TITOLO RELAZIONE:

Nuovi Farmaci per la prevenzione della malattia di Alzheimer

RELATORE:

Matteo Pardini
IRCCS Policlinico San Martino
Università di Genova

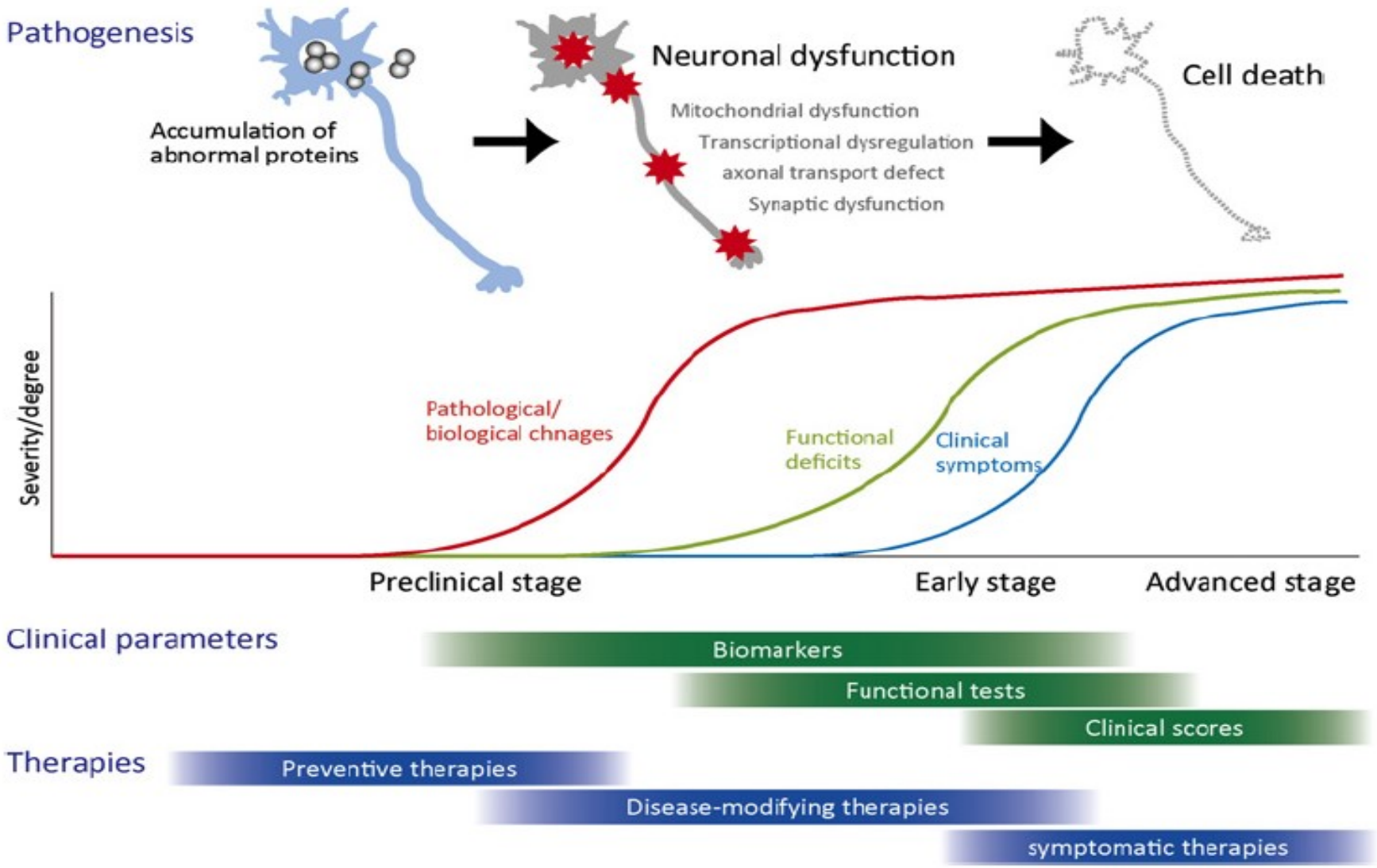
Outline

Criticità nello sviluppo dei DMT nella malattia di Alzheimer

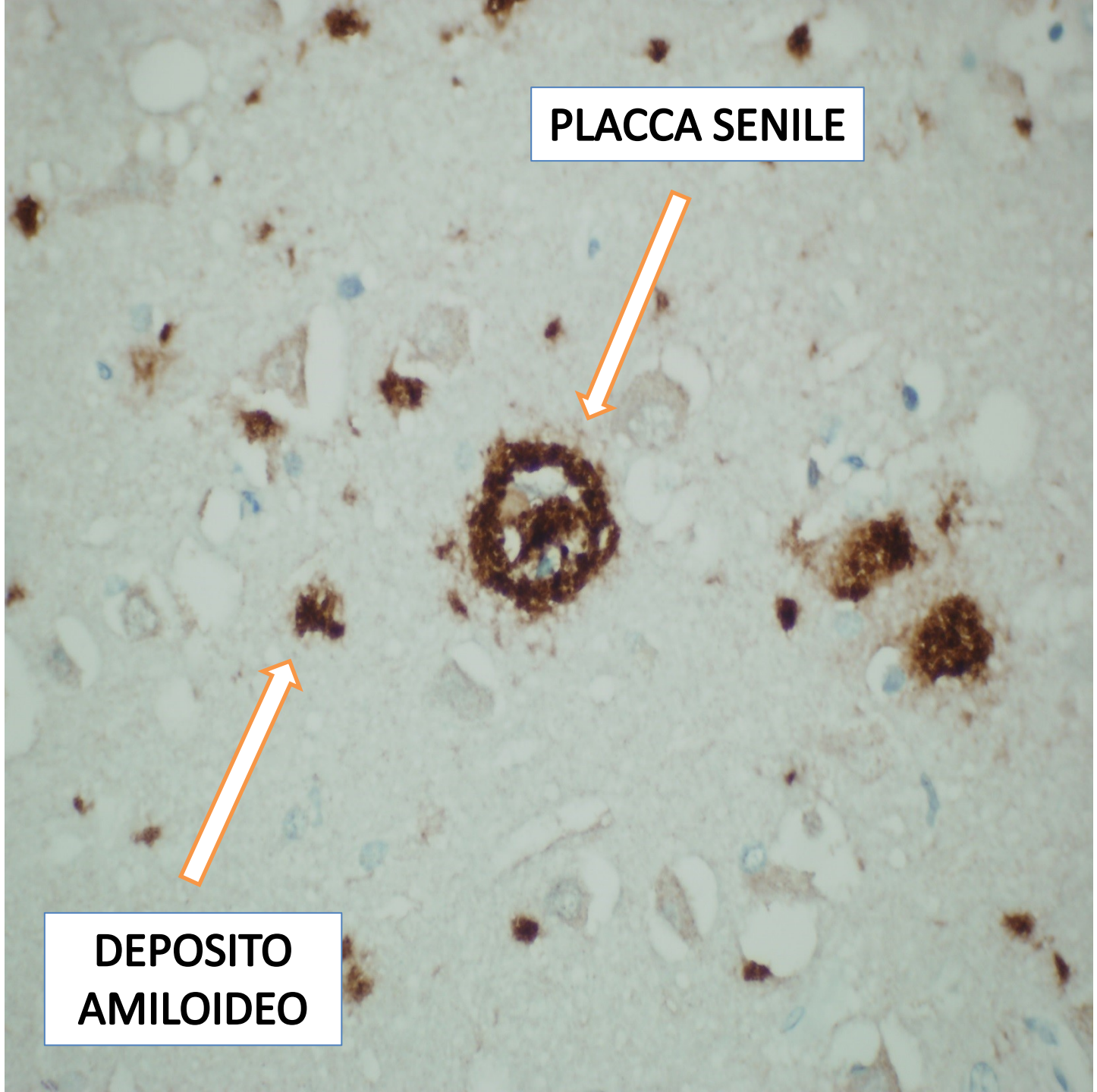
