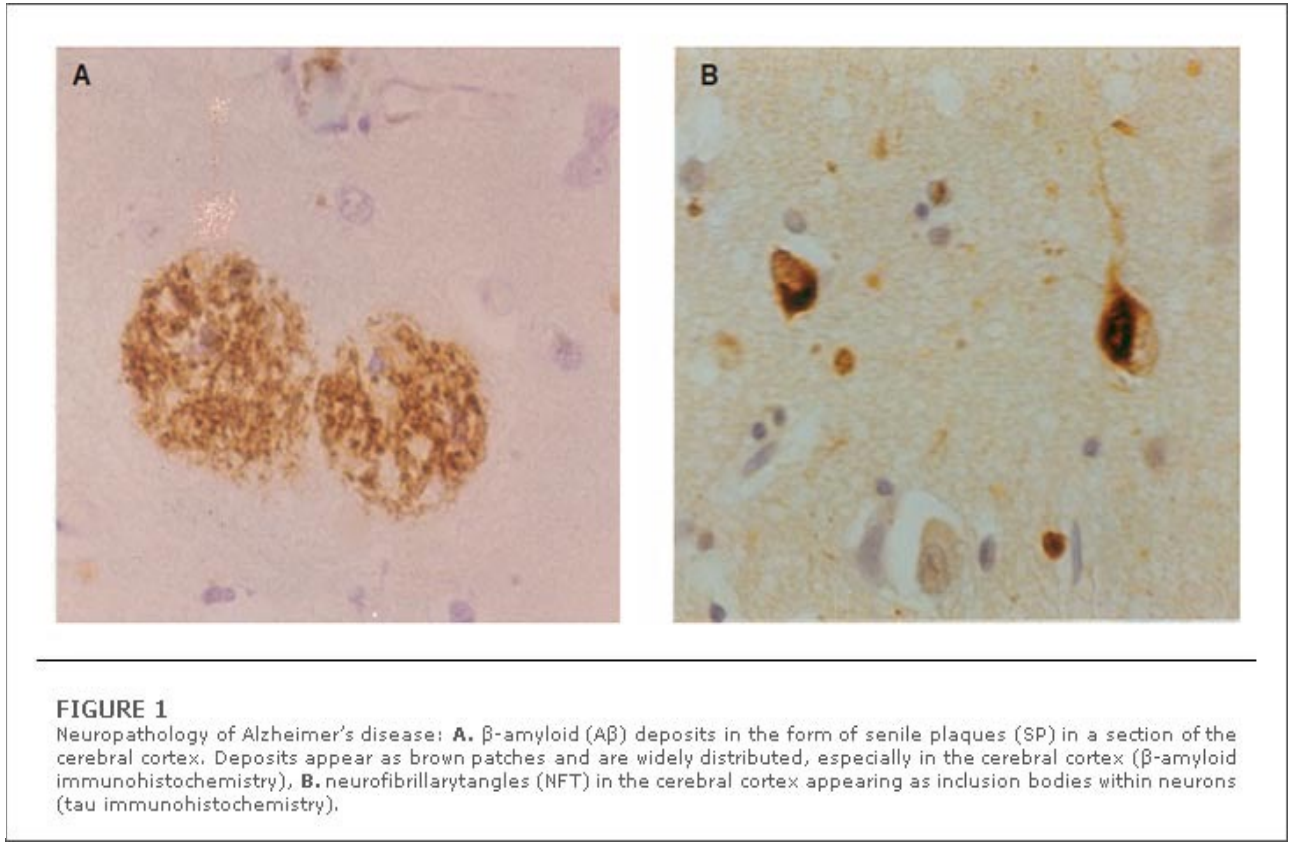


FIGURE 1
Neuropathology of Alzheimer's disease: **A.** β-amyloid (Aβ) deposits in the form of senile plaques (SP) in a section of the cerebral cortex. Deposits appear as brown patches and are widely distributed, especially in the cerebral cortex (β-amyloid immunohistochemistry), **B.** neurofibrillarytangles (NFT) in the cerebral cortex appearing as inclusion bodies within neurons (tau immunohistochemistry).

Alzheimer's markers can now be seen in patients

Brain imaging – PET scans

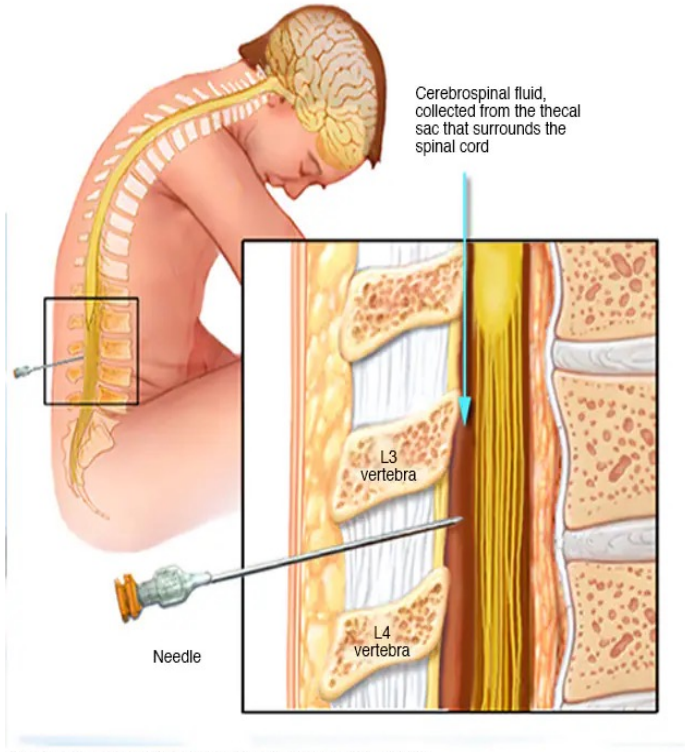
- Amyloid
- Tau

Cerebrospinal fluid (CSF)

