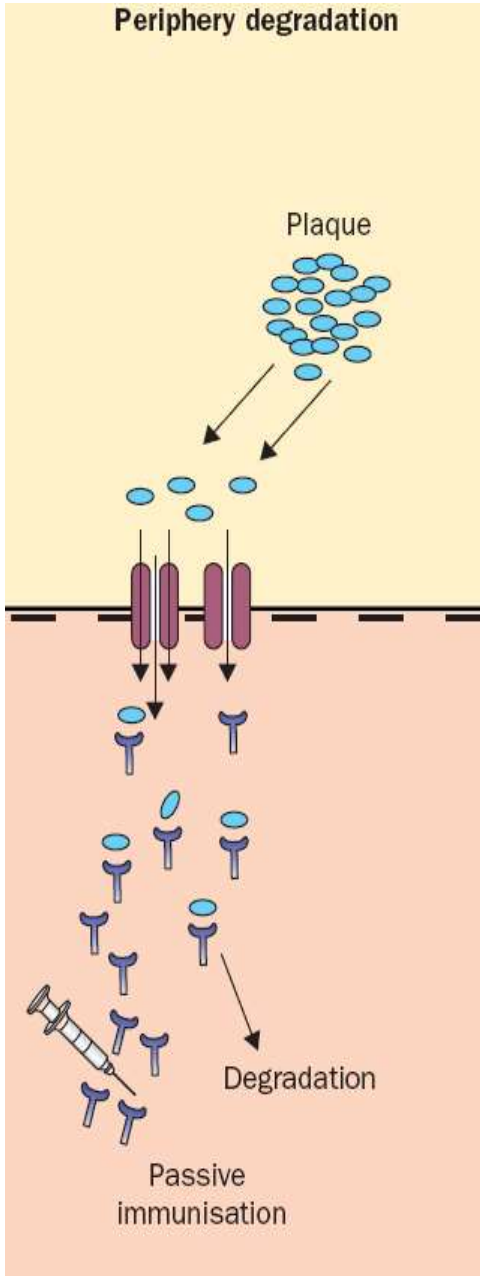
Le terapie biologiche per la Malattia di Alzheimer: benefici realistici, rischi possibili, complessità organizzative. Come ne usciamo?

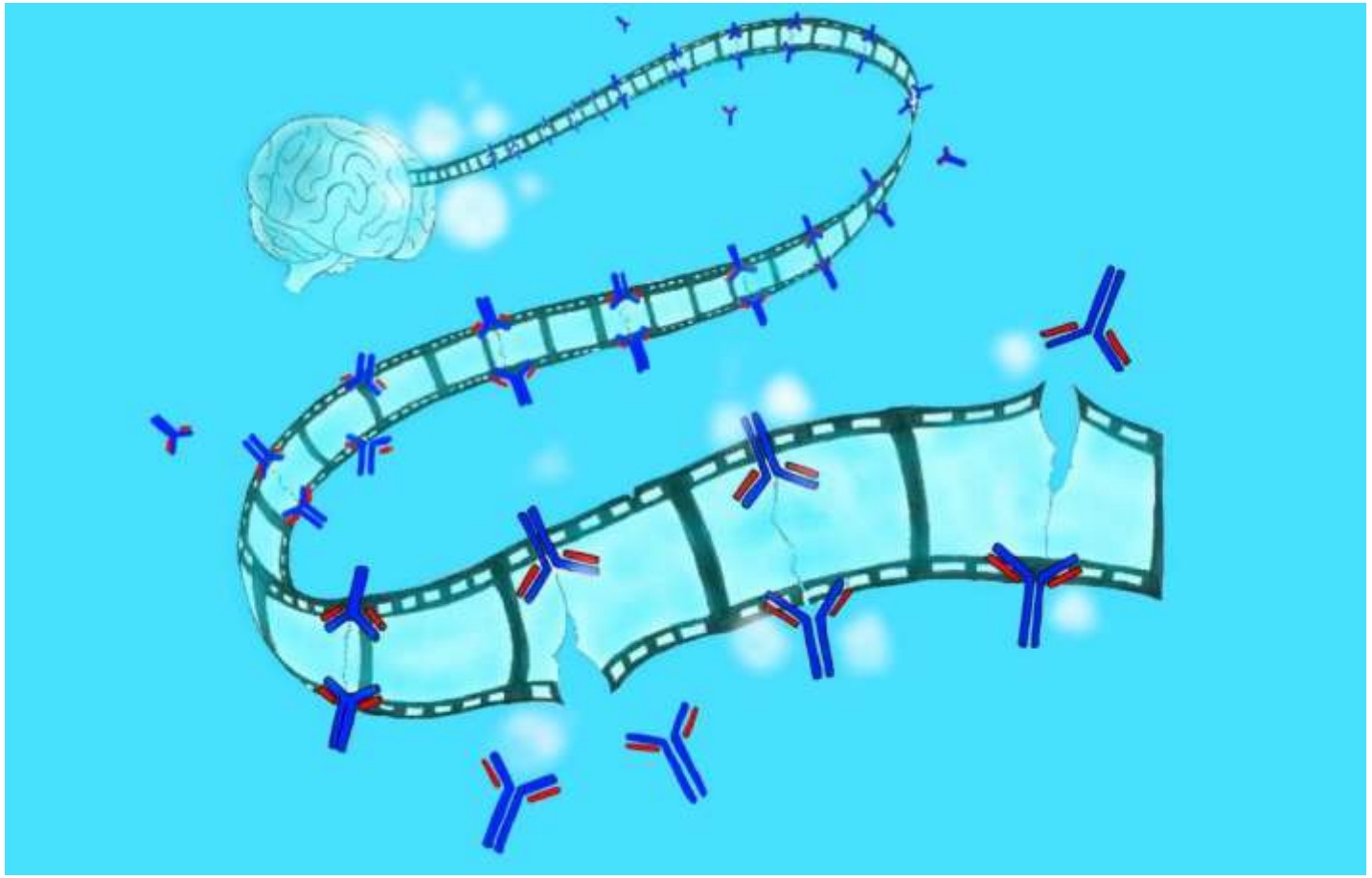
Annachiara Cagnin
Padova

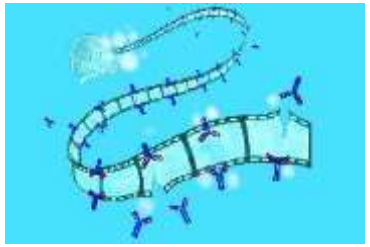
Passive immunotherapy

Humanized monoclonal antibodies



Salloway et al
Neurology 2009





FAIL

FAIL

July 23: FDA

July 24 FDA

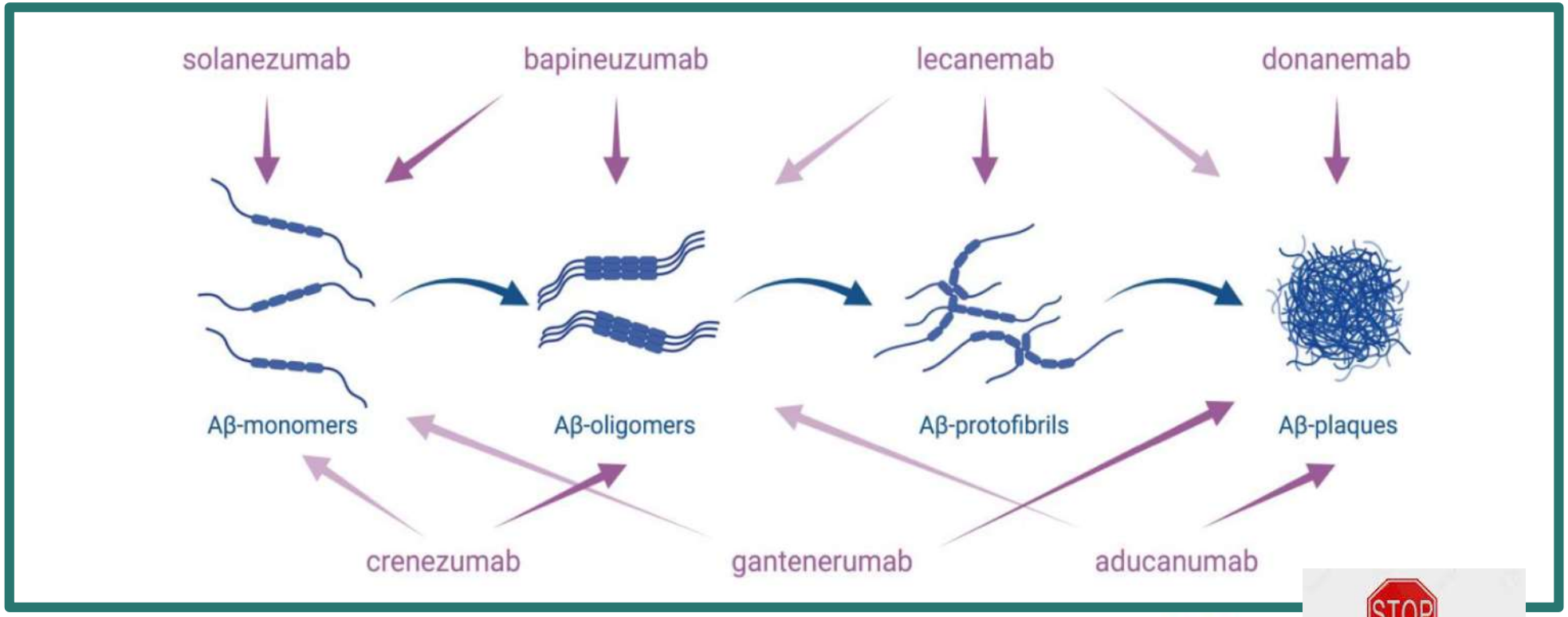
July ‘24: EMA rejection

November ‘24: EMA

April ‘25: final approval EMA

Sept ’25:final approval EMA

AMYLOID clearance



New formulations

New scheme of administration

New MAB (phase 3 trial)

Other classes

PHARMACODYNAMIC MECHANISMS

IgG1 Monoclonal Antibodies driving Microglia-Mediated Clearance

LECANEMAB (Leqembi®)

Target:	Soluble Aβ protofibrils (high affinity).
Mechanism:	Targets the most toxic pathologic amyloid species before they form insoluble, mature plaques.
Administration:	Intravenous infusion every 2 weeks.
Dosing Strategy:	Continuous maintenance dosing.