Terapie attuali

I monoclonali… luci e ombre

AD come malattia neurodegenerativa prototipica

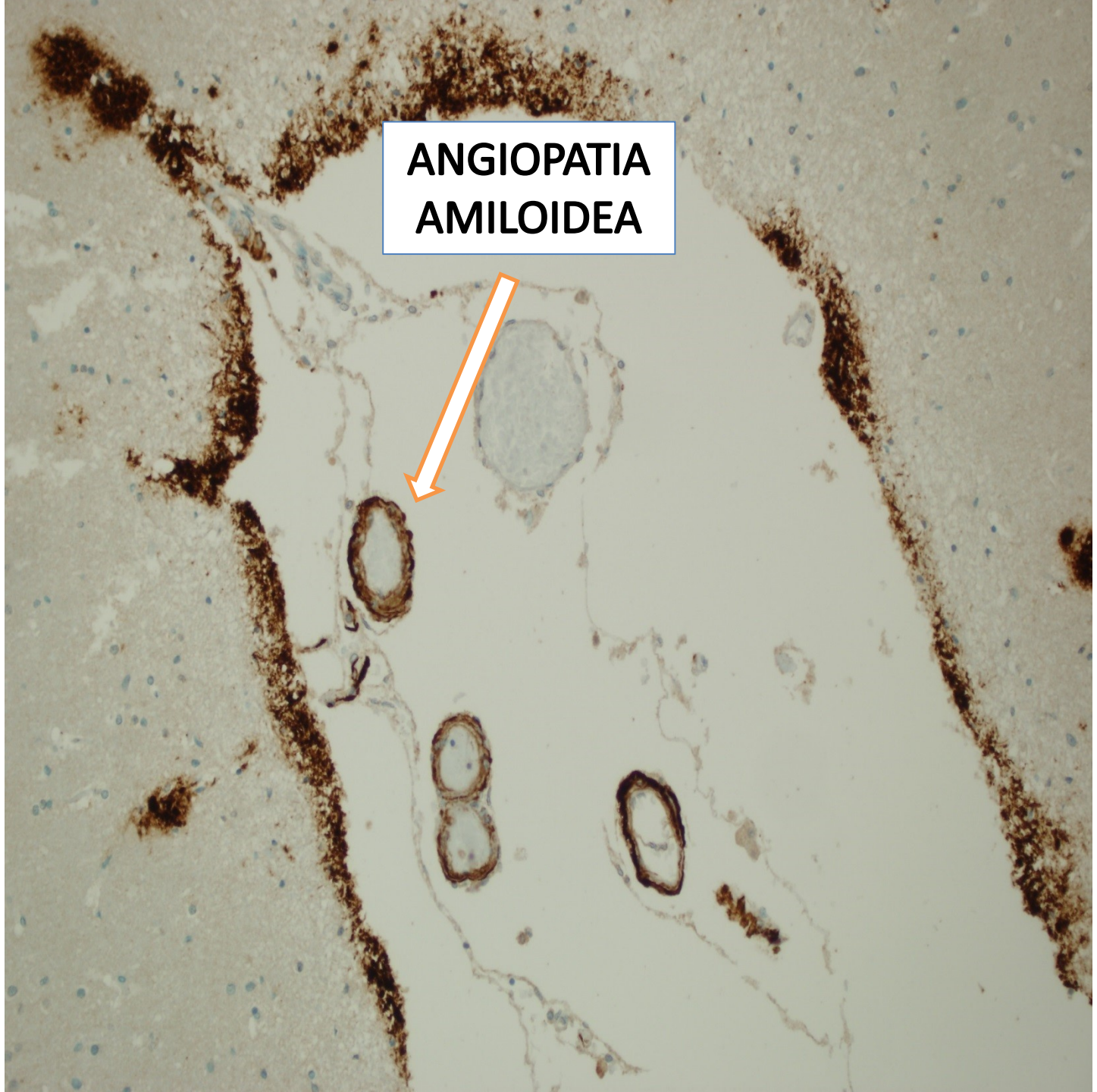


(Katsuno 2011)