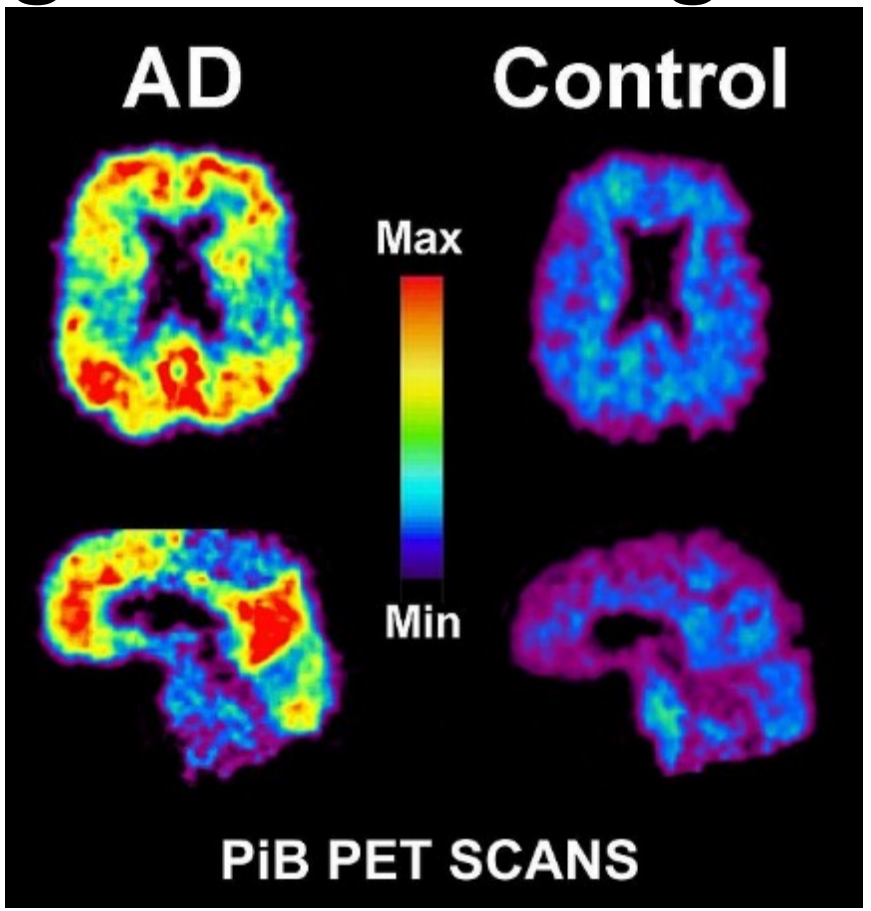
- Amyloid
- Tau

Blood

- Amyloid
- Tau



Amyloid PET scans - an advance for Alzheimer's diagnosis and targeted treatment

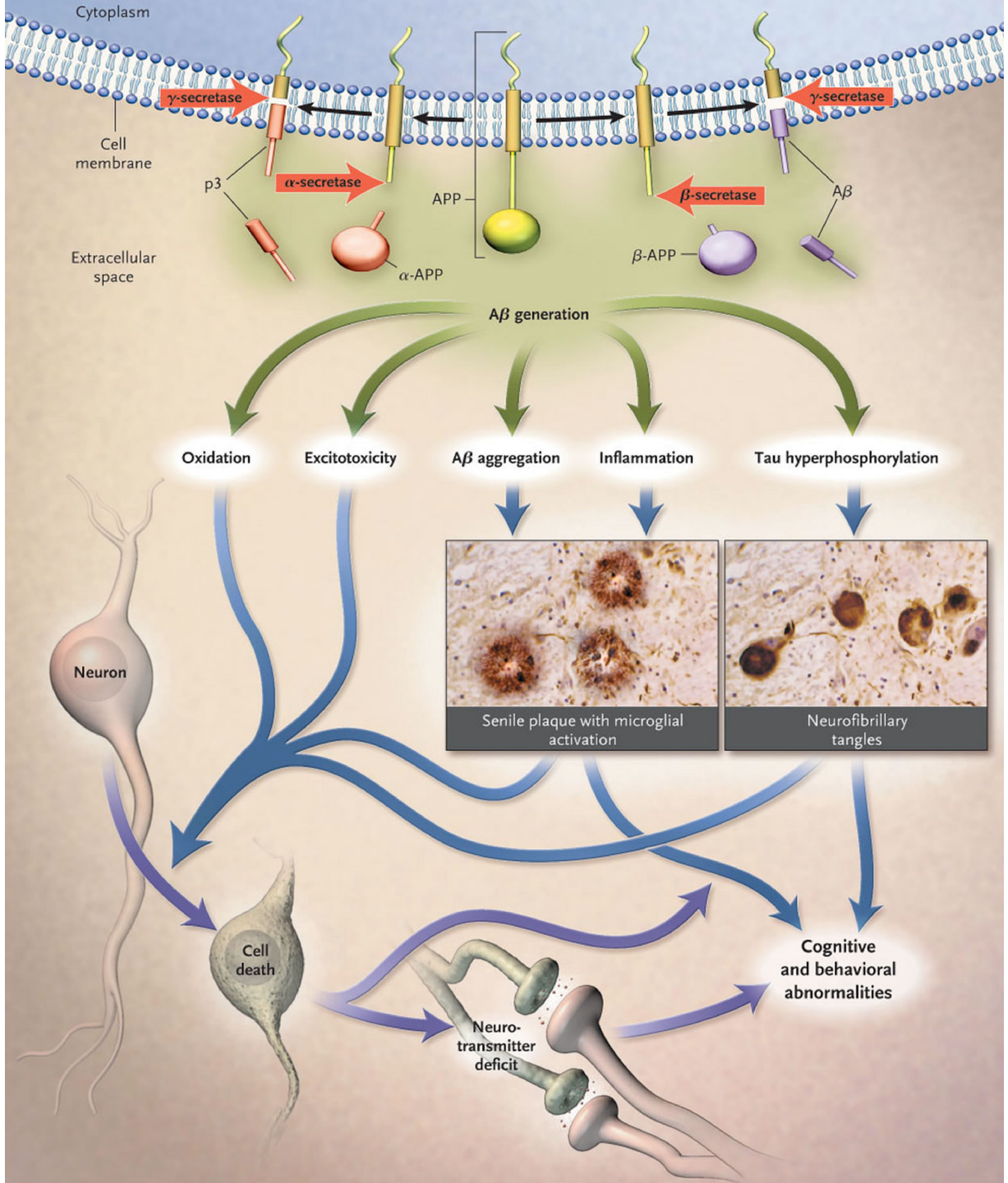


Sperling, Johnson, *NeuroMolecular Med,* 2010

Amyloid Cascade Hypothesis:

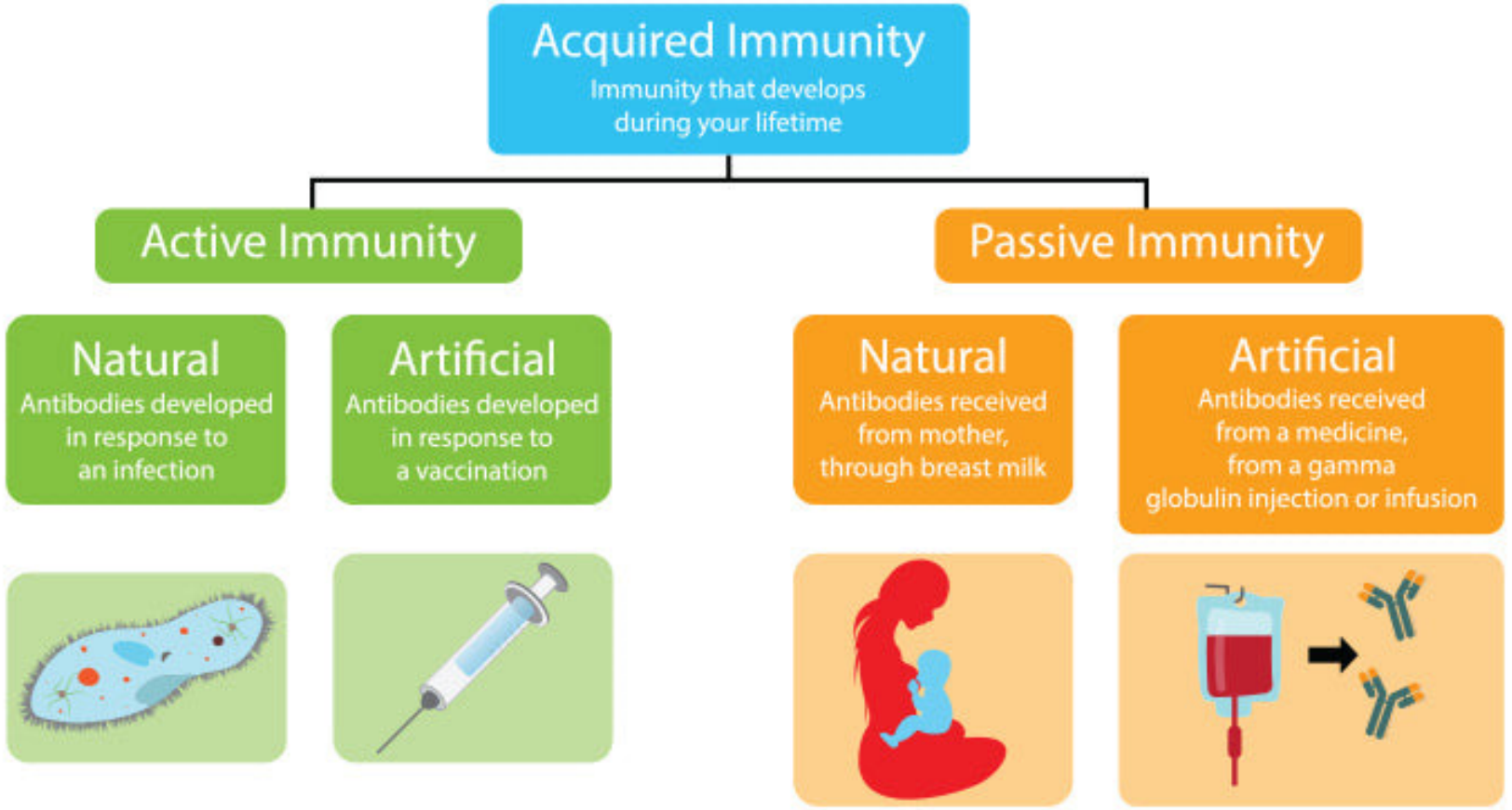
Deposition of amyloid in the brain is
- early
and
- critical

in the development of Alzheimer's disease



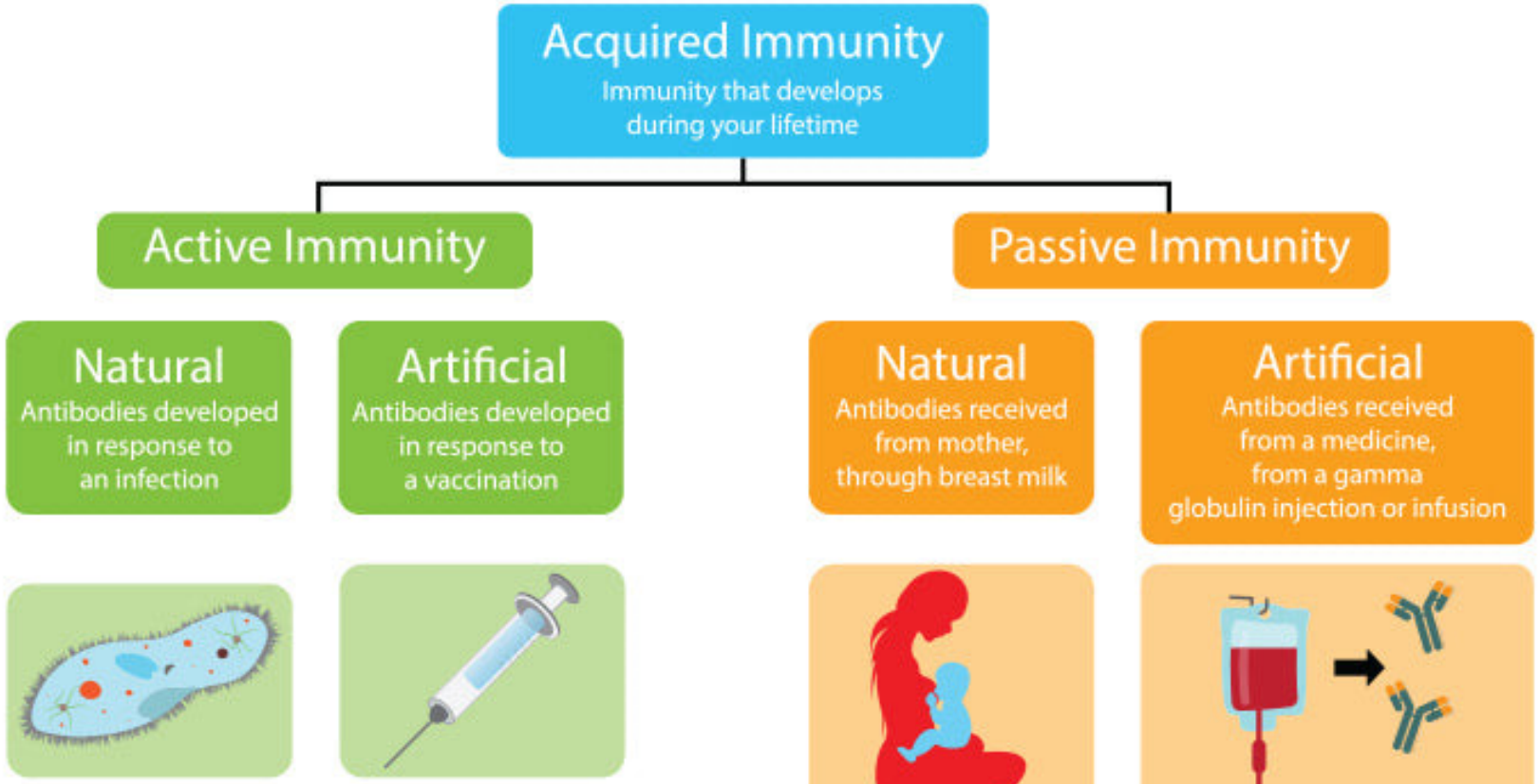
Ghareeb, El-Sayed, *J Biomed Sci and Eng*, 2013