DONANEMAB (Kisunla®)

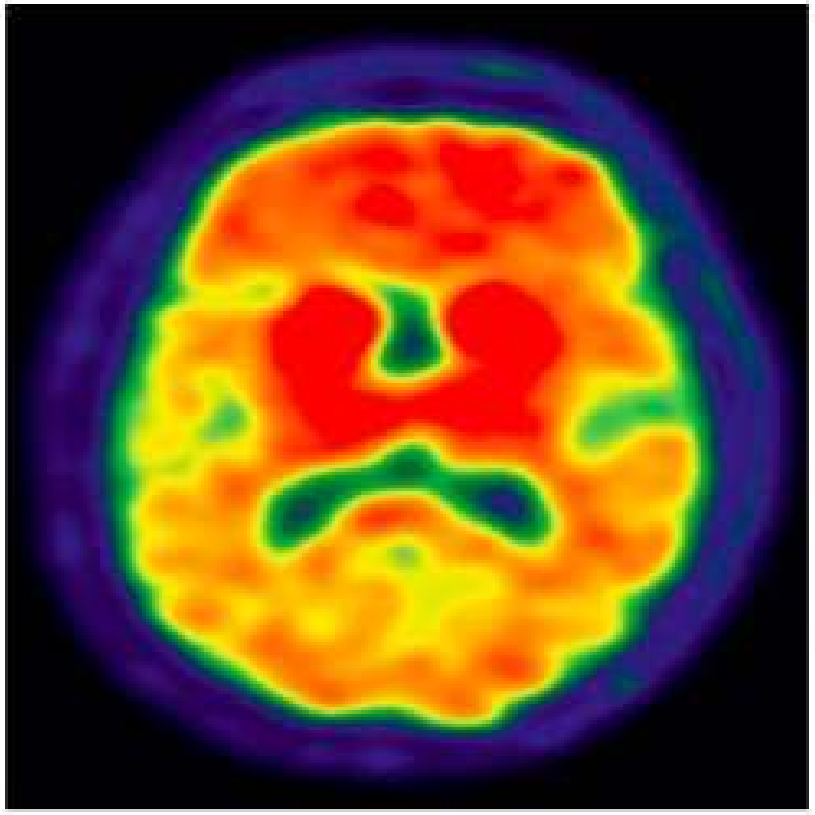
Target:	N-terminal pyroglutamate Aβ (N3pE-Aβ).
Mechanism:	Binds exclusively to insoluble, mature amyloid plaques to aid microglial phagocytosis (leaves monomeric Aβ intact).
Administration:	Intravenous infusion every 4 weeks.
Dosing Strategy:	Treat-to-clear limited duration (treatment stops when amyloid PET is negative).

BENEFICI REALISTICI

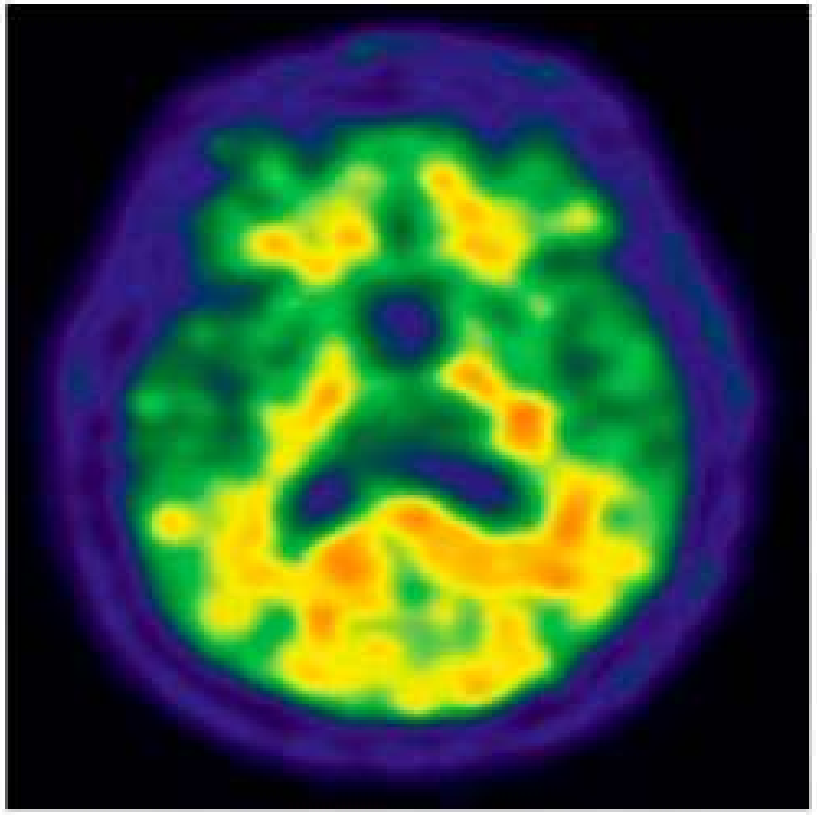
BENEFIT = BIOLOGICAL TARGET

b **Alzheimer disease**

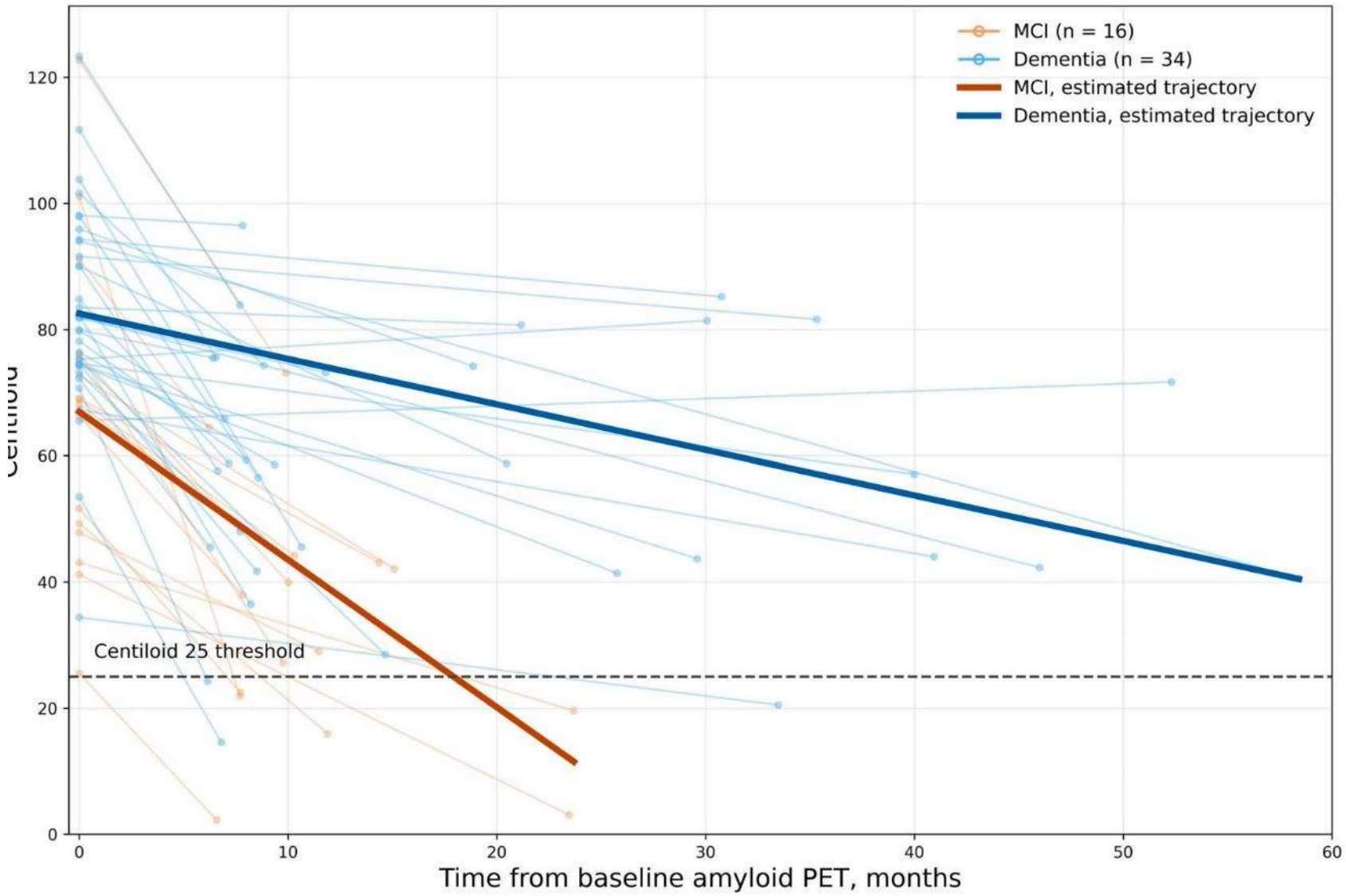
Before treatment



After treatment with gantenerumab

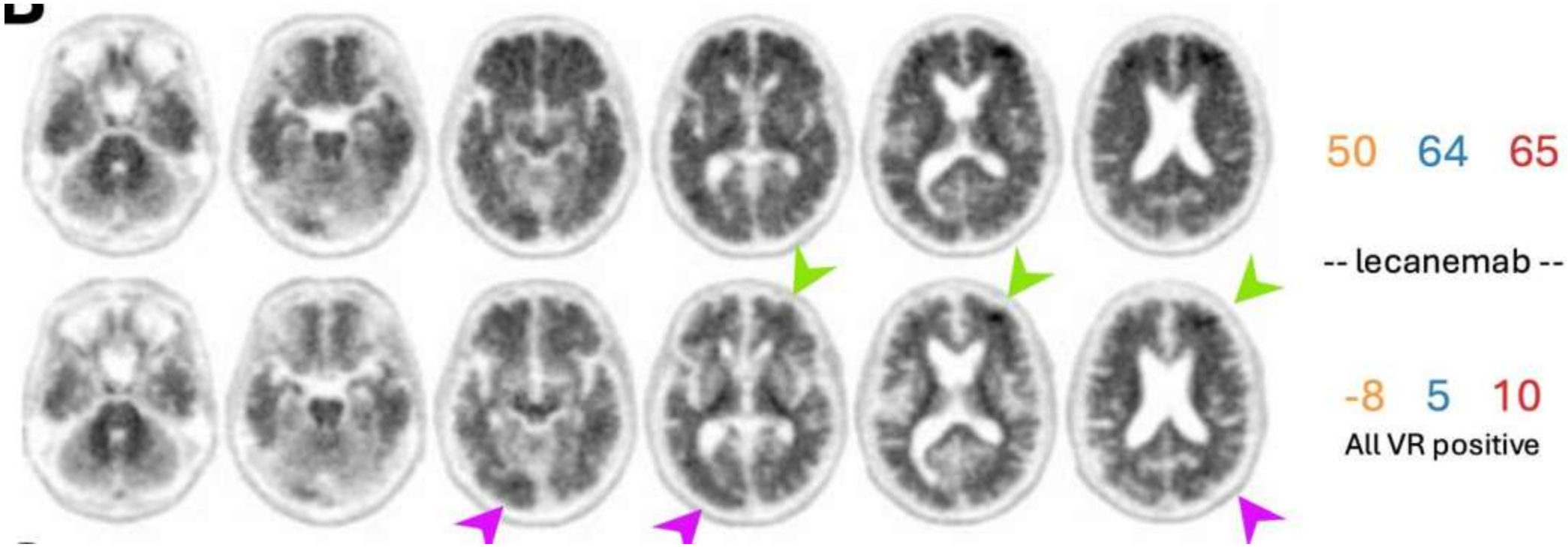


BIOLOGICAL EFFECT IS EARLIER IN MCI



Kim GH, Alzh & Dementia 2026

WHEN AMYLOID IS CLEARED?



