ALZHEIMER'S DISEASE ADVANCEMENTS

THE BEGINNING OF THE END

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UPDATED NOV 2025

DISCLAIMER/CONFLICT OF INTEREST

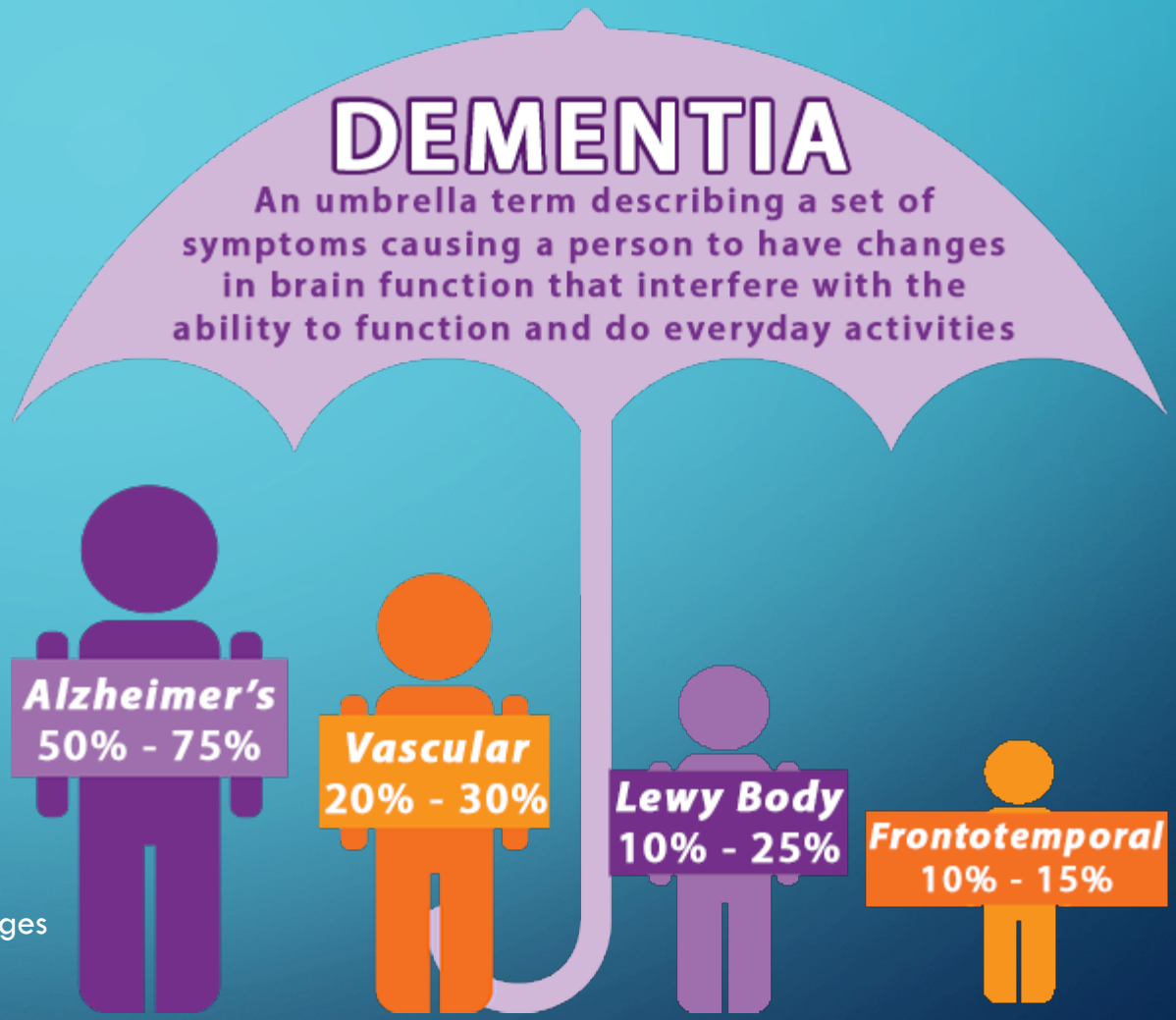
- Paid speaker and consultant for
  - Eisai Pharmaceuticals (Leqembi)
  - Lilly Pharmaceuticals (Kisunla)

CLINICAL DEFINITIONS

- Normal aging
  - "Benign forgetfulness" one room to another, tip of the tongue: NORMAL.
    - Does not interfere with daily life
- Mild Cognitive Impairment (MCI)
  - Cognitive problems interfere with daily life
  - Still independent with ADLs (dressing, eating, hygiene, +/- driving…)
- Dementia
  - Cognitive problems + need help with ADLs (mild, moderate, or severe)

MAIN TYPES OF DEMENTIA BY PATHOPHYSIOLOGY

1. Alzheimer's Disease: Up to 4/5 cases.
   a. Amyloid and Tau pathology
   b. Progressive short term memory loss hallmark
2. Vascular Dementia: over-diagnosed.
   a. Atherosclerotic pathology
   b. Stepwise (NOT gradual and progressive worsening)
3. Lewy Body Dementia:
   a. Lewy body (alpha synuclein) pathology
   b. Parkinsonism, hallucinations, fluctuations, REM behavior.
4. Frontotemporal Dementia
   a. Tau pathology
   b. Younger onset: personality/language > memory changes
   c. Up to 30% have AD pathology



DEMENTIA WORKUP

- History and Physical
  - ETOH, TBIs, sleep, PMHx (autoimmune, Ca/chemo)
  - MOCA…
- Imaging
  - MRI, mostly for rule-out purposes (vascular dz, tumor, NPH, CAA)
- Labs
  - CBC, CMP, B12, TSH, RPR?
  - APOE, AB42/40, pTau 217***

***FDA approved

ALZHEIMER'S DISEASE HISTORY

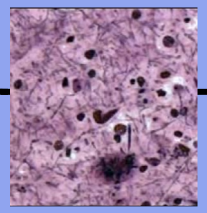
Before 1900s

Ancient descriptions of old age, senility, memory loss.

2400 BC: Ptah-hotep "old age descends… remembers not yesterday"

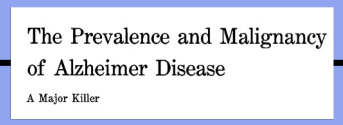
1906

Alois Alzheimer presents Auguste Deter's pathology: plaques and neurofibrillary tangles.



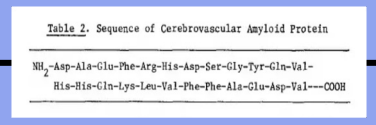
1976

Katzman's Essay highlighting AD as 4th or 5th cause of death. "Neither the clinician, the neuropathologist… can distinguish" AD and senility.