Understanding the concept of immunity



NIH

Can we promote immunity to Alzheimer's disease?



Natural antibodies to amyloid are found in blood

Vaccine – amyloid, tau

Antibody therapy – amyloid, tau

NIH

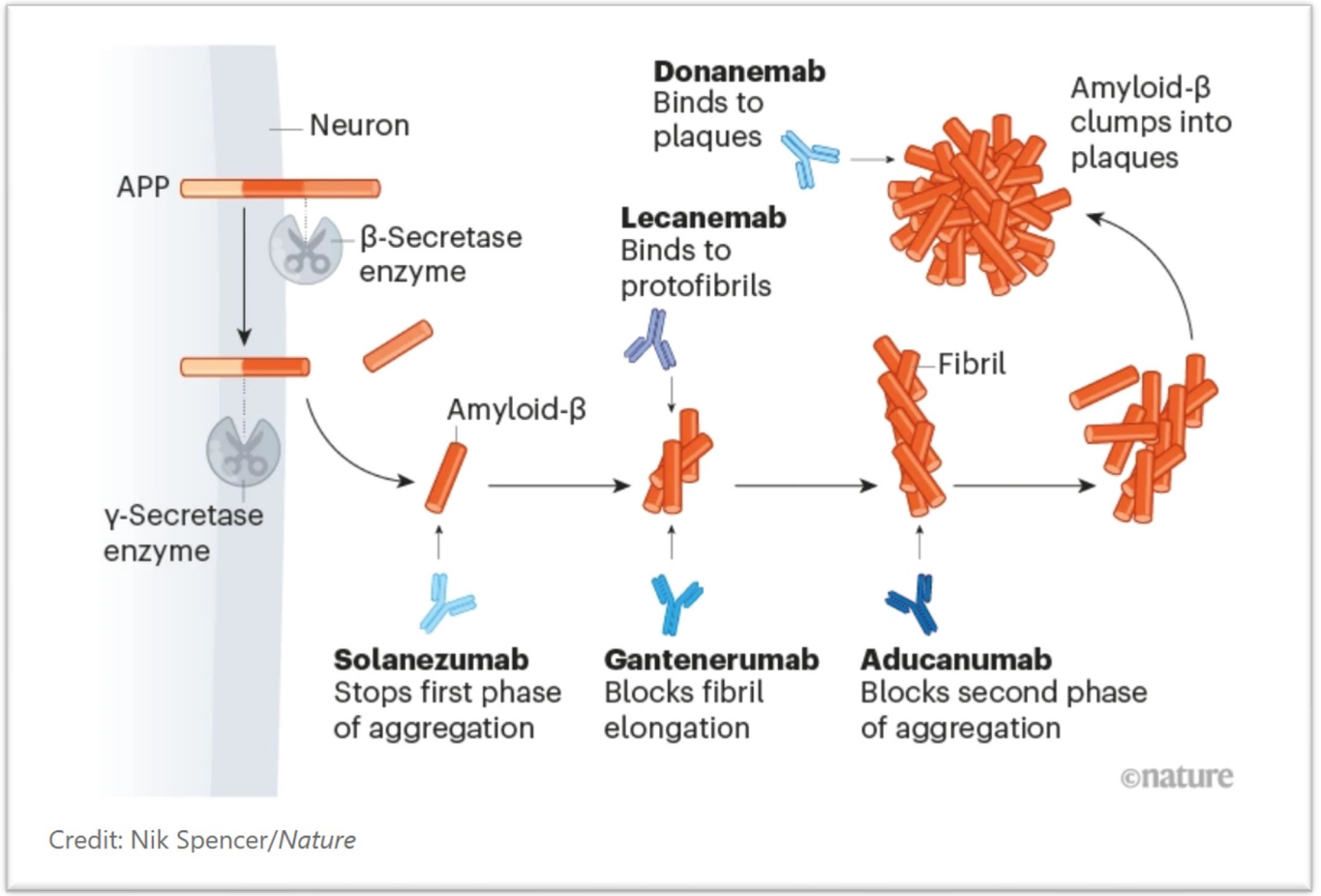
Anti-amyloid treatment

-Many clinical trials targeting amyloid were negative, until…

-FDA approval for anti-amyloid antibodies - aducanumab (2021), lecanemab (2023), donanemab (2024)

-Every antibody is different – those which can reduce plaques have shown benefit on memory