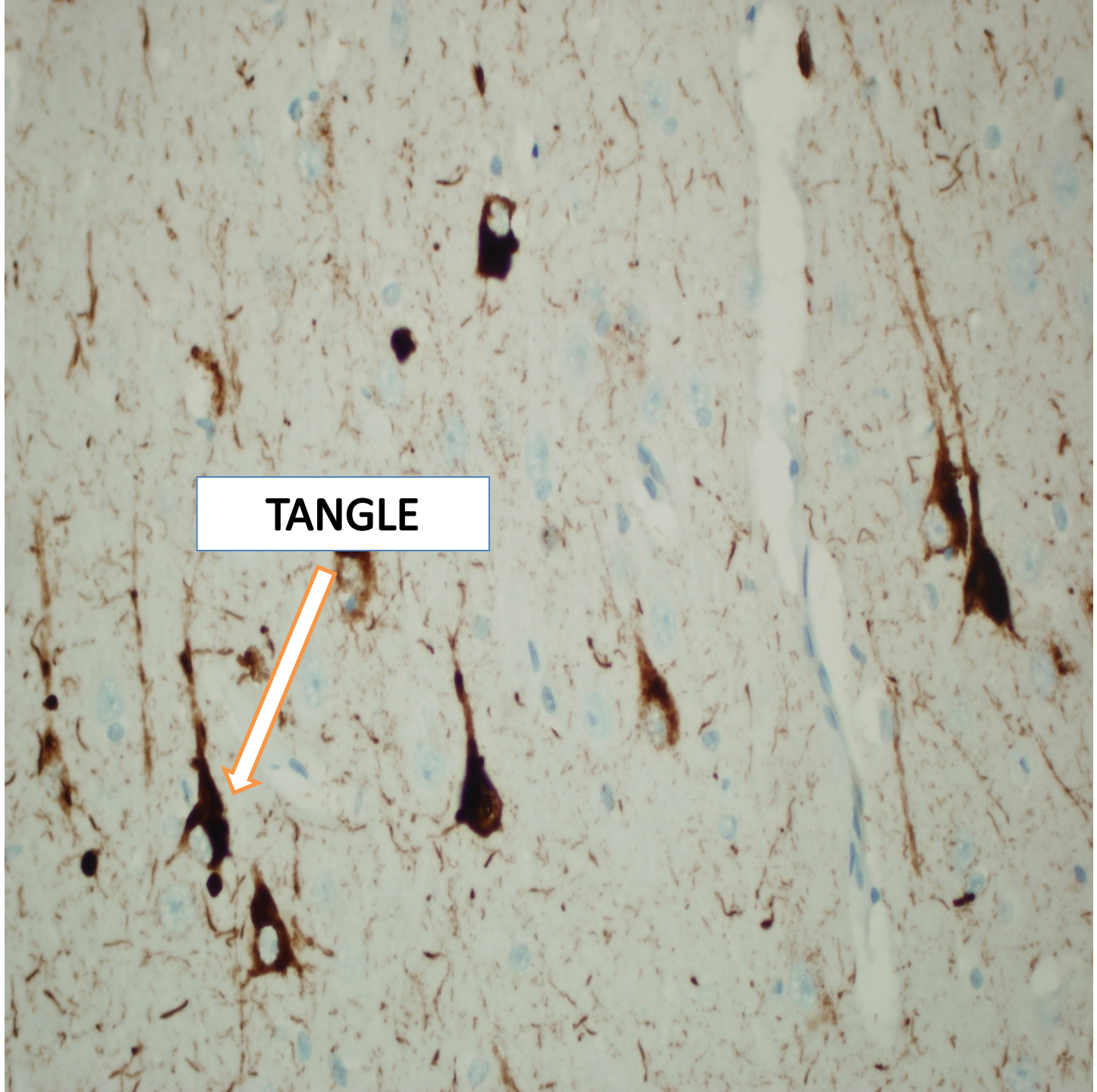


Beta-Amiloide

(Ippocampo 60x)