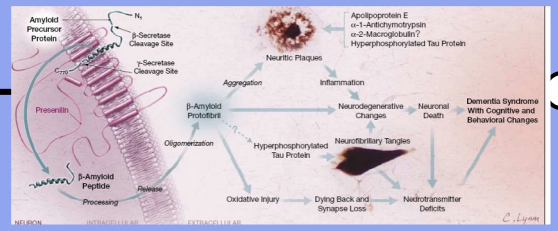


1984

Dr. George Glenner, Caine Wong identify amyloid beta protein as the primary component of the amyloid plaques.



1987: First gene associated with familial Alzheimer's disease, APP identified on chromosome 21. **1993**: ADAD: presenilin 1 and 2 discovered. **1995:** amyloid hypothesis. Amyloid low in CSF: sink?



1996-

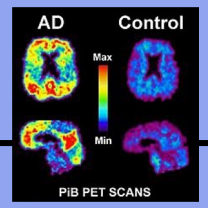
Positive trials and adoption of ACHE-I.

2001-2002

AN-1792: active immunotherapy. Development terminated due to 6% risk aseptic meningoencephalitis.

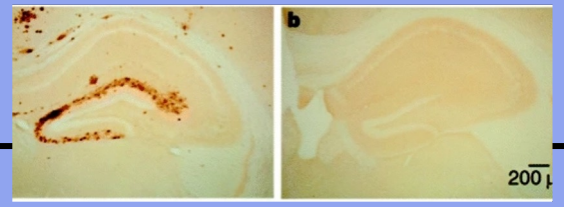
Path: markedly cleared plaque from the brain in those with AB response

Imaging: Inc atrophy in treatment group.



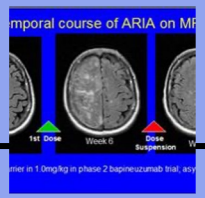
2002

First amyloid PET radiotracer, called Pittsburgh Compound B (PIB), detects amyloid in living brain. 11C has T1/2 20 min



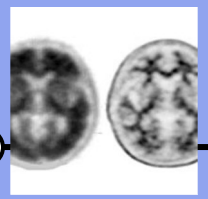
2006

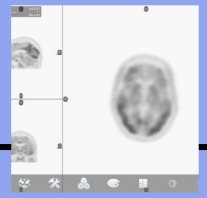
First passive immunotherapies: bapi, sola in phase 2 trials: ARIA-H in mice!!!



2008

Neg bapi phase 2 trial, "vasogenic edema" now ARIA noted mostly in APOE4 carriers.



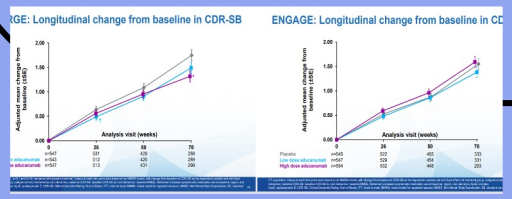


2012

2020

Fluorine-18 PET imaging agents, approved by the FDA, T1/2 of 110 min

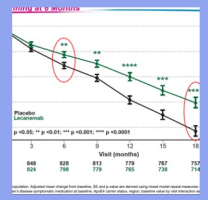
2020: F18 tau imaging approved



2019

ADU +/-.

2021 FDA approves aducanumab using amyloid reduction, first DMT in AD



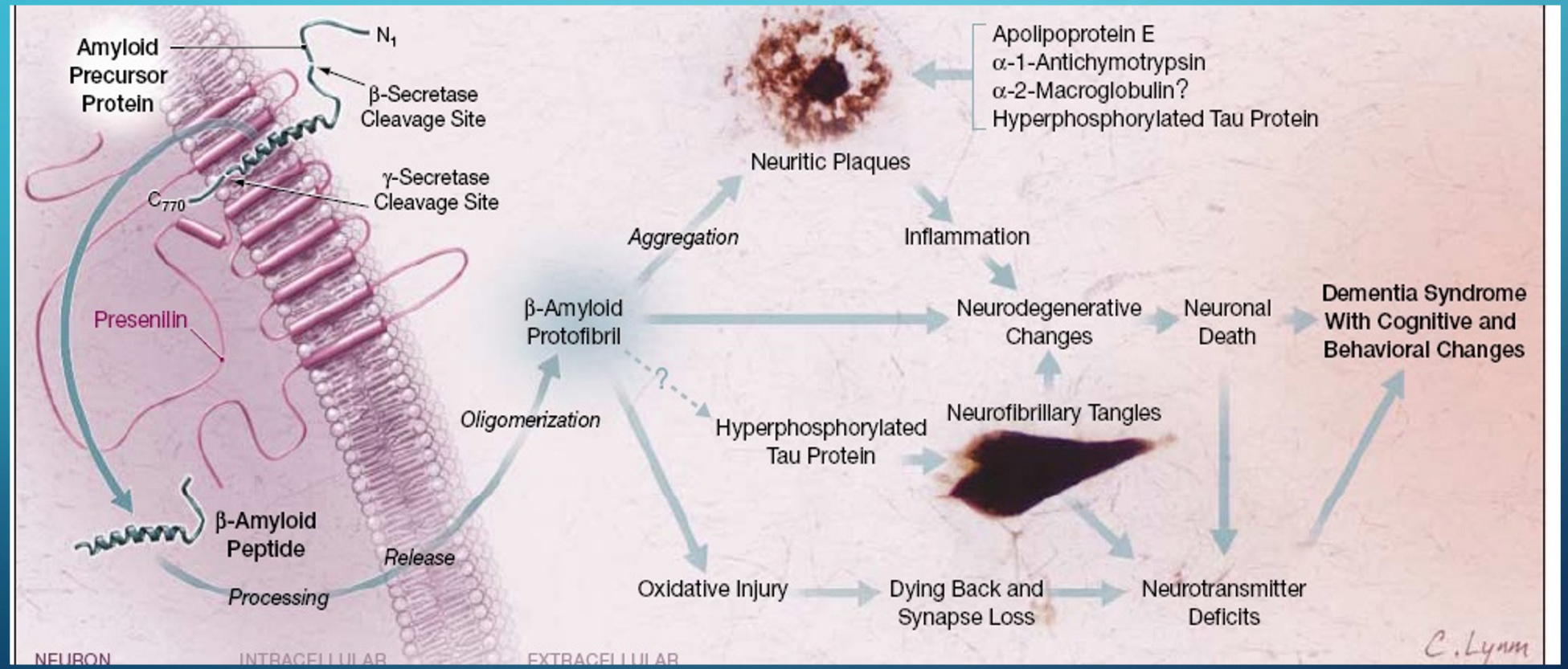
2022-24

+ results from lecanemab and donanemab.