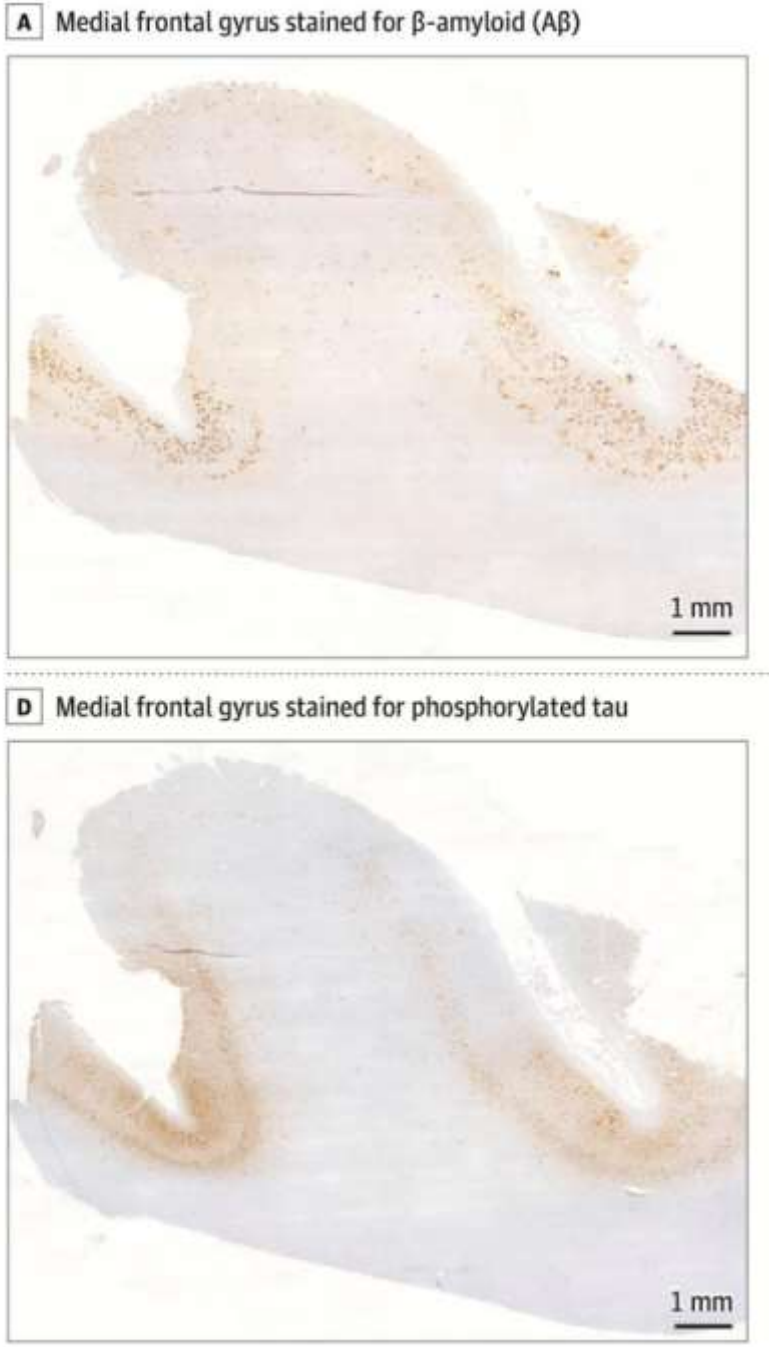
La Joie, Alzh & Dementia 2026

NEUROPATHOLOGY

Regions with extensive amyloid clearance are associated with:

- lower tau pathology

- lower rate of atrophy



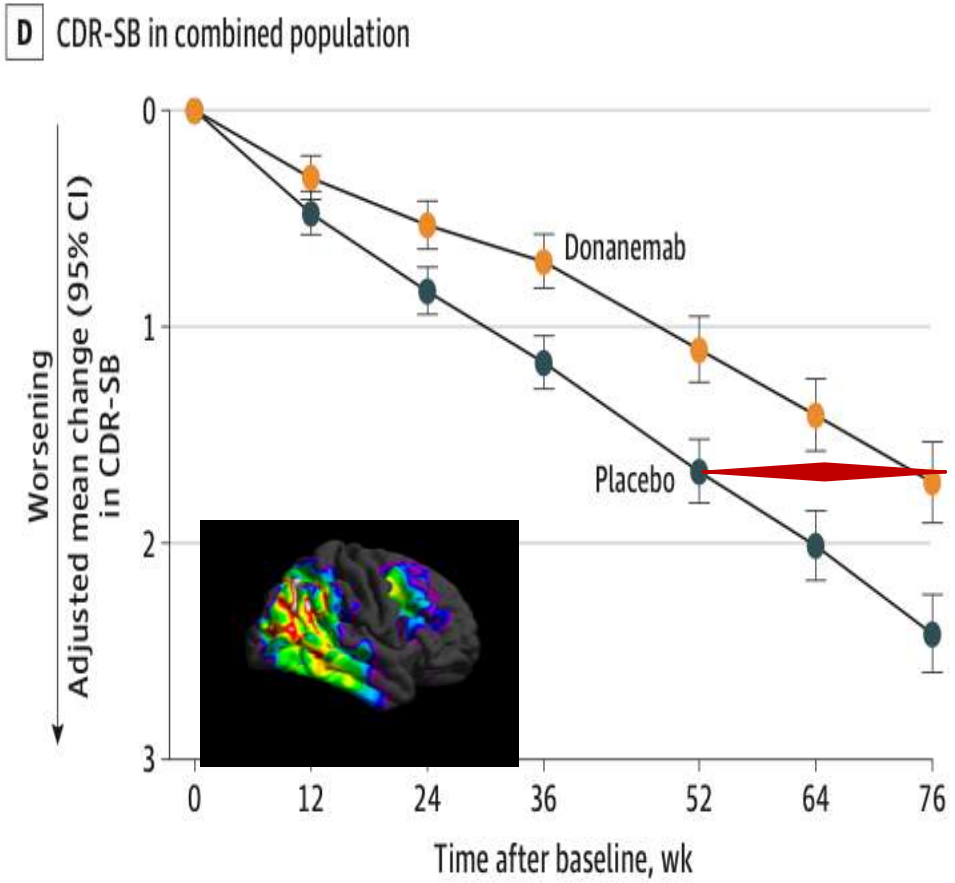
Brown CA, JAMA 2026

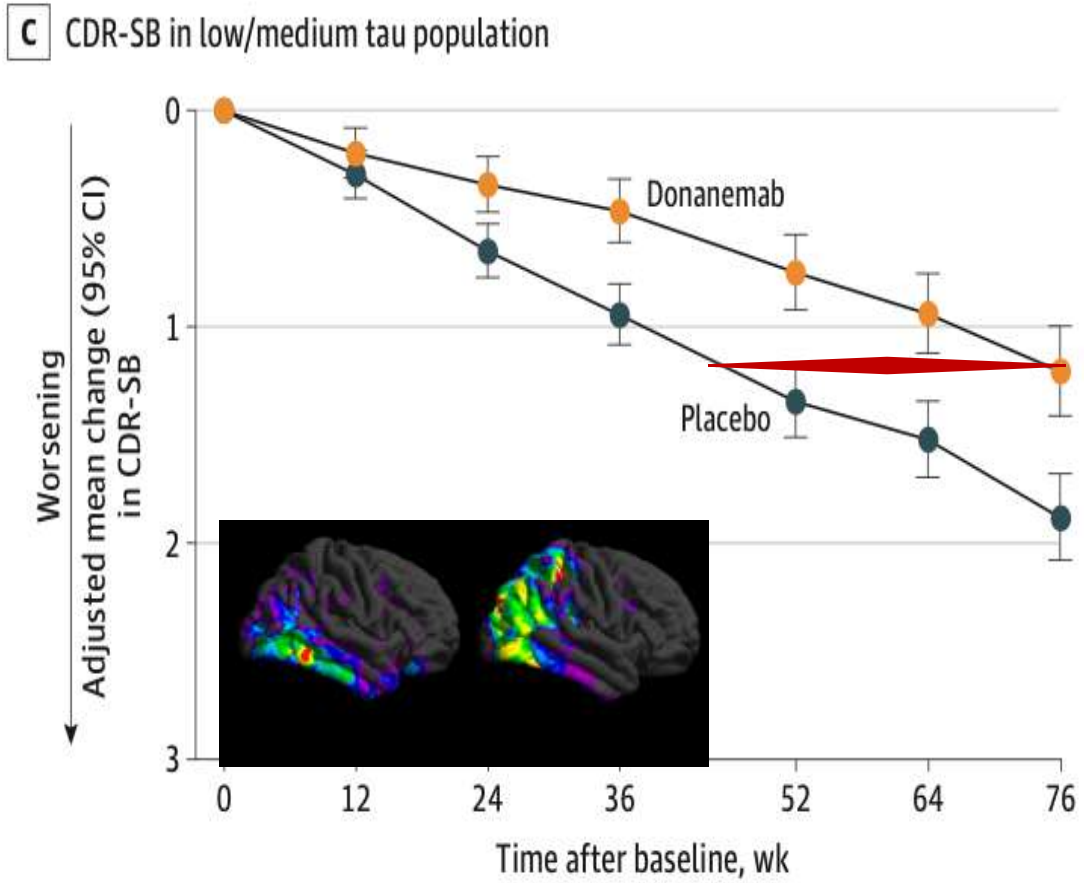
CLINICAL BENEFIT- time saved

4,4 months of delay progression

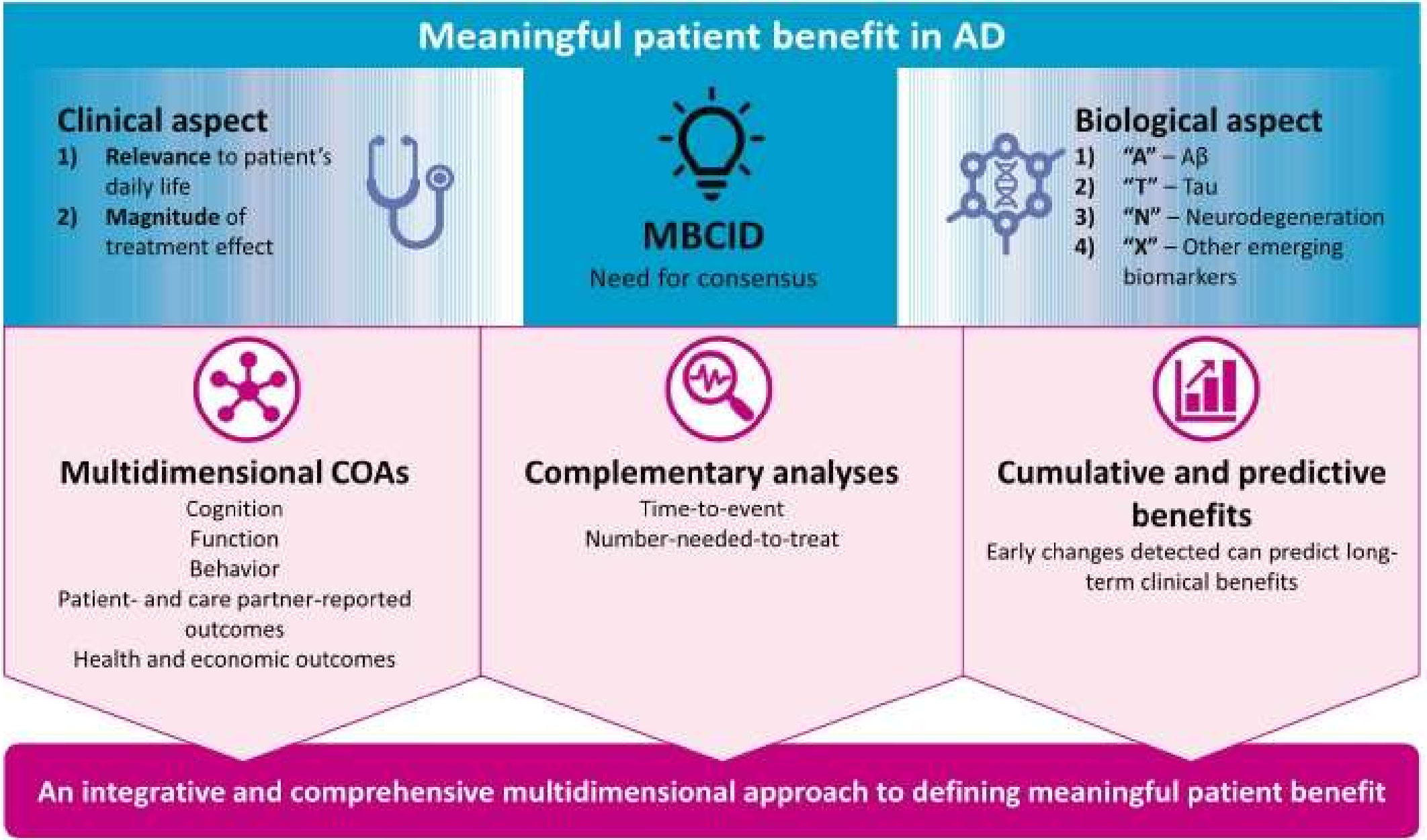
CDR-SB

7.5 months of delay progression





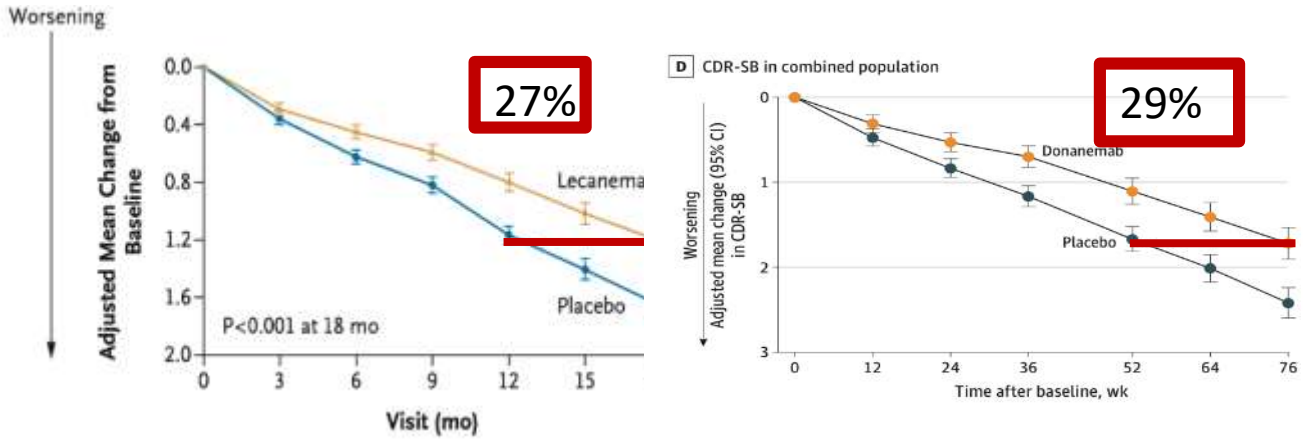
Sims JR, JAMA 2023



Elhage, Alzh&Dem 2024

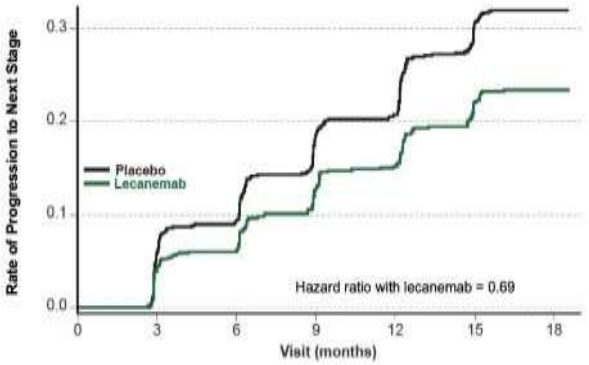
CLINICAL OUTCOME MEASURES

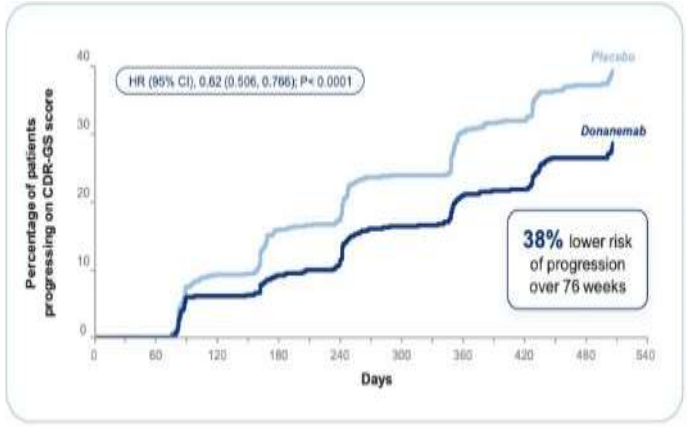
- Time-saved with treatment



- Change of chance of progression to next grade of severity

- Progression-free “survival”





- Difference of slopes between pre- and post-treatment trajectories

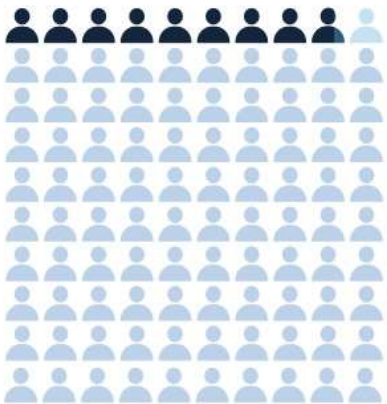
- Number needed to treat

AD – Donanemab

Treating **~9 patients** will result in 1 showing **no progression** on the CDR-G at Week 52*

NNT

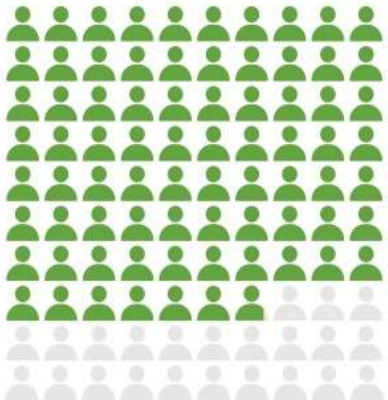
8.6



Treating **~77 patients** will result in 1 patient having serious ARIA-E*

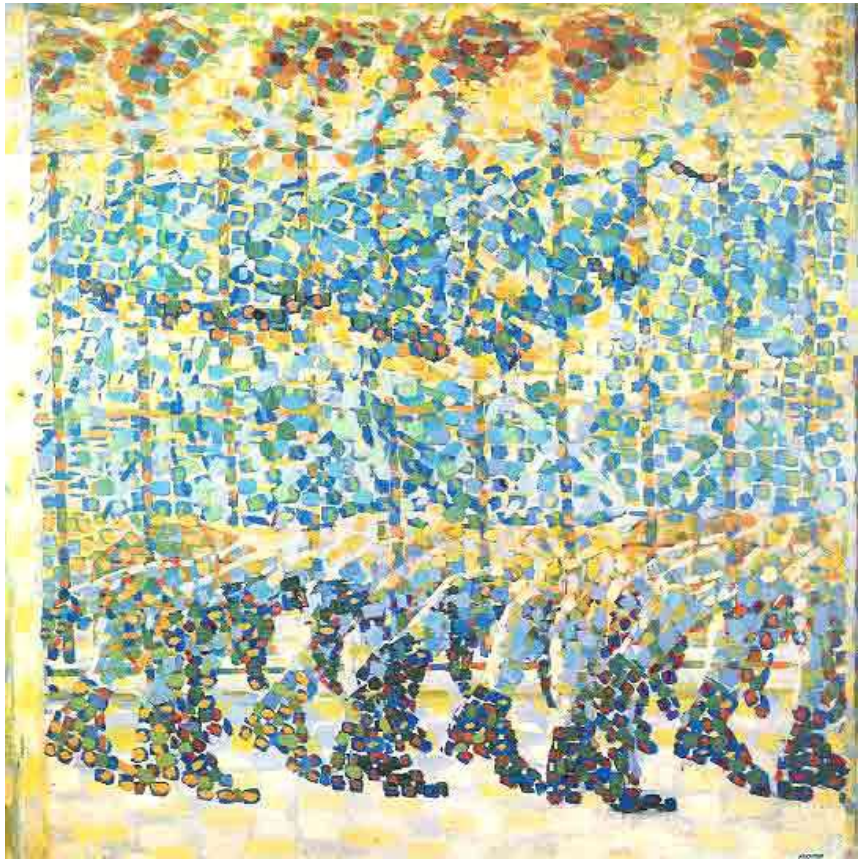
NNH

76.9



Courtesy of Benussi A

The post-modern world of Alzheimer's disease trials: how much is an ADAS-cog point worth in central London?