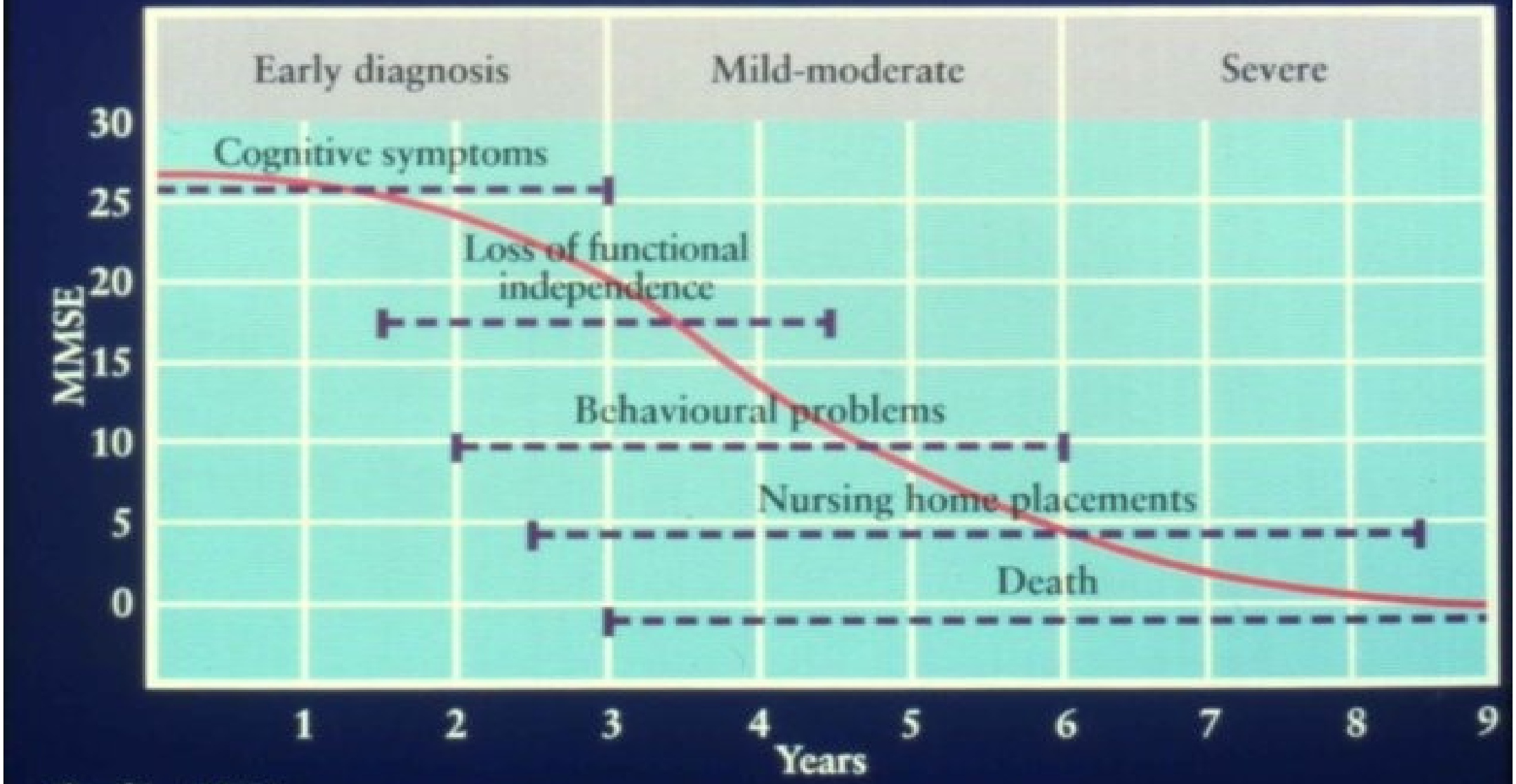
Beta-Amiloide
(20x)



pTAU

(Ippocampo 40x)