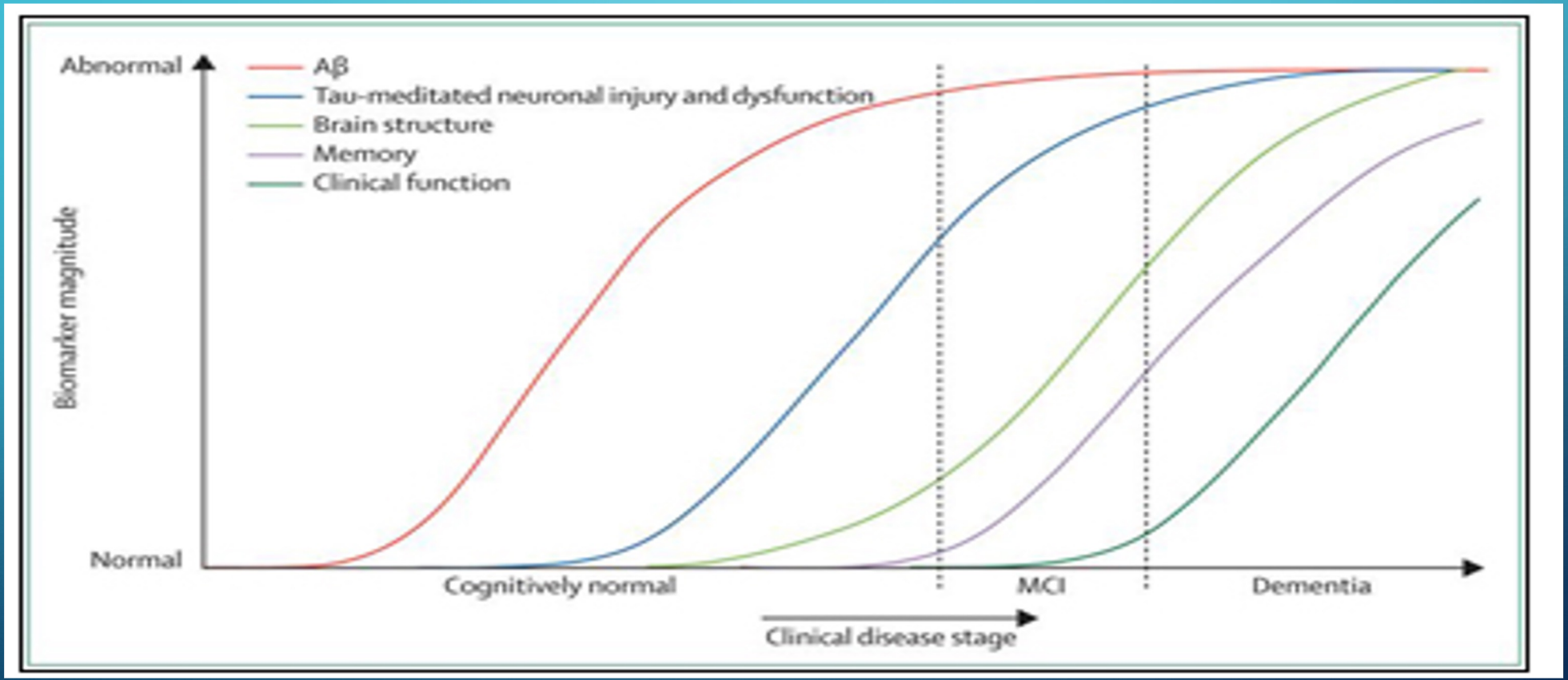
2023: FDA approves lecanemab (DMT) ANA doses 2/22/23. Brexpiprazole (agitation).