L Schneider, Int J Geriatr Psychiatry 2006

JNNP

2009

Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease

O L Lopez, J T Becker, A S Wahed, J Saxton, R A Sweet, D A Wolk, W Klunk and S T DeKosky

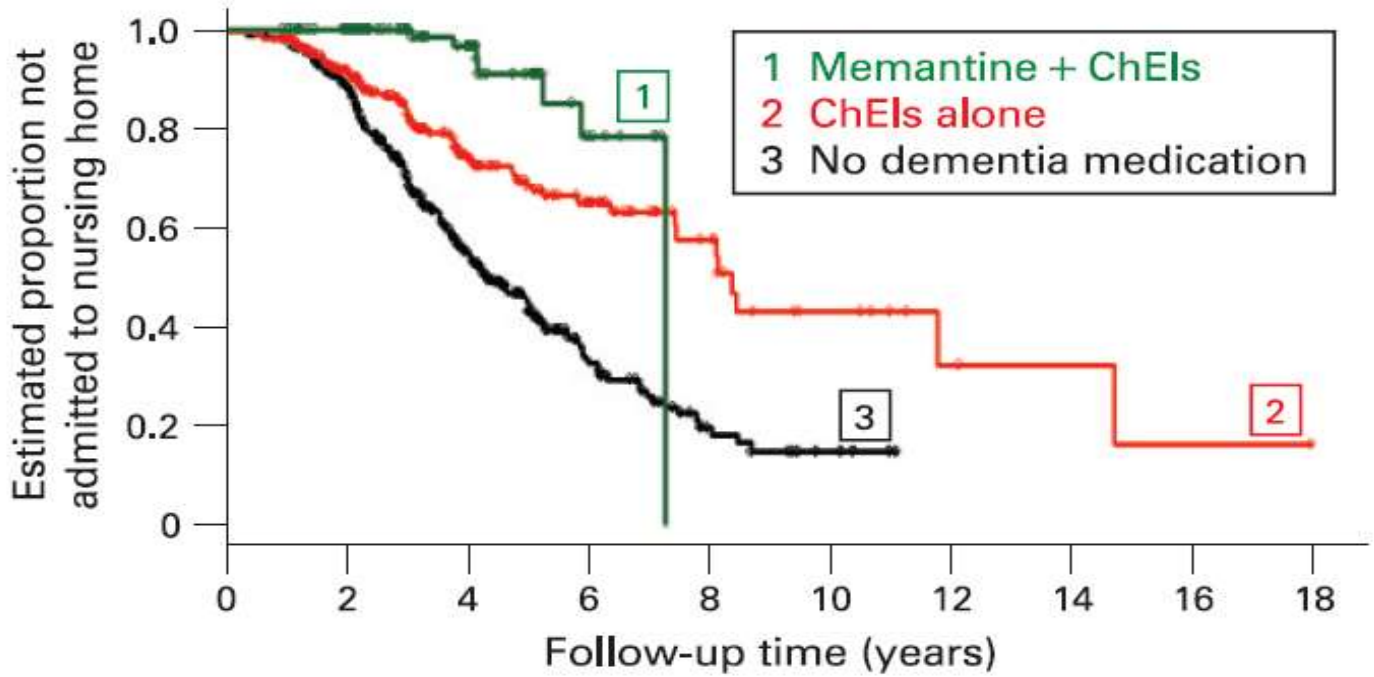


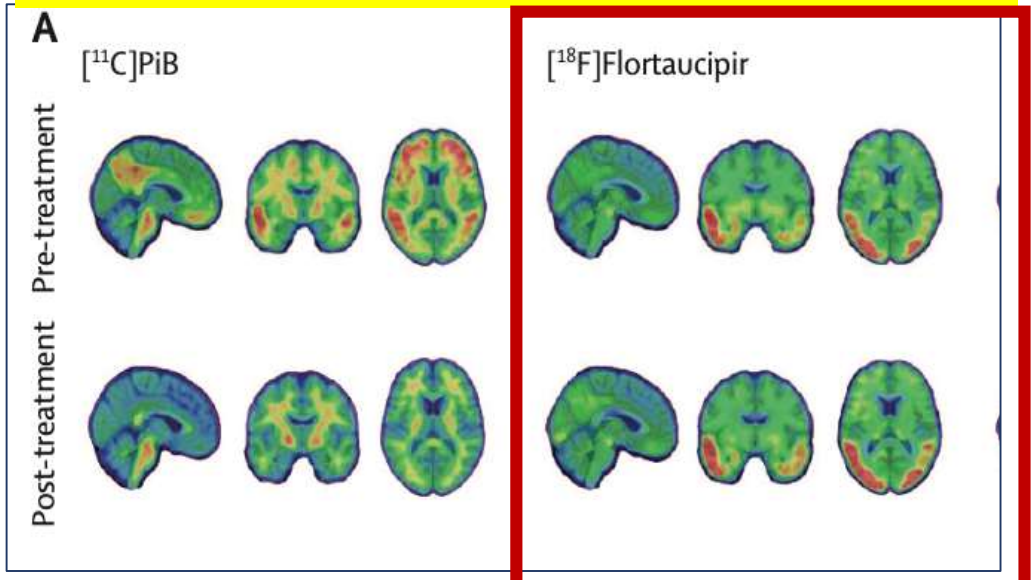
Figure 2 Time to nursing home admission in Cohort 1. ChEIs, cholinesterase inhibitors.