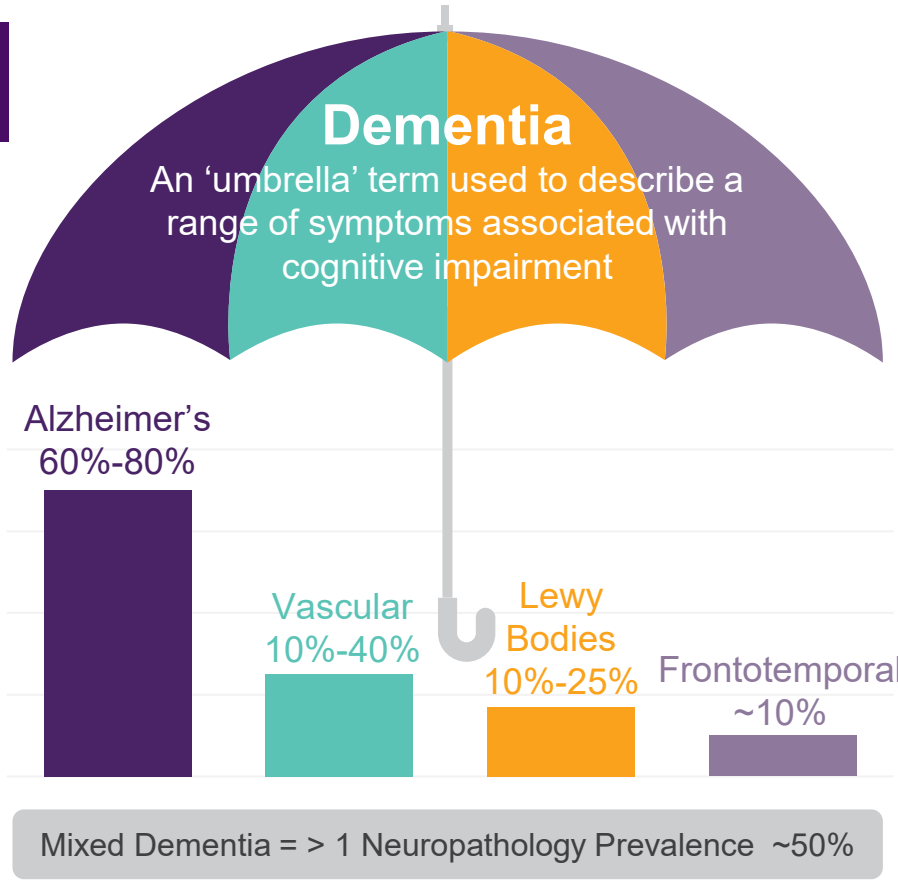
Natural history of AD



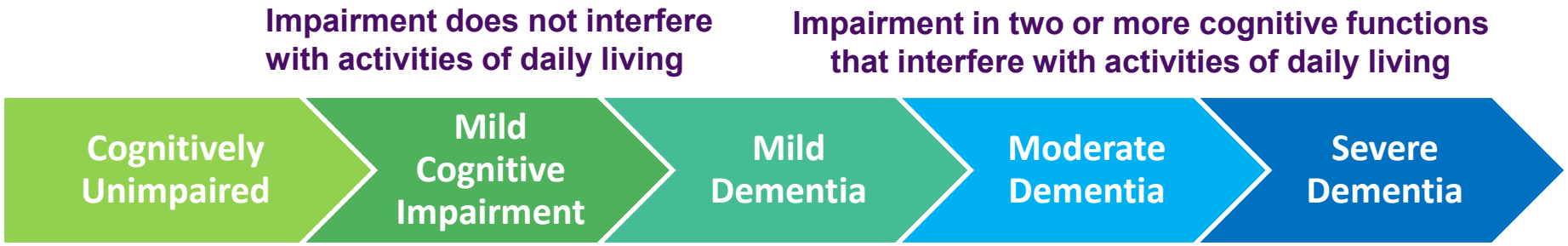
Gauthier (1996)