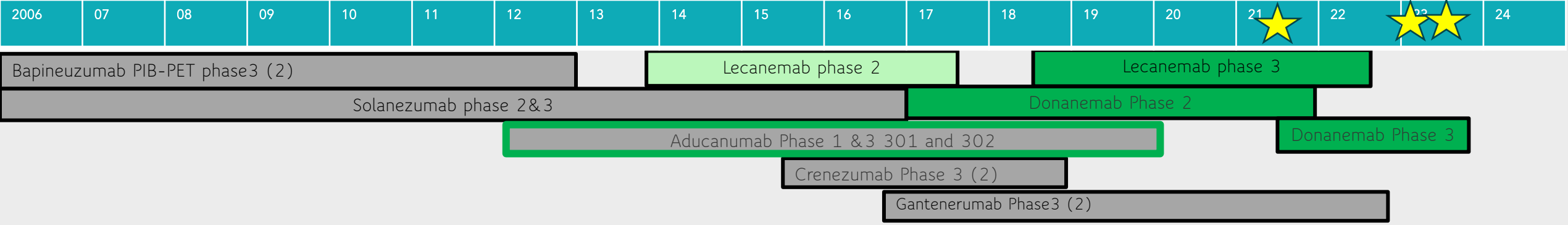
2024: FDA approved donanemab

ALZHEIMER'S PATHOPHYSIOLOGY ATN



ALZHEIMER'S BIOMARKER PROGRESSION: ATN




2006
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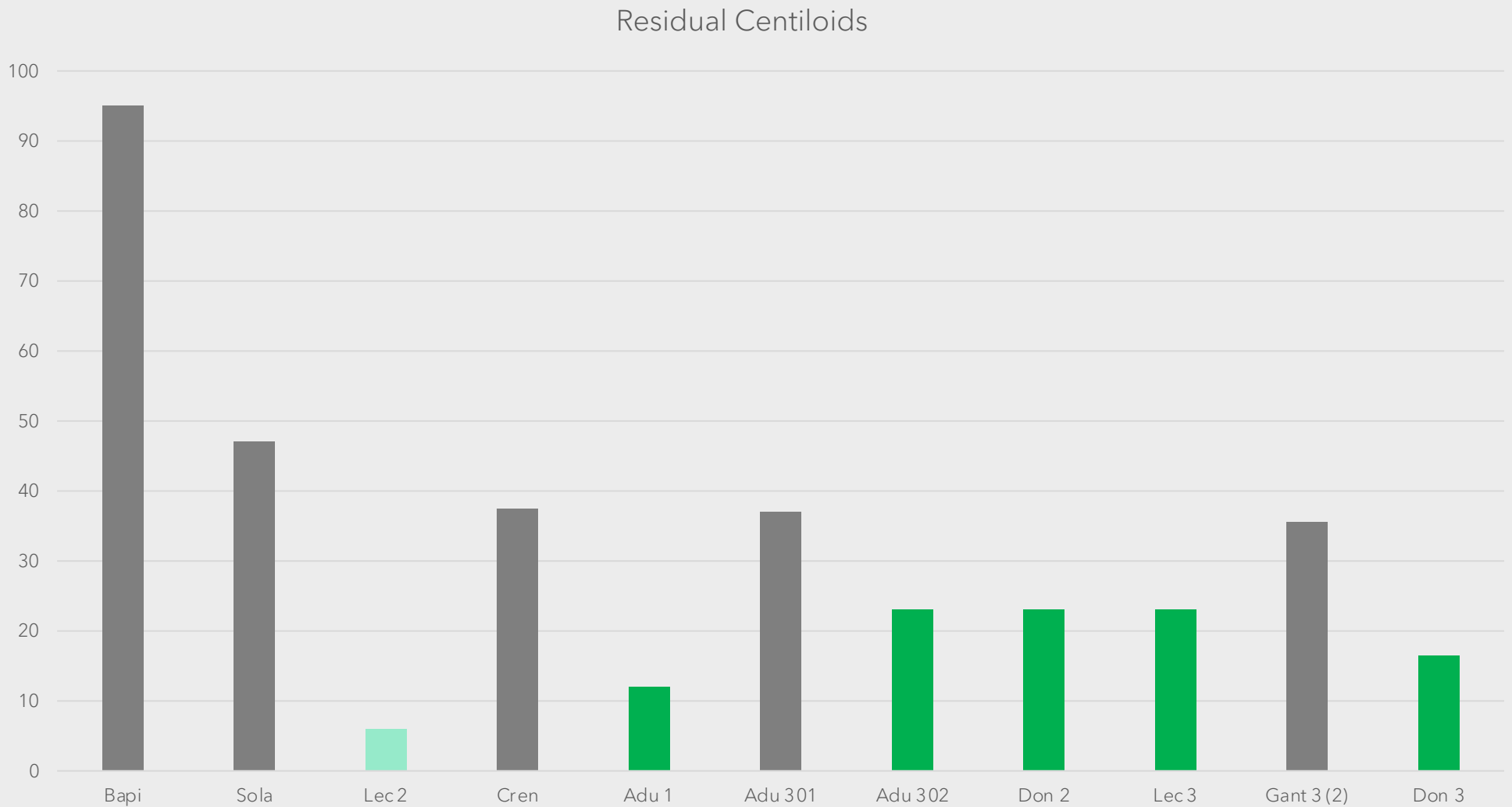
Bapineuzumab PIB-PET phase3 (2)
Lecanemab phase 2
Lecanemab phase 3
Solanezumab phase 2&3
Donanemab Phase 2
Aducanumab Phase 1 &3 301 and 302
Donanemab Phase 3
Crenezumab Phase 3 (2)
Gantenerumab Phase3 (2)

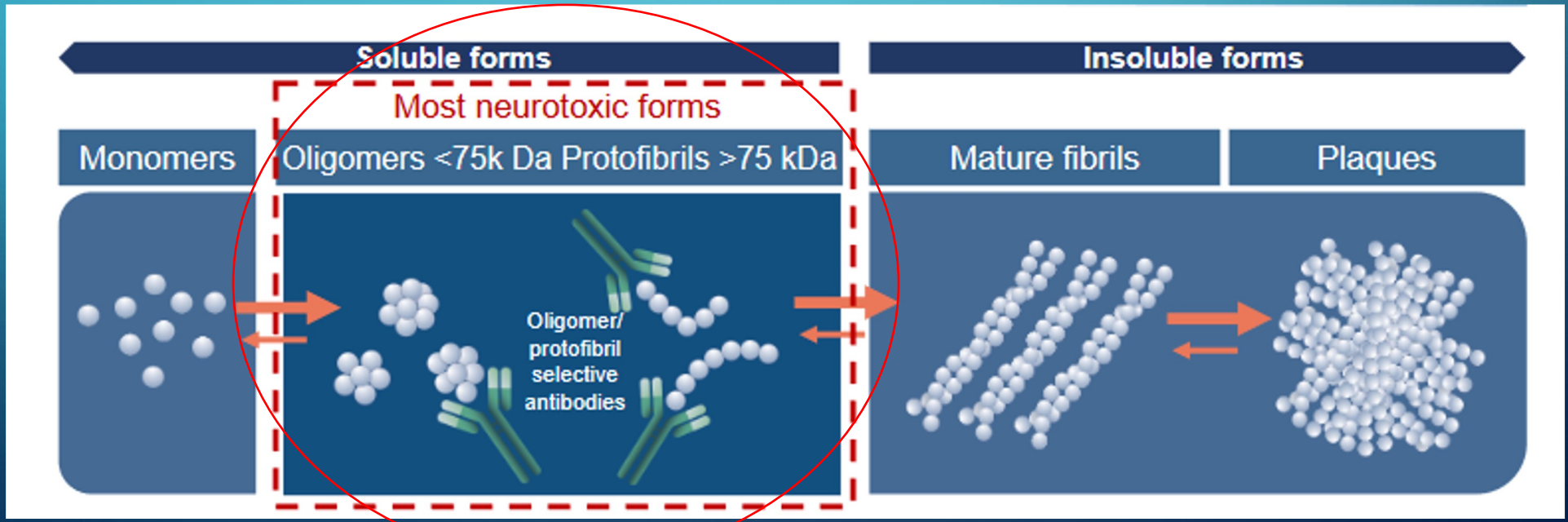

Residual Centiloids
100
90
80
70
60
50
40
30
20
10
0
Bapi
Sola
Lec 2
Cren
Adu 1
Adu 301
Adu 302
Don 2
Lec 3
Gant 3 (2)
Don 3

AMYLOID BAD, BUT THEN WHY DID AMYLOID MAB TRIALS FAIL?
A: EACH TRIAL ALLOWED US TO SEE FURTHER, STANDING ON SHOULDERS

- Right dose (BBB)
- Right target (not monomers)
- Right subjects (not late)
- Right primary endpoints (CDR and combinations)
- Right timeline (not ½ a year)
- Right risk tolerance (ARIA)