PROGNOSIS OF BENEFIT: low tau pathology

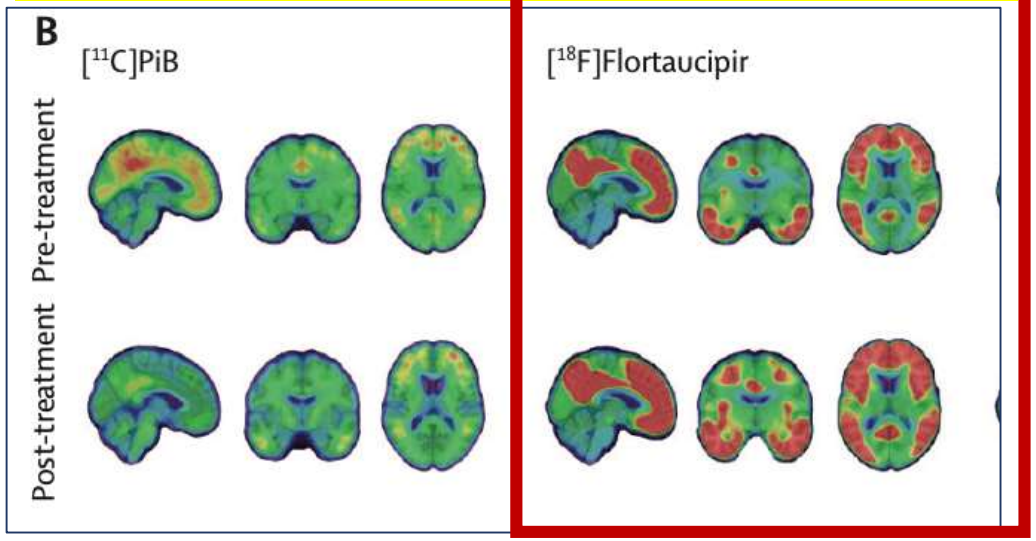
PRE

POST

NON PROGRESSOR CDR= 0.5 to 0.5



PROGRESSOR CDR = 0.5 to 1



PRE

POST

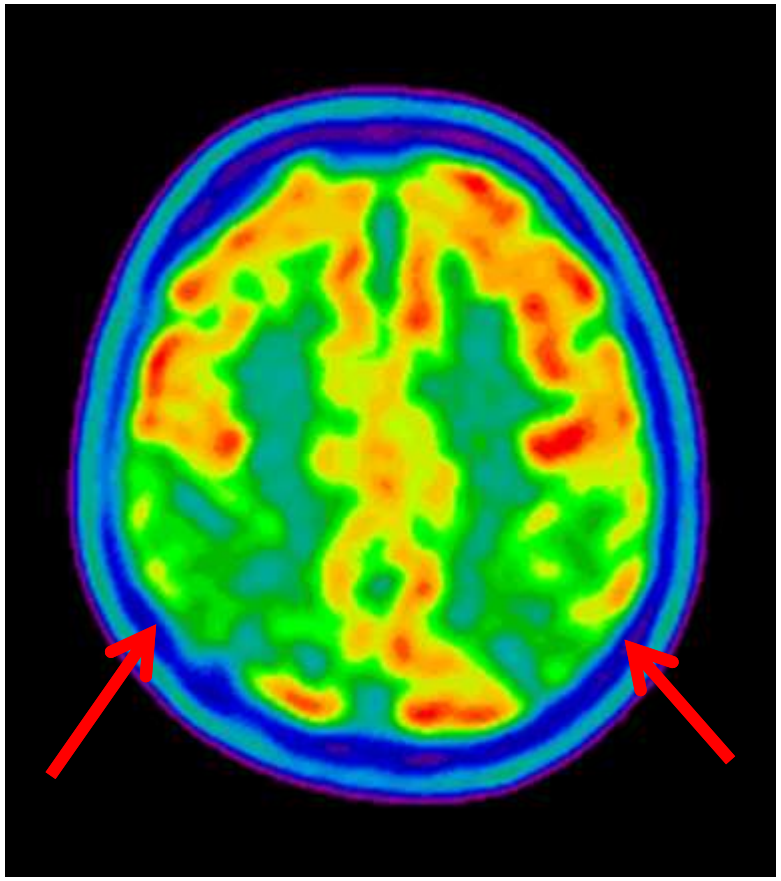
Serrano-Pozo, Lancet 2026

The BEST ELIGIBLE PATIENT

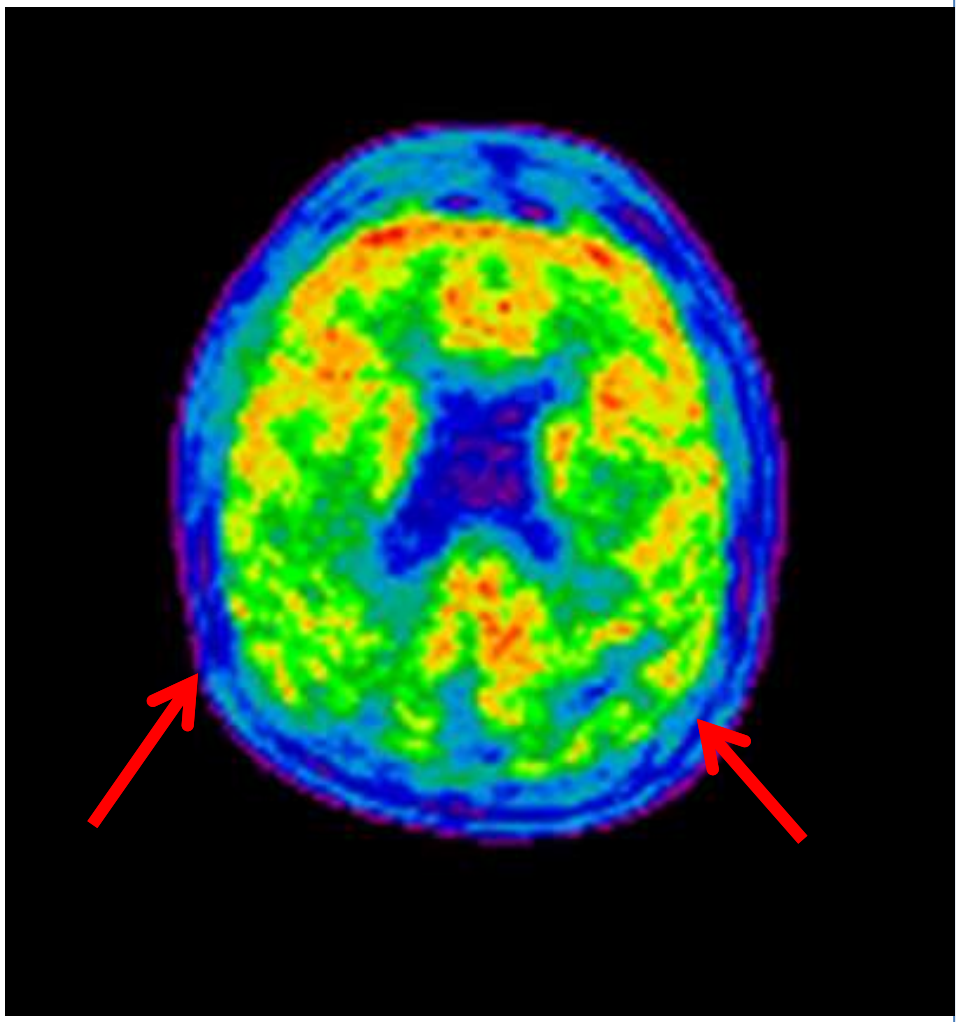
MCI WITH RISK OF PROGRESSION TO DEMENTIA

- Cognitive and IADL features
- Fluid biomarkers (within pTAU 217): MTBR, NFL, GFAP, t-tau
- When TAU-degeneration spread into neocortex
  - Amyloid PET: threshold variable with age (60 ctl.)
  - Functional features (FDG-surrogate)
- Absent/minimal comorbidity

PET-FDG



AMILOIDE – primi 10 min



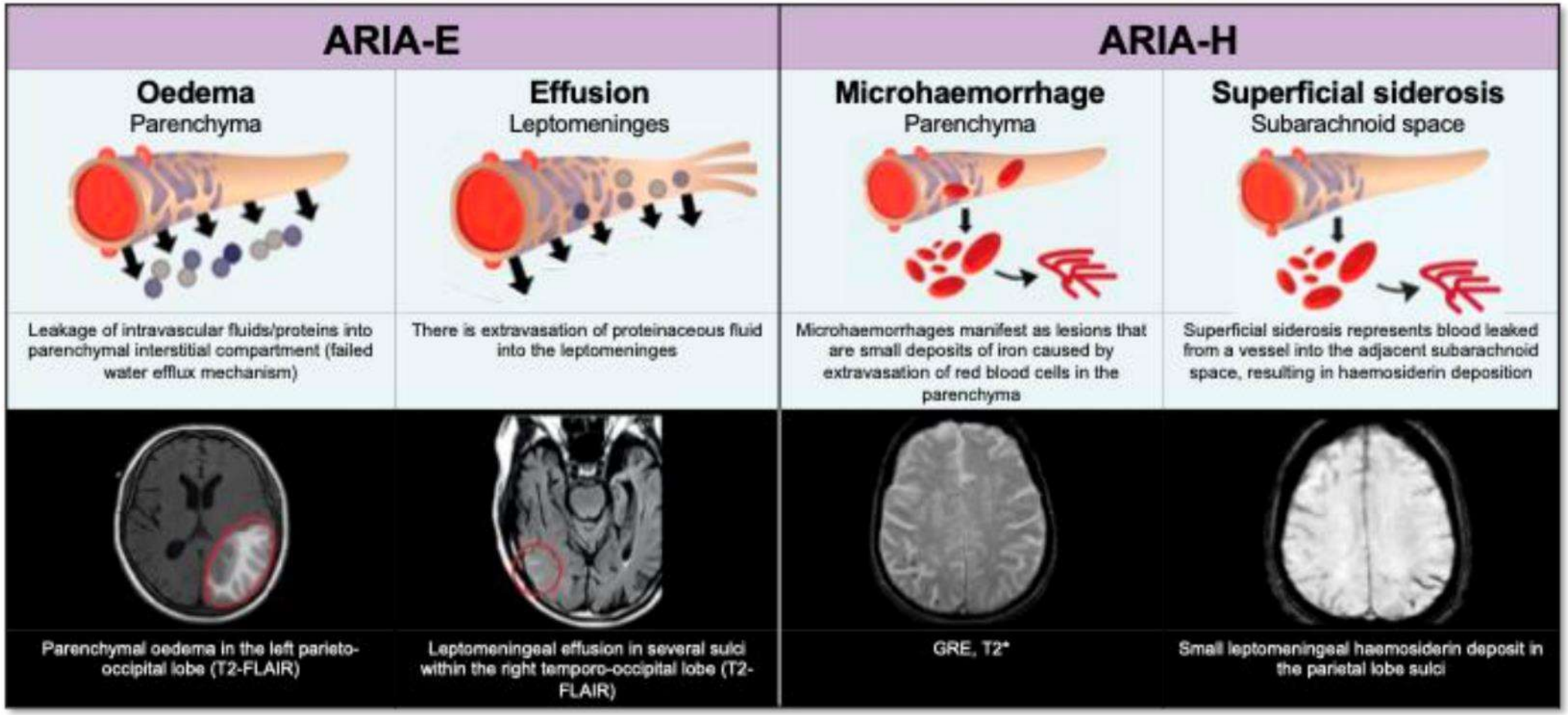
COURTESY PROF CECCHIN D (PADOVA)

RISCHI POSSIBILI

RISK

ARIA

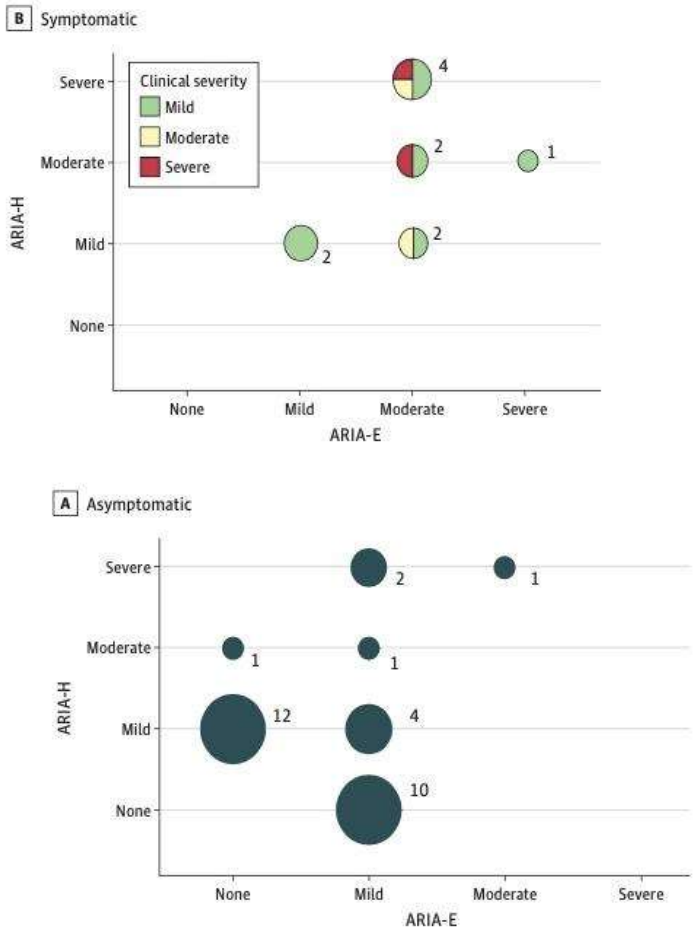
Amyloid Related Imaging Abnormalities

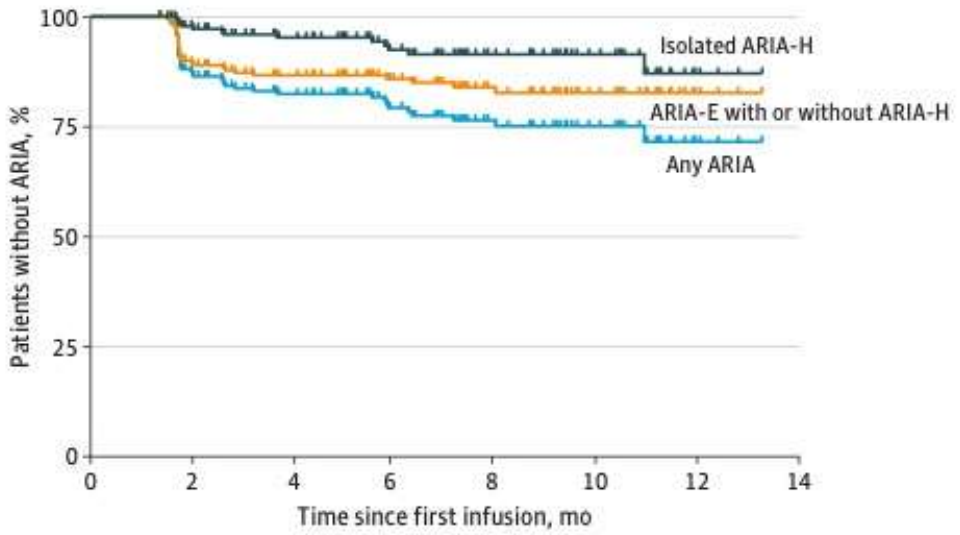


Cogswell AJNR 2025; Hampel 2023

Real-world safety

Figure 2. Percent of Patients With Amyloid-Related Imaging Abnormalities (ARIA) Over the First 14 Months of Treatment