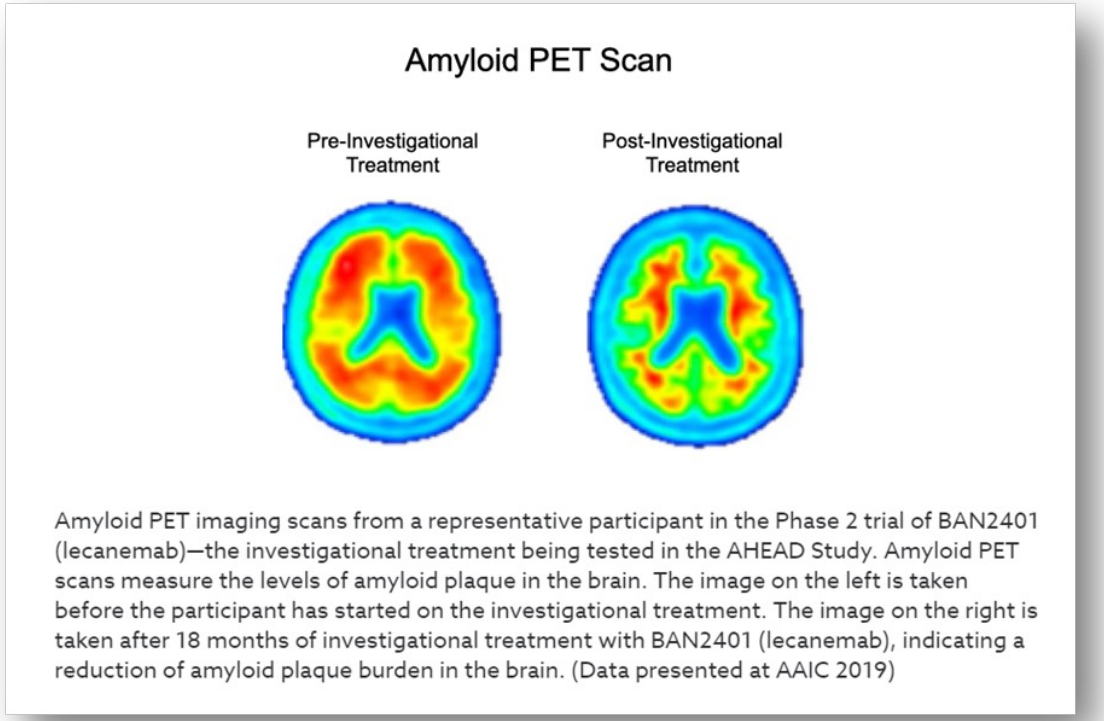
-Current trials selected participants more stringently and treat earlier and longer



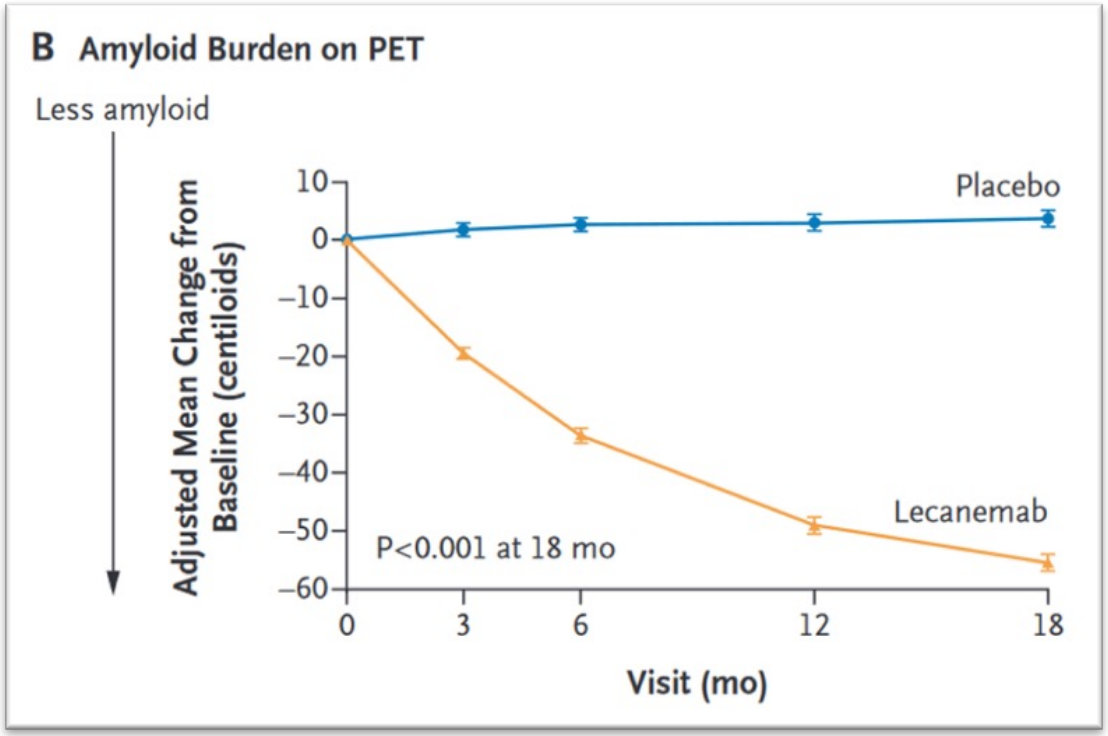
Abbott, *Nature* 2022.

Lecanemab reduced brain amyloid plaques

- Lecanemab – humanized monoclonal antibody that binds to soluble amyloid-beta protofibrils
- Lecanemab Phase 3 trial: 18 months, randomized, double-blind, placebo-controlled, 1795 participants, early Alzheimer's disease with evidence of amyloid-beta on PET brain



Amyloid PET imaging scans from a representative participant in the Phase 2 trial of BAN2401 (lecanemab)—the investigational treatment being tested in the AHEAD Study. Amyloid PET scans measure the levels of amyloid plaque in the brain. The image on the left is taken before the participant has started on the investigational treatment. The image on the right is taken after 18 months of investigational treatment with BAN2401 (lecanemab), indicating a reduction of amyloid plaque burden in the brain. (Data presented at AAIC 2019)



Van Dyck et al, *NEJM,* 2023.

Lecanemab slowed progression of cognitive and functional decline by 27% over 18 months