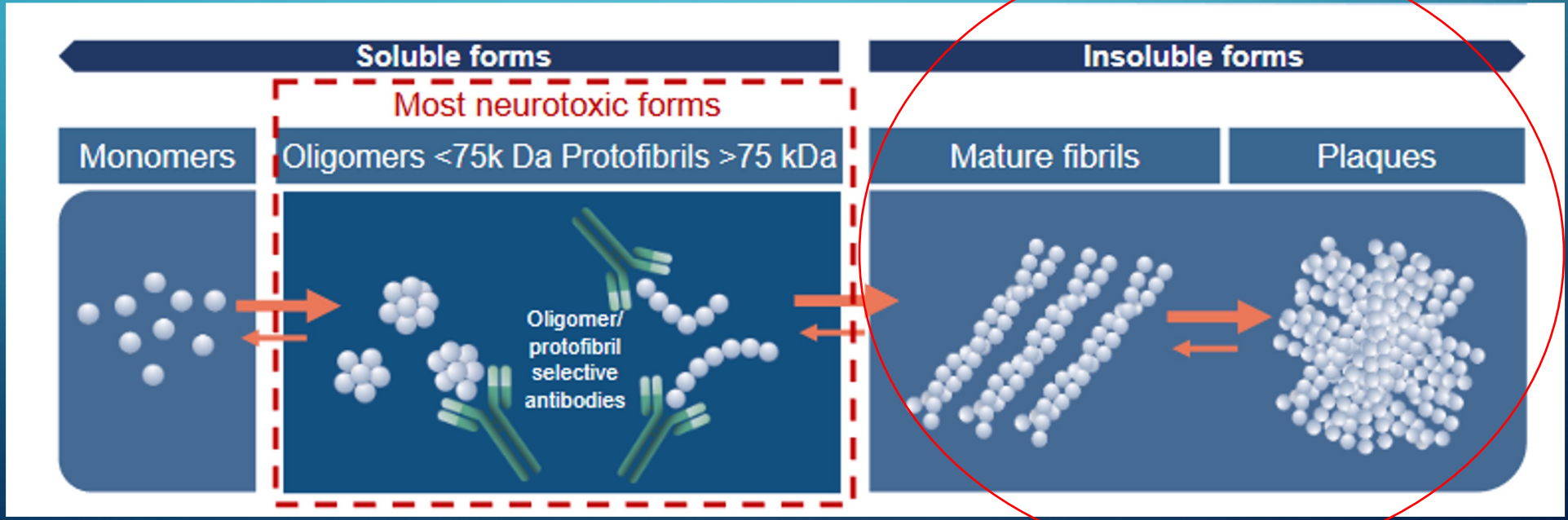
LECANEMAB (LEQEMBI) FDA APPROVAL JULY 2023

- Binds to large, soluble Aβ protofibrils.
- Based on Dr. Lars Lannfelt development of mab against Arctic ADAD mutation (early Alzheimer's with high Aβ protofibrils, but sparse amyloid plaques).

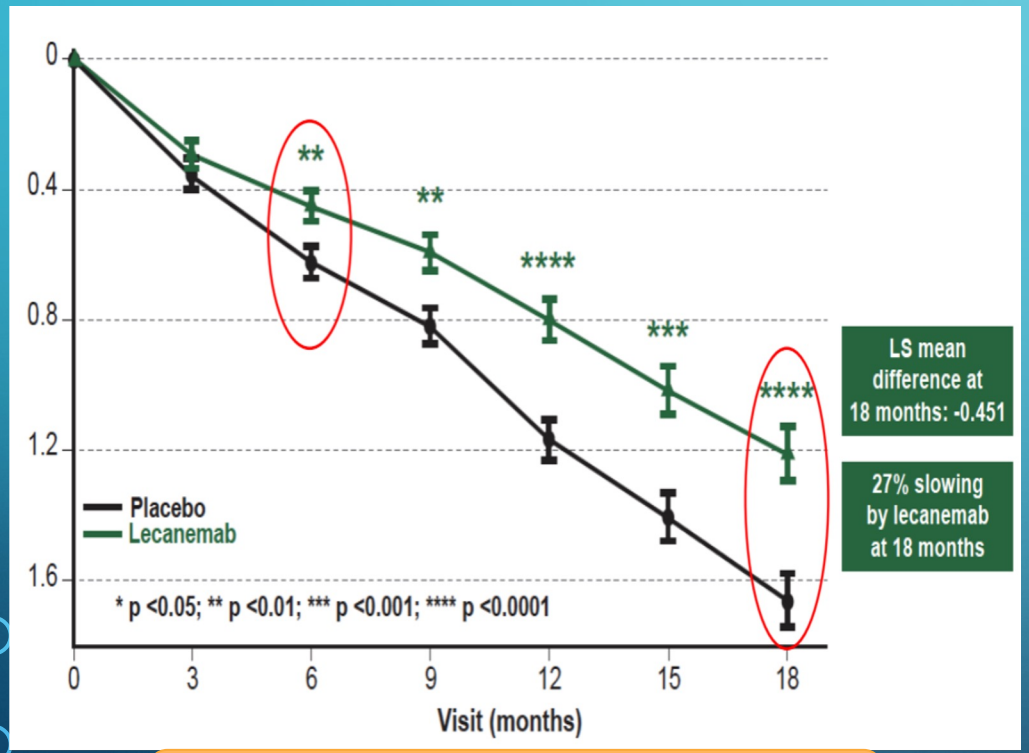


DONANEMAB (KISUNLA) FDA APPROVAL JULY 2024

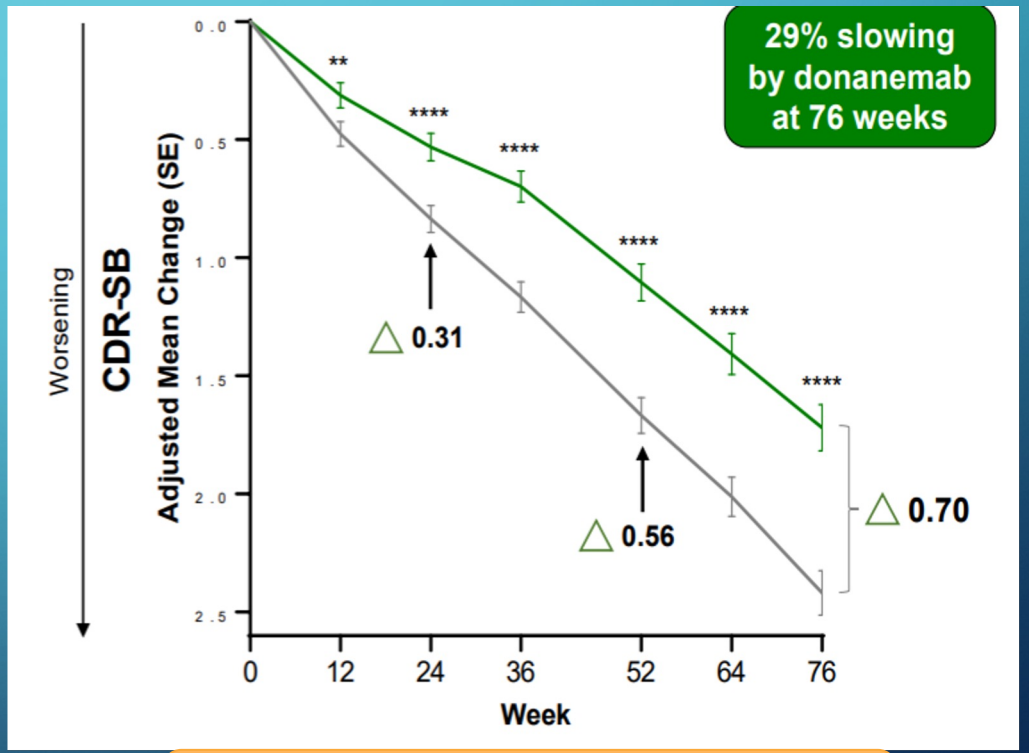
- Antibody against pyroglutamate modification of the third amino acid of amyloid beta. Epitope found on amyloid plaques