ALZ-NET (ALZHEIMER ASSOCIATION REGISTRY)
1300 patients
14-15% ARIA

SYMPTOMATIC: 1.9% (D) 1.3% (L)
Better selection
Underdiagnoses

Paczynski et al, JAMA Neurol 2025

ALZ-NET REGISTRY

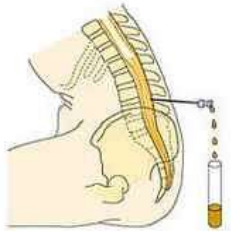
5007 enrolled patients, 1326 started AAT (99.4% MCI/mild AD)

- Clinical outcomes: MMSE and FAQ: most participants remained stable over 12 months

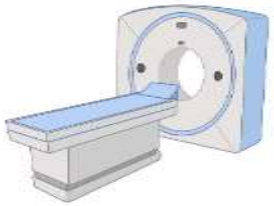
- Safety outcomes: ARIA occurred in 14.3% participants, mostly mild/moderate.

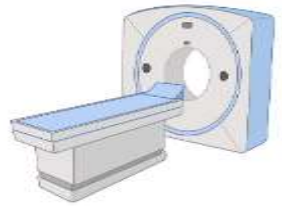
  2 ARIA-related death

RISK / BENEFIT OF AAT



AMY-PET

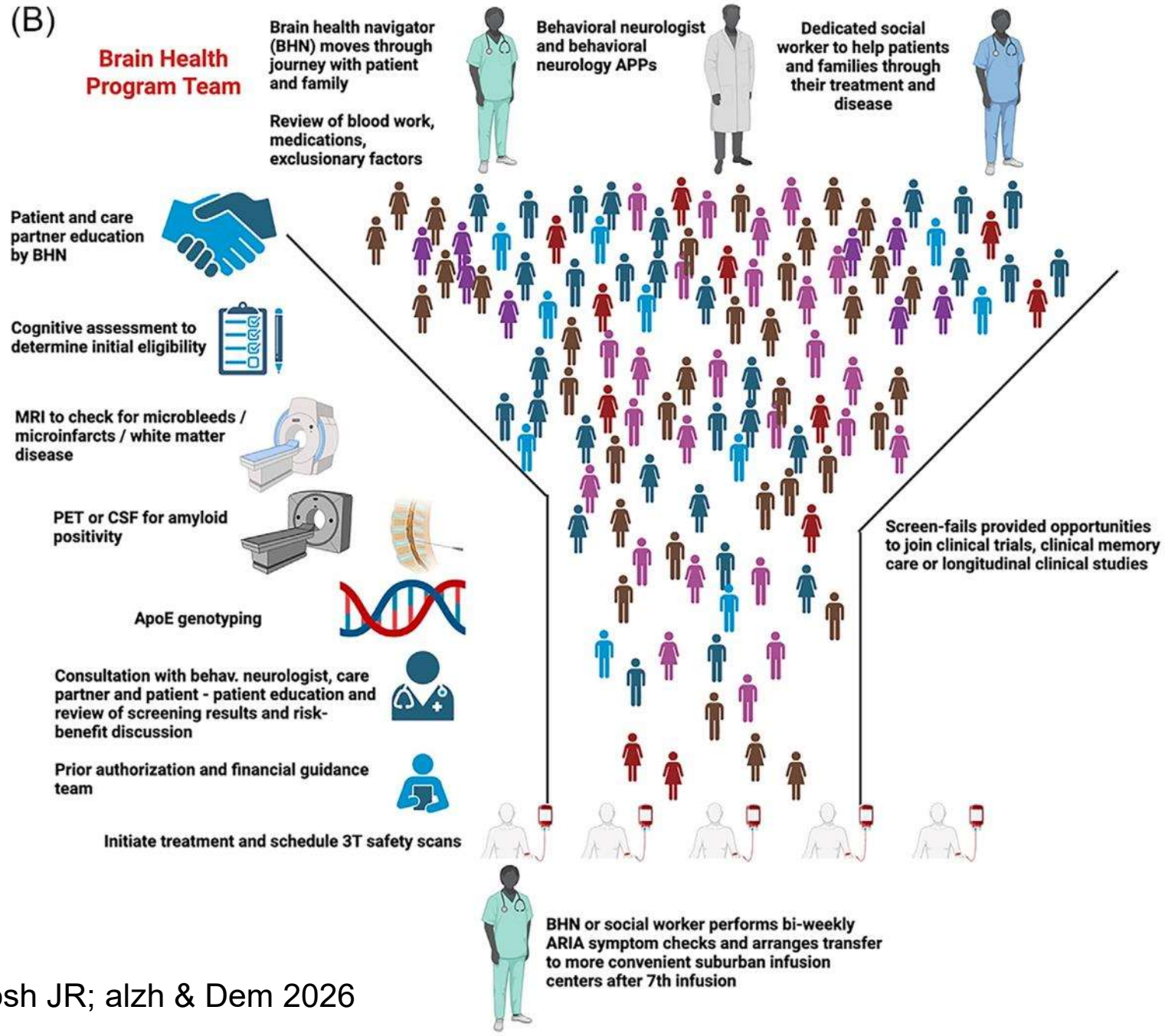




BRAIN MRI

Cagnin et al , Neurol Sci 2025

COMPLESSITA’ ORGANIZZATIVA



Brosh JR; alzh & Dem 2026

MODENA REGISTRY

1080 /anno

50 (4,6%)

Zamboni et al, J Alz Dis Prev 2026

+12,4%

(range 1,5% fino al 28%)

incremento volume attività diagnostica

+208%

(range +68% fino al +305%)

incremento volume esami di follow-up

+7,4 - 11,7%

(range +0,9% fino al 43%)

incremento attività day hospital infusionale

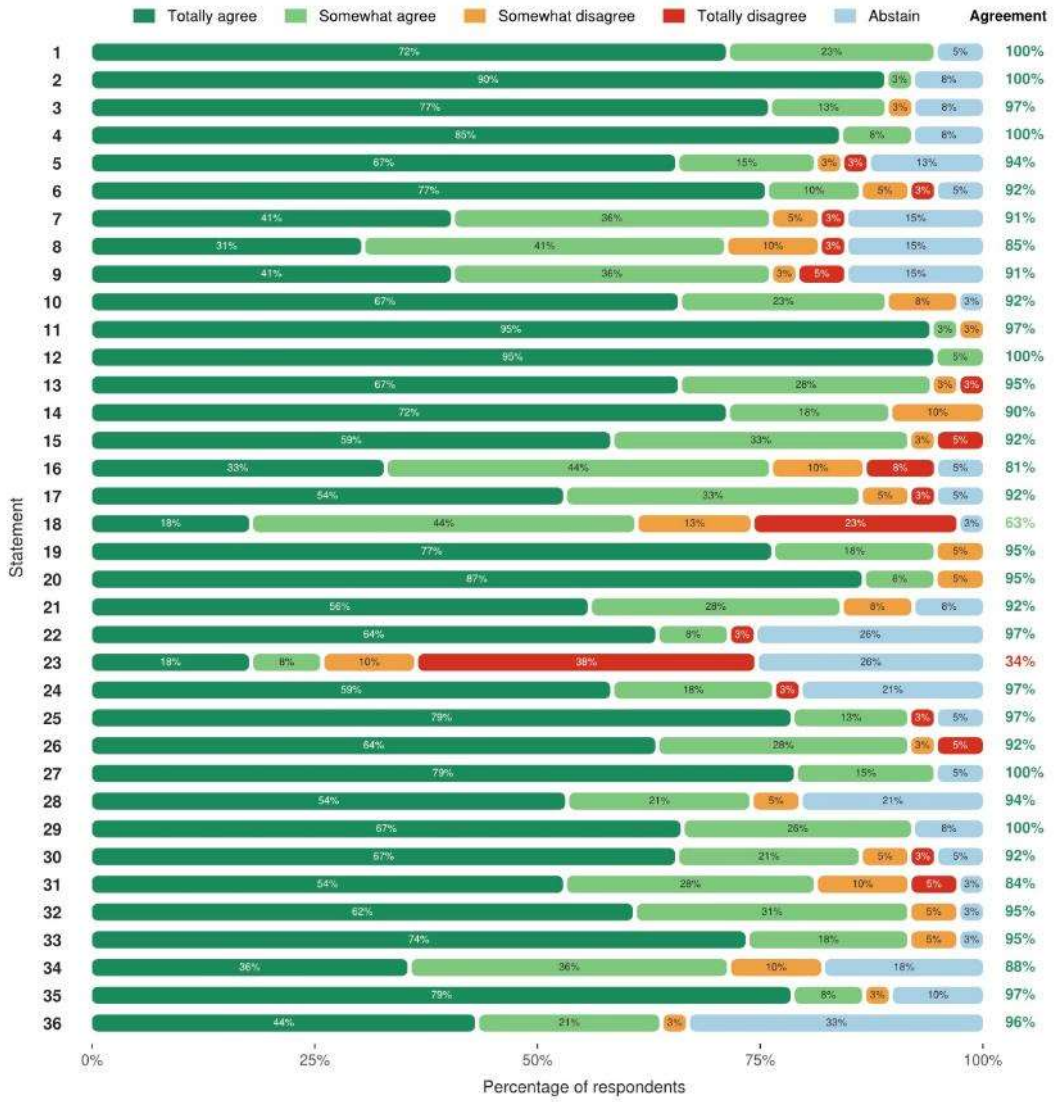
19 slot

(range 10 fino a 33 slots)

fabbisogno monitoraggio RM al mese

Special Article

Updated Italian intersocietal recommendations for the appropriate use of anti-amyloid monoclonal antibodies in Alzheimer's disease



ORGANIZATION OF CDCD
CLINICAL STAGING AND TREATMENT MONITORING
MULTIDISCIPLINARY TEAM
ELIGIBILITY
ARIA MONITORING (MRI…)
FLUID BIOMARKERS
AMYLOID PET
APOE