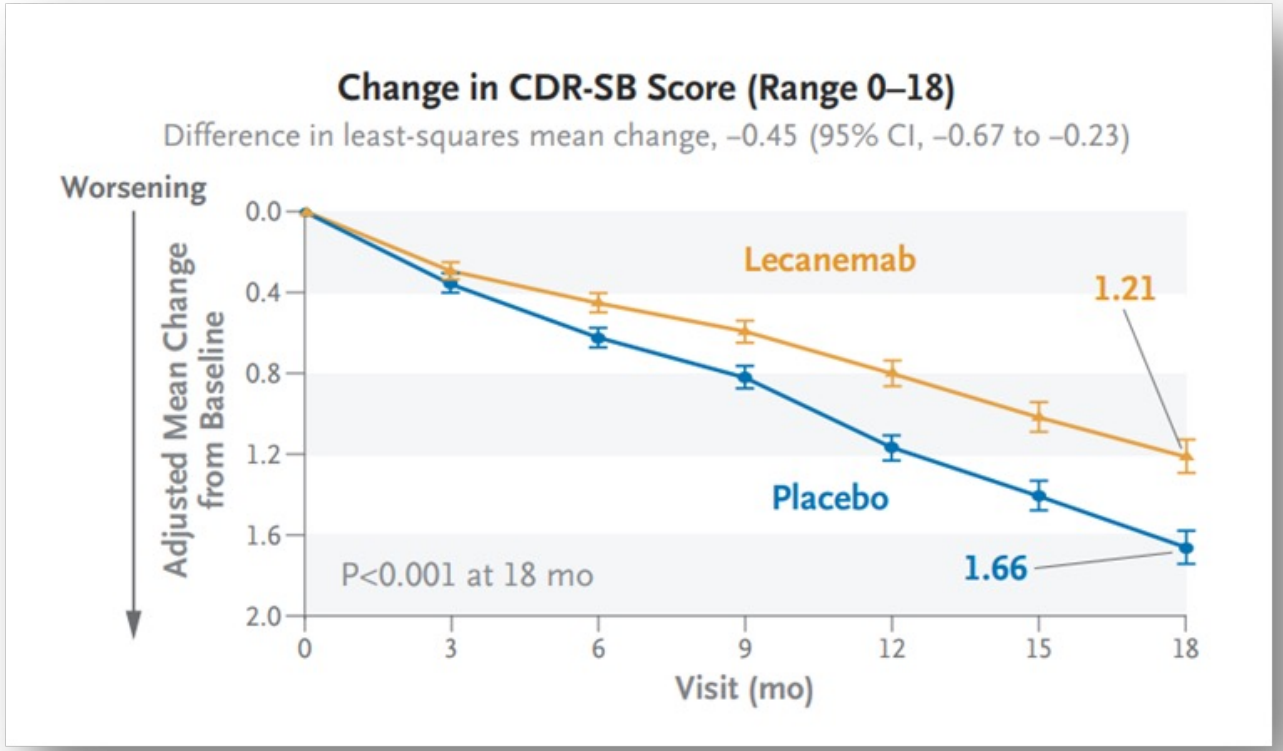
Primary end point: change in the score on the clinical dementia rating (CDR) – sum of boxes

Evaluates cognition and function in:

- Memory
- Orientation
- Judgement and Problem Solving
- Community Affairs
- Home and Hobbies
- Personal Care

Based on interview with participants and care partners

CDR-SB ranges from 0-18, higher score indicates advancing dementia, 0.5-6 indicates early AD



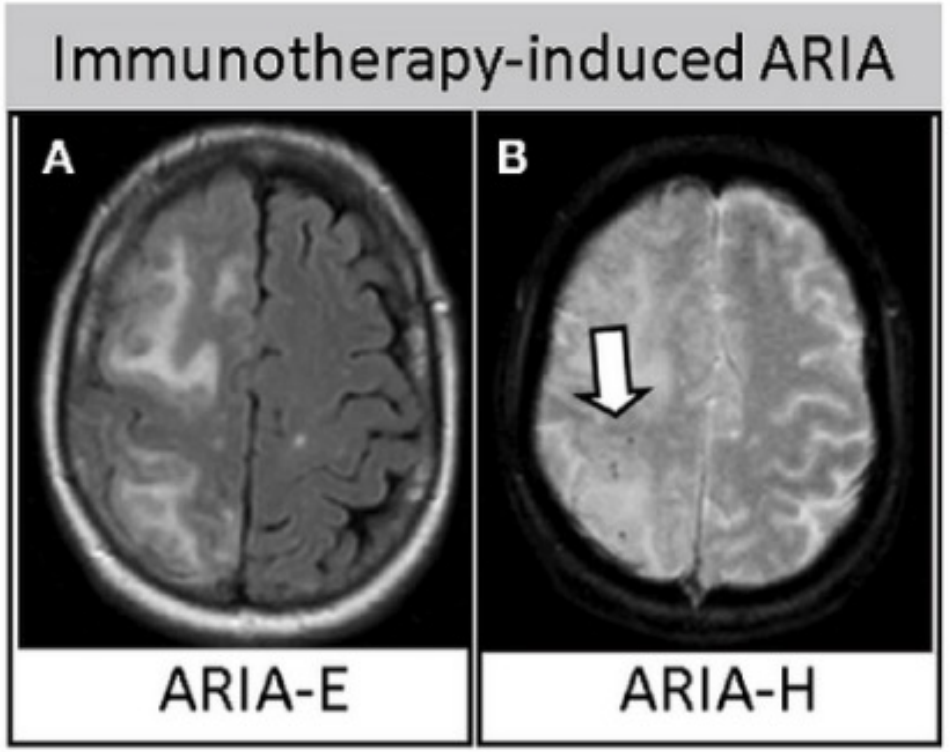
Van Dyck et al, *NEJM,* 2023.

Adverse effects of lecanemab

- Infusion-related reactions: 26% of patients receiving lecanemab (7% on placebo). Majority (75%) of reactions occurred with first infusion and were mostly mild or moderate
- Infusion-related reaction symptoms: fever, flu-like symptoms (chills, generalized aches, feeling shaky, joint pain), nausea, vomiting, blood pressure changes, drop in oxygen level
- Headache: 11% of patients receiving lecanemab (8% on placebo)

Black Box Warning - Adverse effects of lecanemab ARIA: Amyloid-related imaging abnormalities

- ARIA-E (edema), ARIA-H (hemorrhage)
- ARIA occurred in 21% of patients on lecanemab (9% on placebo)
- ARIA-E in 13% of patients overall on lecanemab (2% on placebo)
- ARIA-H in 17% of patients on lecanemab (9% on placebo)
- Symptomatic ARIA in 3% of lecanemab patients, 0.7% serious, symptoms resolved in 79%



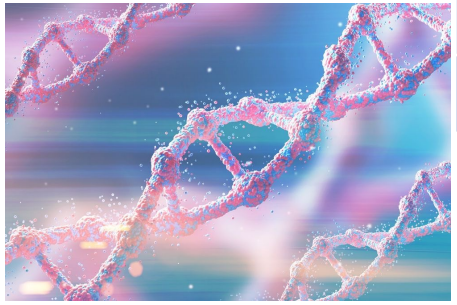
DiFrancesco J, *Frontiers in Neurology,* 2015.