PHASE 3 POSITIVE RESULTS FOR PRIMARY AND ALL SECONDARY OUTCOME MEASURES

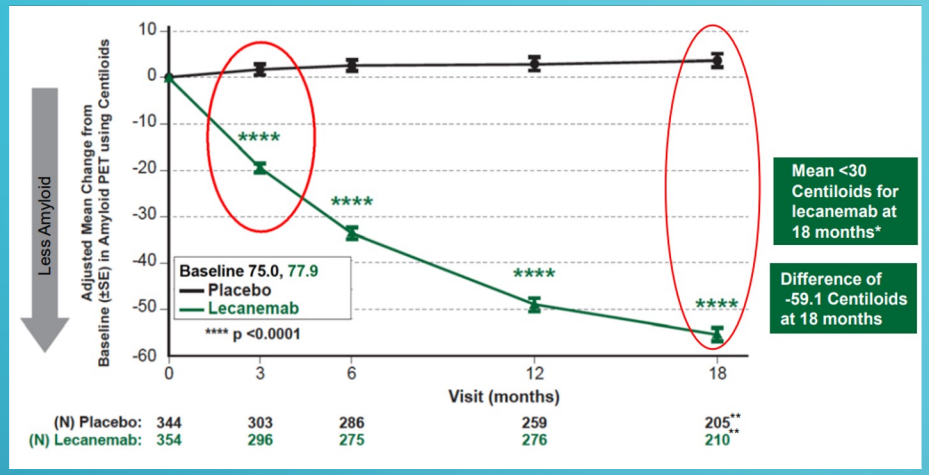


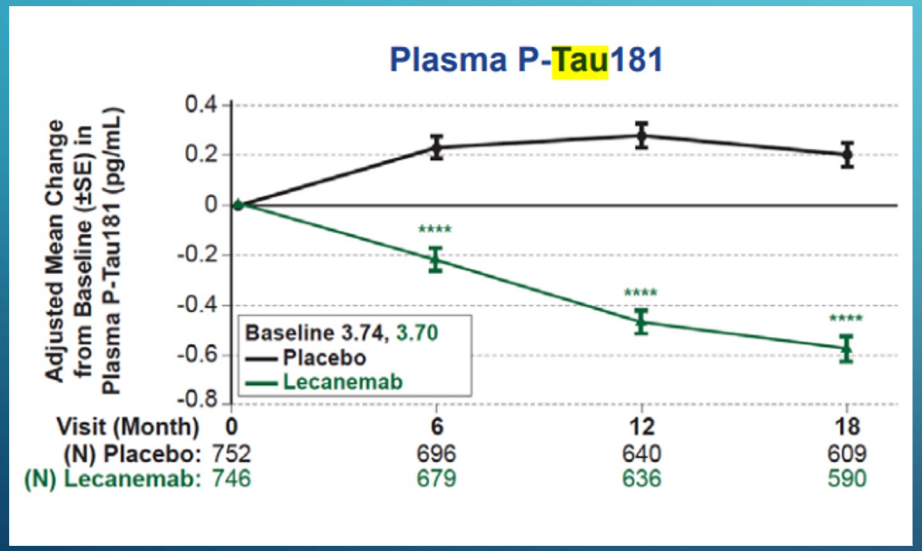
LECANEMAB

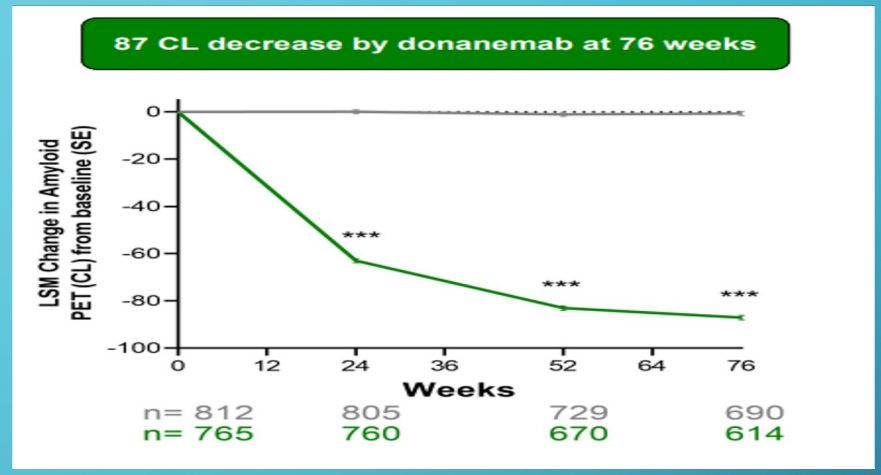