Moderate agreement: MCI should demonstrate progression

Totally disagree: MRI exclusion set at >1 MB on GRE-MRI

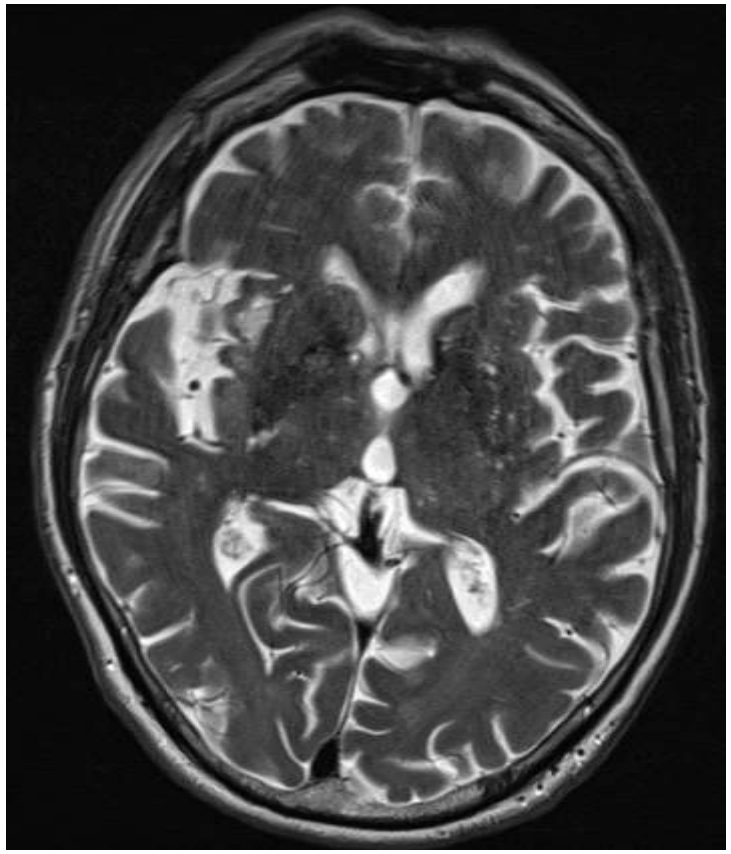
Benussi et al, J Alz Dis Prev 2026
21 Scientific Societies

MULTIDISCIPLINARY ELIGIBILITY STUDY FOR AAT

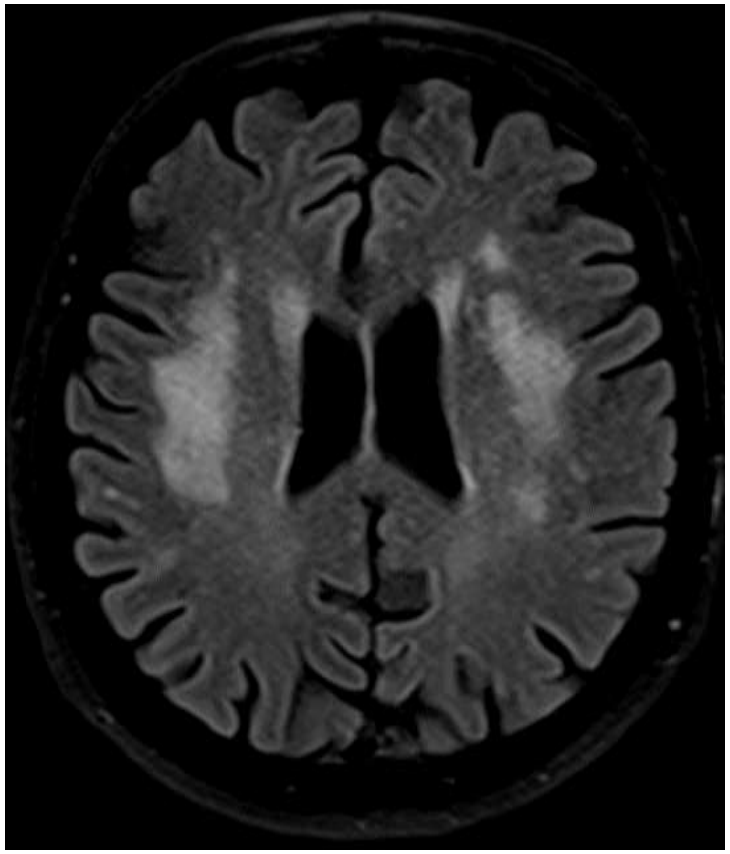
1/3 passed the eligibility evaluation

PERSONAL EXPERIENCE

THE NEURORADIOLOGIST



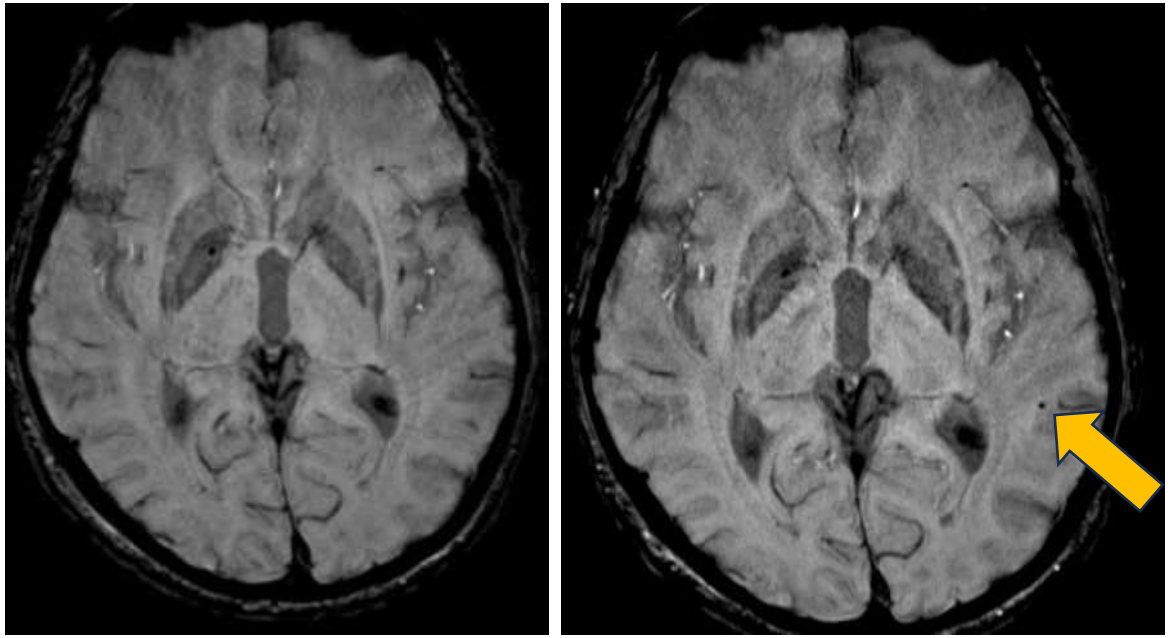
Patient 23: Under-reported lacunes



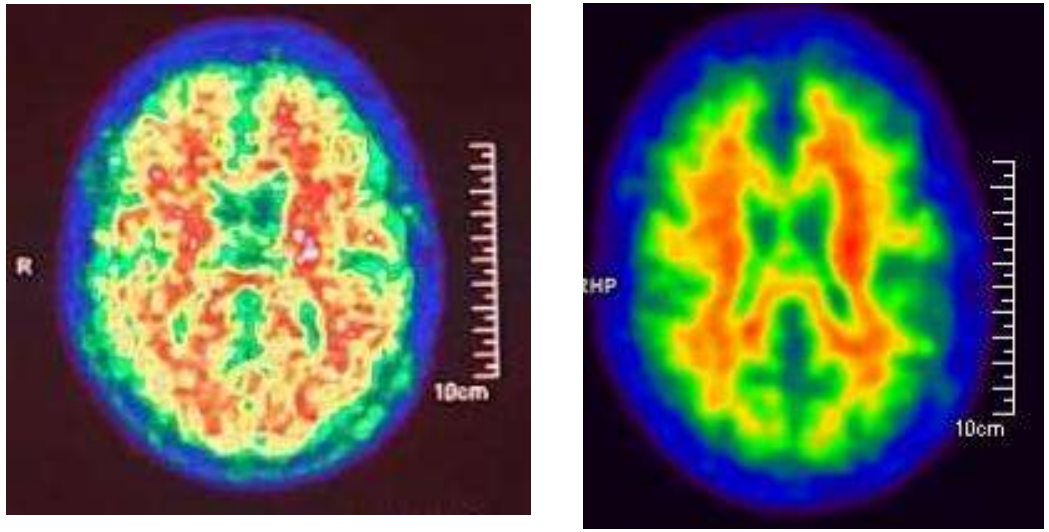
Patient 38: atypical small vessel disease

MULTIDISCIPLINARY TEAM DURING MONITORING

BASELINE **SIX-MONTH**



BASELINE **SIX-MONTH**



66 CTL 22 CTL

PERSONAL EXPERIENCE

Considerations for clinical practice

- Start to evaluate clinical and radiological exclusion criteria
- Request complete MRI sequences acquisition and specific reports
- Ascertain willingness to engage in effortful pathway
- Reduce expectations in individuals possibly not eligible
- Decrease requests of un-needed investigations
- Increase connections with biological labs, MRI and PET sites

HOW MANY ELIGIBLE (WHAT EFFORT)

Modena dementia-care network.

Eligibility level	Definition	Numerator / denominator	Estimate	Main implementation meaning
Service cohort	All patients with ≥1 visit in 2024–2025	1080 / 1080	100%	Referral, triage, and service-level diagnostic workload
Clinical cohort	MCI or mild AD dementia	596 / 1080	55.2%	Population requiring diagnostic-pathway stratification
Clinical-biological AD cohort	Compatible syndrome plus AD biomarkers	230 / 596	38.6%	Biomarker-confirmed pool for treatment-readiness assessment
Eligible before APOE assessment	Fulfilled criteria up to MRI and bleeding-risk steps	62 / 1080	5.7%	Pre-genotyping treatment-readiness workload
After excluding APOE ε4/ε4	EMA-aligned APOE restriction applied	57 / 1080	5.3%	Potentially eligible under APOE restriction
Conservative treatment-ready estimate	APOE ε4/ε4 and missing APOE excluded	50 / 1080	4.6%	Final treatment-ready service-level estimate

MODERATE_SEVERE DEMENTIA 45%

BIOMARKER NEGATIVE 20%

CONTRAINDICATION 30%

APOE 0,4%

Zamboni et al, J Alz Dis Prev 2026