- Symptoms: headache, confusion, visual changes, dizziness, nausea, gait difficulty, focal neurologic deficits (seizure)
- Monitoring for ARIA via MRI

ARIA risk is higher in APOE 4 carriers on lecanemab

- APOE 4 genotype is a strong genetic risk factor for Alzheimer's disease
- There are 3 possible variants of APOE gene: 2, 3, or 4
- One copy is received from each parent
- Higher risk of ARIA in APOE 4 carriers, particularly APOE 4/4 (aka "two copies" or "homozygous")

	Two copies APOE 4	One copy APOE 4	Non-carrier
Any ARIA	45%	19%	13%
ARIA with symptoms	9%	2%	1%
Serious ARIA	3%	1%	1%



Lecanemab (Leqembi) – FDA approval July 2023

- Indication: Treatment of Alzheimer's disease in a mild cognitive impairment or mild dementia stage
- Mechanism of Action: Recombinant humanized IgG1 monoclonal antibody against aggregated forms of amyloid beta, which promotes clearance of amyloid beta plaques from the brain
- Patient selection:
- Amyloid positivity (PET scan or cerebrospinal fluid)
- APOE genotype (APOE 4 carriers at higher risk of ARIA)
- Brain MRI within 1 year prior: > 4 microhemorrhages on brain MRI may be exclusionary
- Use of blood thinners warrants caution
- Dosing 10mg/kg intravenous infusion over one hour, every 2 weeks

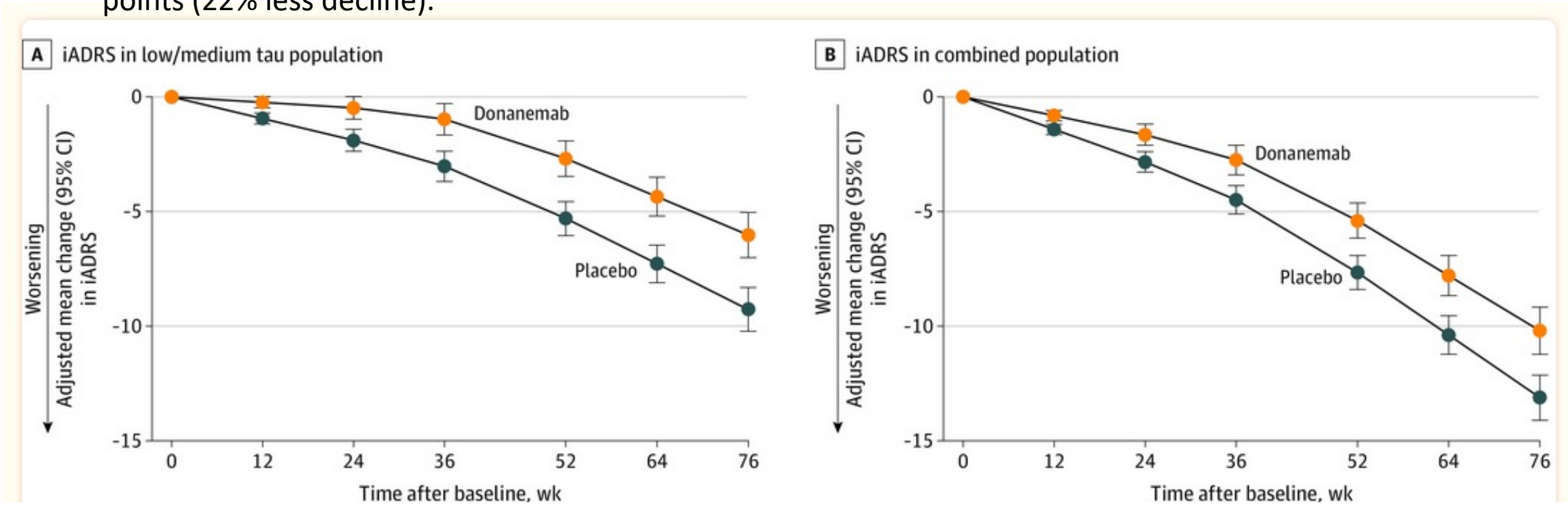
Donanemab – some similarities, some differences

- Donanemab –monoclonal antibody directed against insoluble form of beta-amyloid only present in plaques
- Donanemab Phase 3 trial: 18 months, randomized, double-blind, placebo-controlled, 1736 participants, early Alzheimer's disease with evidence of beta-amyloid and tau on PET brain
- Amyloid PETs at 24 and 52 weeks allowed early switch to placebo if reduction of brain amyloid achieved
- Donanemab cleared amyloid plaques: 29.7% of patients reached amyloid clearance at 24 weeks, 76.4% at 76 weeks

Sims et al, *JAMA,* 2023.

Donanemab slowed progression of cognitive and functional decline by 22-35% over 18 months

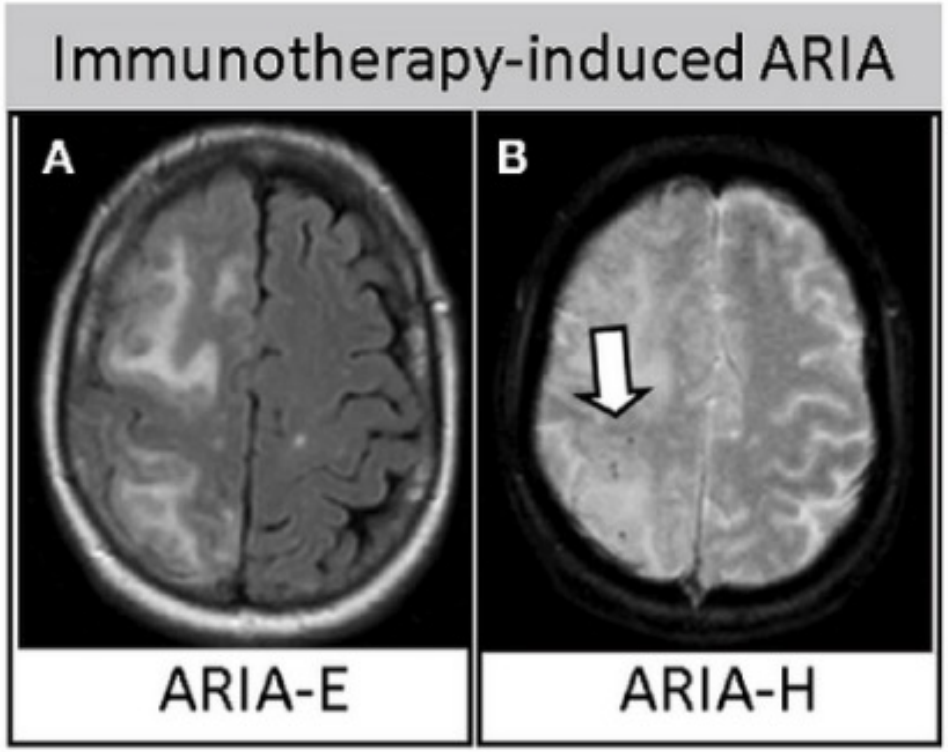
- Primary end point: change in the score on the iADRS (integrated Alzheimer's Disease Rating Scale), an integrated assessment of cognition and daily function
- In the low/medium tau group, donanemab group declined by 6.02 points, placebo group declined by 9.27 points (35% less decline).
- In the combined tau group, donanemab group declined by 10.2 points and placebo group declined by 13.1 points (22% less decline).