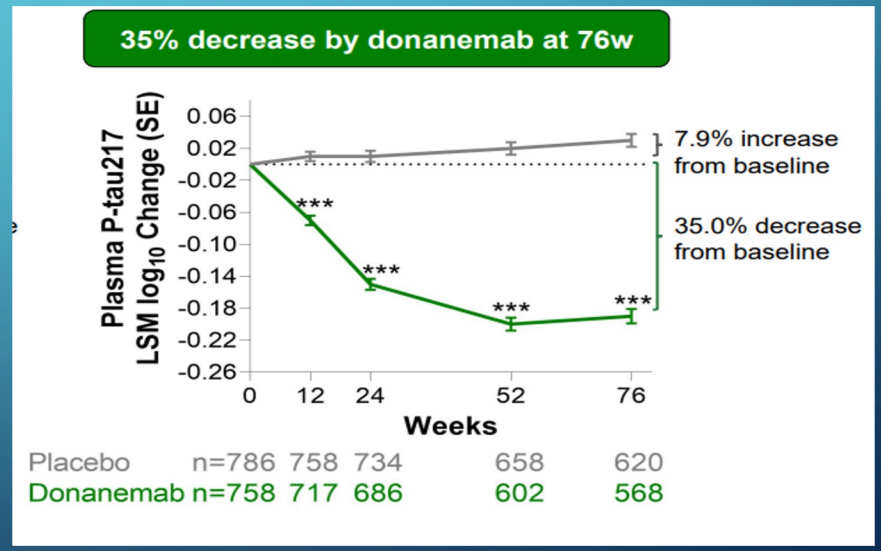
DONANEMAB

BIOMARKER DATA





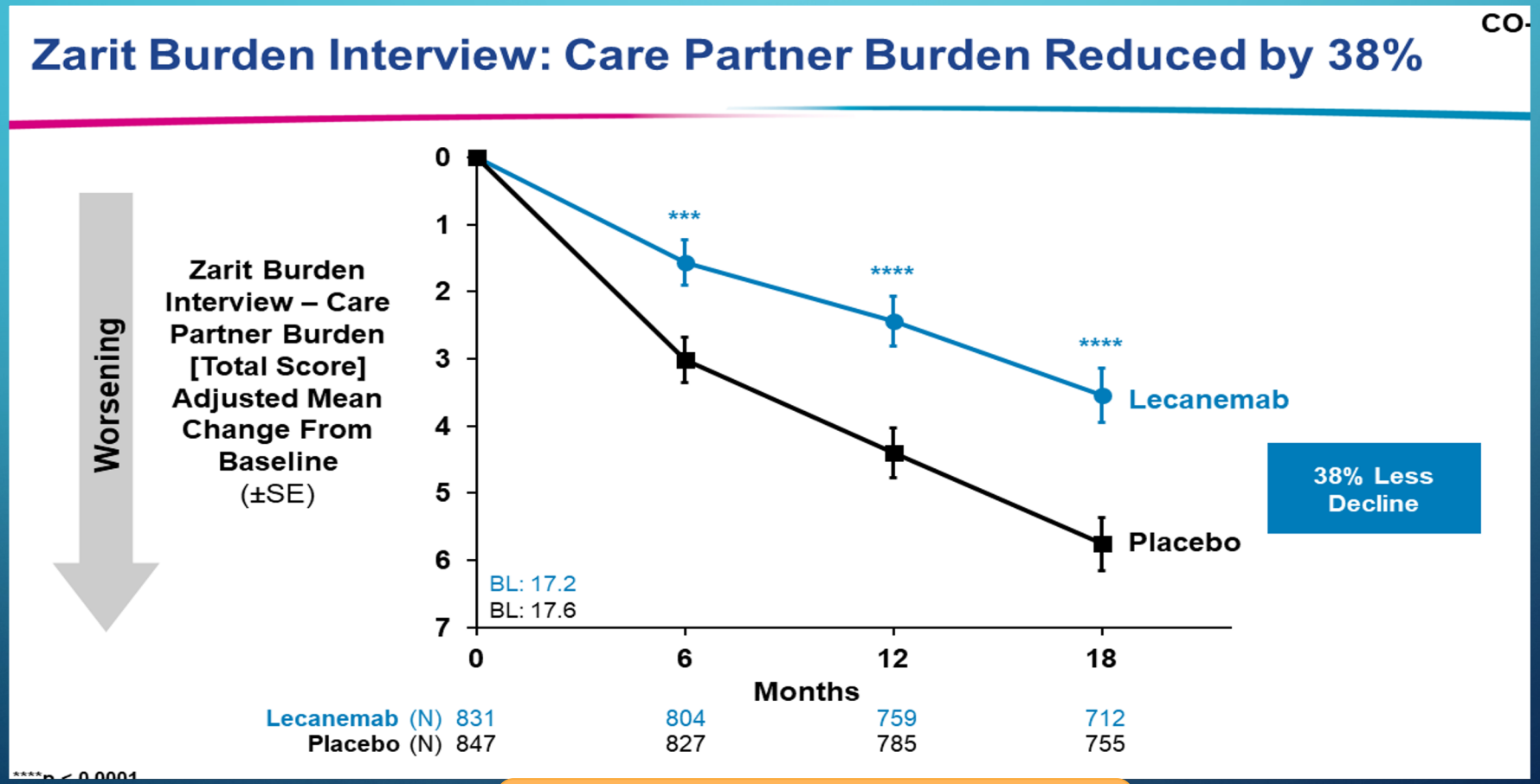




LECANEMAB

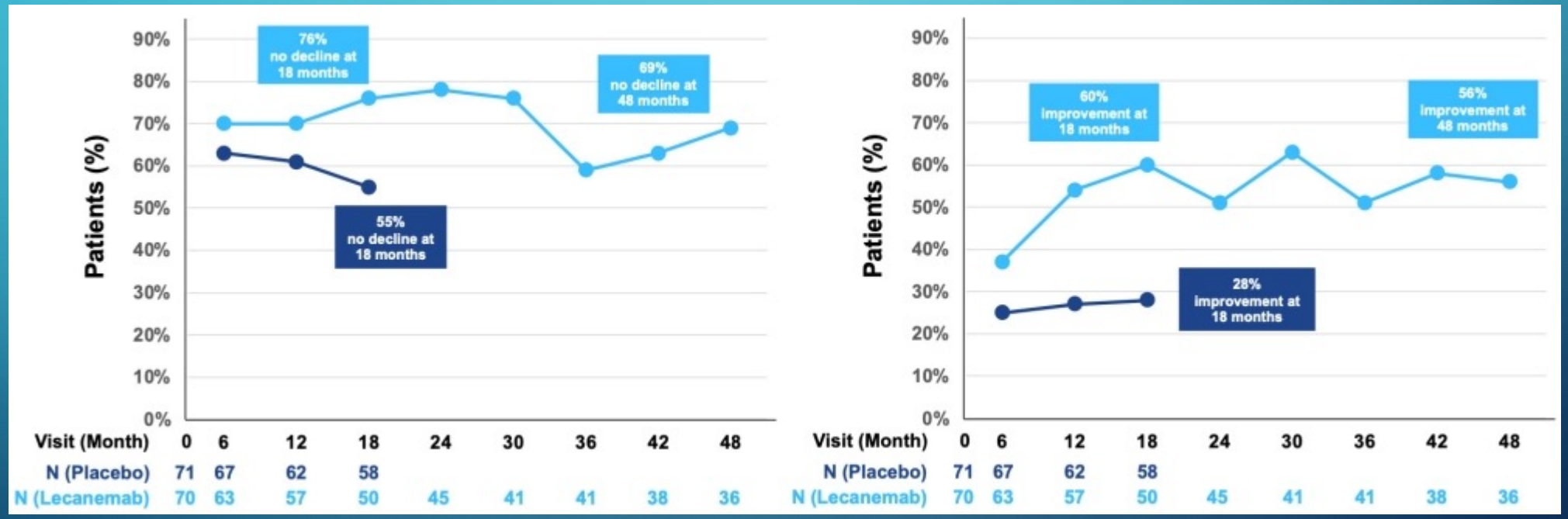
DONANEMAB

IMPACT ON CAREGIVERS



LECANEMAB

LOW TAU SUBSET (EARLIER DISEASE)