Sims et al, *JAMA*, 2023.

Risks and side effects of donanemab

- Infusion reactions: 8.7%
- ARIA – amyloid related imaging abnormality – is the most concerning risk
- ARIA occurred in 37% of patients on donanemab (15% on placebo)
- ARIA-E in 24% of patients overall on donanemab (2% on placebo)
- ARIA-H in 31% of patients on donanemab (14% on placebo)
- Symptomatic ARIA in 6% of donanemab patients, 1.5% serious, symptoms resolved in 87%
- ARIA risk is higher in APOE 4 carriers on donanemab, particularly patients with two copies (APOE 4/4)



Sims et al, *JAMA,* 2023.

Comparison of lecanemab and donanemab

***with all of the important caveats*

	Lecanemab	Donanemab
Approval date	July 2023	July 2024
Mode of delivery	Intravenous	Intravenous
Frequency of infusions	Every 2 weeks	Every 4 weeks
Treatment duration	18+ months	Variable (minimum 6 months)
Slowing of progression	27%	22-35%
ARIA-E - APOE 4 non-carriers	5.4%	15.7%
ARIA-E - one copy APOE 4	10.9%	22.8%
ARIA-E – two copies APOE 4	32.6%	40.6%
ARIA-H (drug versus placebo)	17.3% vs 9%	31.4% vs 13.6%
Infusion reaction	26.4%	8.7%
Deaths	6 on drug, 7 on placebo	16 on drug, 10 on placebo
Cost per year	$26,500	$32,000

Patient perspective

- Infusion reactions can be severe – headaches, chills, fatigue, generalized body weakness
- May not want to be tied to their infusion schedule, extended treatment course, travel burden
- Concern about side effects
- Affordability
- Regular MRI safety imaging can be unpleasant or unsafe (pacemakers)

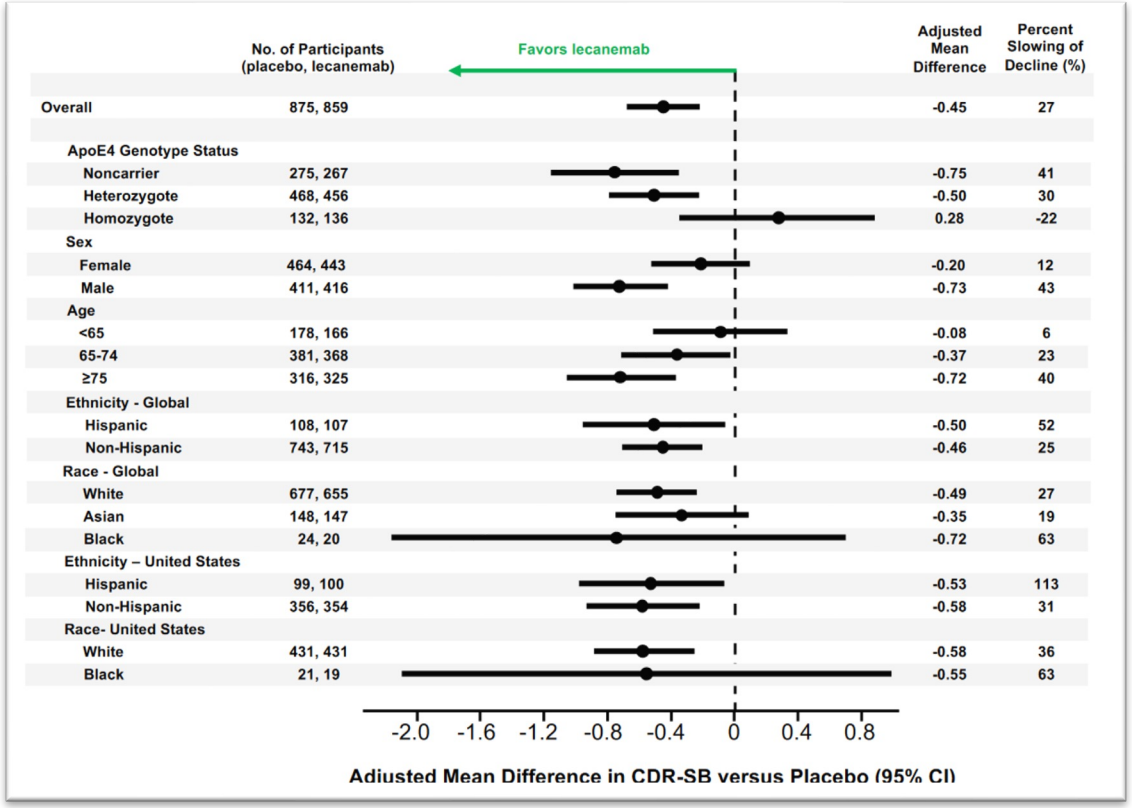
“Anything I can do to slow progression – I want that – I want to be there to see my grandkids.”

“I just want to live my life right now the best way I can – without worry about infusions, side effects, travel limitations.”

Important questions about use of anti-amyloid antibodies

- Are the treatments safe and effective for racially diverse populations?
- What about mixed forms of dementia?
- What is the optimal length of treatment? When can treatment stop?
- Should APOE4 homozygotes be treated?
- What about multiple medical conditions?
- What about switching between treatments?

Subgroup analysis – lecanemab



Van Dyck et al, *NEJM,* 2023.

Future directions

- Testing anti-amyloid antibodies in racially diverse populations
- Real world efficacy and safety data from patient registries
- Testing subcutaneous form of lecanemab
- Extension to pre-symptomatic populations, lecanemab and donanemab
- Combination therapy in clinical trials (START trial, Tau therapies)
- Testing in familial Alzheimer's disease (DIAN-TU trial) and potentially patients with Down Syndrome
- Screening and monitoring of patients with blood markers of amyloid and tau

In summary:
the future of Alzheimer's treatment is just beginning

- For patients with early Alzheimer's disease, two new anti-amyloid treatments, lecanemab and donanemab, have been shown to:
  - reduce amyloid in the brain and
  - slow decline of cognition and daily function
- The most concerning risks are brain swelling and bleeding (ARIA) – this risk depends upon APOE 4 genetic status
- Treatment course is prolonged and involves frequent intravenous infusions
- Patient-guided decision making is important
- These discoveries are hopefully the first among many future treatments that will benefit patients and families with Alzheimer's disease and other forms of dementia

Thank you!

Any questions?