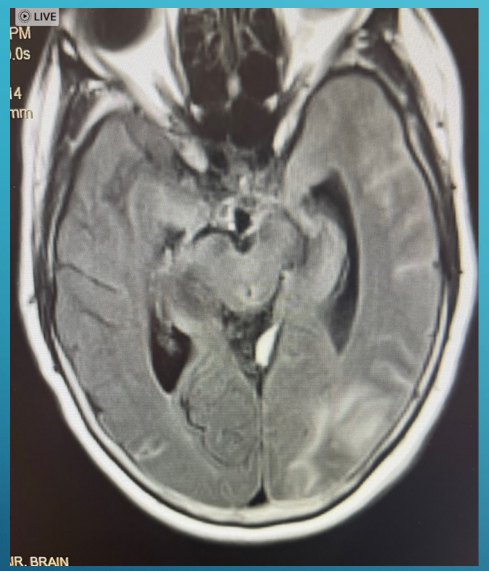


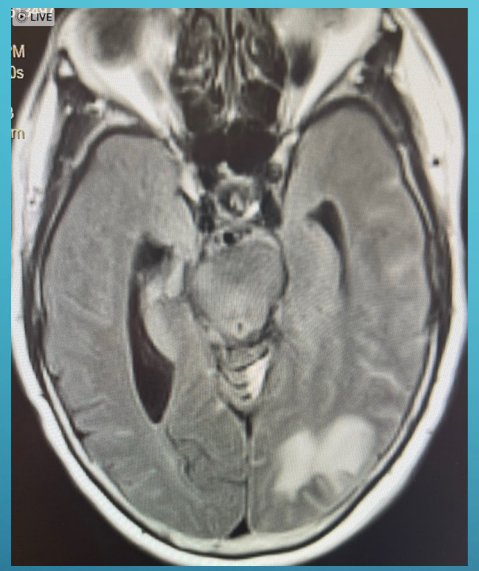
LECANEMAB

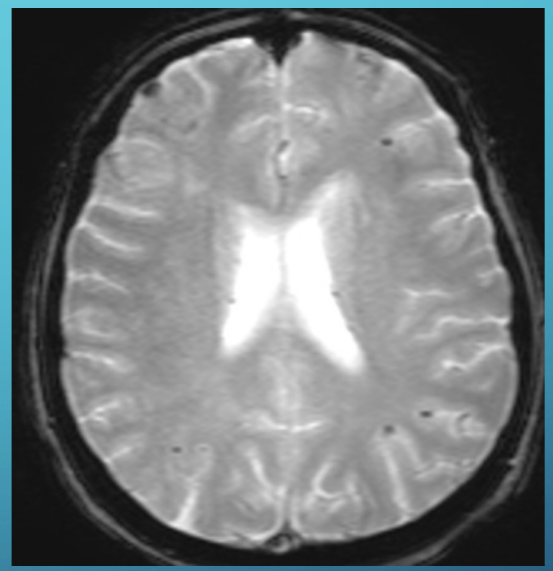
AMYLOID RELATED IMAGING ABNORMALITIES ARIA

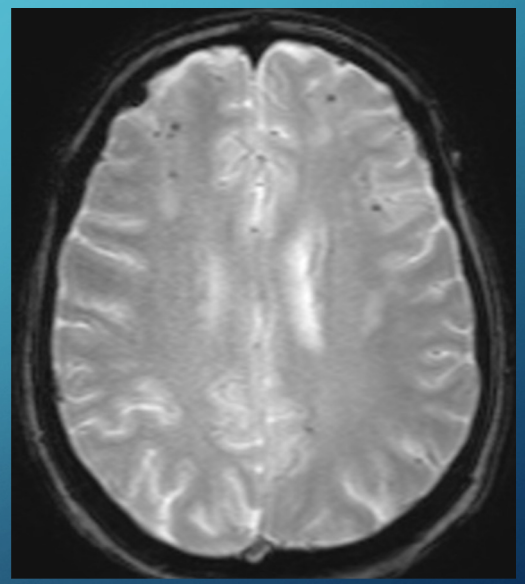
- Aside from infusion reactions, main side effect of amyloid targeting therapies
- Side effect? Or antibody doing its job?
  - All AD patients have amyloid in blood vessels (high level=CAA, AD variant syndrome)
  - Removing amyloid may render blood vessels "leaky"
  - Risk based on APOE status and screening MRI (microheme/siderosis)
  - Present > placebo early in treatment course (first 6 months)
  - Always ARIA E, +/- ARIA H (ARIA H alone equal in tx and placebo groups)

ARIA E(DEMA) & H(EMORRHAGE)









ARIA E PERCENTAGES INCLUDING SYMPTOMATIC

% ARIA-E	LEC (896 Lec, 897 placebo)	DON (860 Don, 876 placebo)
Non-carrier	5.4% (0.3% placebo), 1.4% symptoms	15.7% (0.8% placebo) 3.9% symptoms
One APOE4	10.9% (1.9% placebo), 1.7% symptoms	22.6%, (1.9% placebo) 6.6% symptoms
APOE44	32.6% (3.8% placebo), 9.2% symptoms	40.6%, (3.4% placebo) 8.4% symptoms https://www.fda.gov/media/179166/download

SEVERE SYMPTOMATIC ARIA RATES BY APOE

- ARIA is overwhelmingly asymptomatic (hence the name)

APOE	Noncarrier (E3/E3)	Hetero (E3/E4)	Homo (E4/E4)
Lecanemab	1%	1%	3%
Donanemab	1%	2%	3%

BLOOD BASED BIOMARKERS

- Amyloid PET and CSF are gold standard for AD confirmation
- FDA has now approved pTau 217 and pTau 181 for AD diagnosis
  - pTau217 is >90% sensitive and specific
    - High pre-test probability? Some think we are there
    - Routine screening lab? Almost there
    - Can be ordered at any Labcorp or Quest

REAL DLROW DATA

- Published AAIC, Toronto, July 2025, re Leqembi (https://www.eisai.com/news/2025/news202552.html)
- 178 patients from 9 US centers, no control group
- Median treatment time 375 days
- 87% of patients remained on therapy, 13% discontinued
- <1% of ARIA was symptomatic

REAL DLROW DATA

APOE	Noncarrier (E3/E3)	Hetero (E3/E4)	Homo (E4/E4)
Clinically Improved	9%	5%	7%
Clinically Stable	76%	83%	66%
ARIA	15%	10%	20%

WHAT'S THE POINT?

- We're neurologists, there's stuff WE CAN DO
- ARIA is a concern
  - But risk for severe symptomatic ARIA is low (1-3% based on APOE)
  - Can be personalized
- In the real world, >60% of MCI patients have remained stable
- You can cheaply screen with pTau 217
- Shift the odds away from moderate or severe dementia

WHAT WE ARE LOOKING FOR

- Early symptomatic patients (MCI)
- Motivated patients
- Engaged caregivers
- Our “village” of providers
- What the future might look like…