DEMENTIA IS A SYNDROME

- Dementia is a collection of symptoms related to cognitive decline
- Can include cognitive, behavioral and psychological symptoms
- Due to biological changes in the brain
- Alzheimer's is most common cause
- Mixed dementia is very prevalent
- Some causes of cognitive decline are reversible and not truly dementia



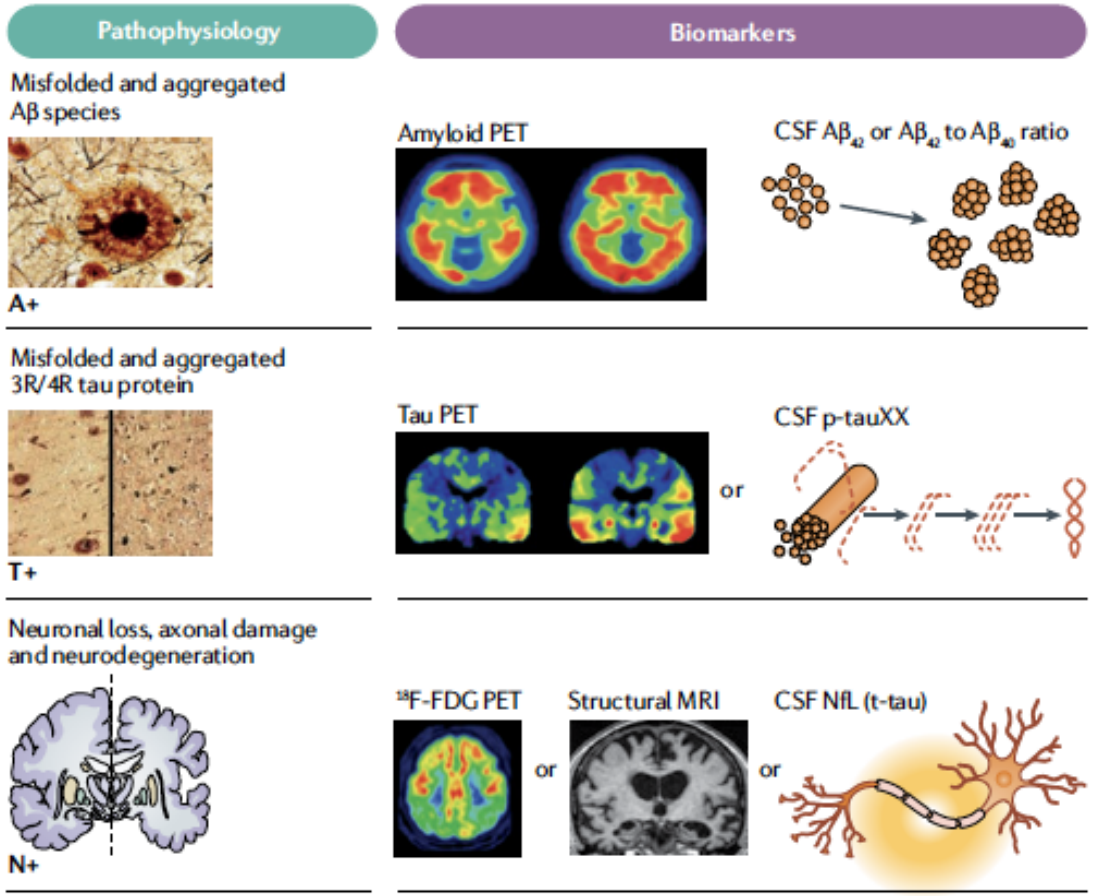
CONTINUUM OF COGNITIVE IMPAIRMENT



MCI is a known risk factor for dementia

Everyone who experiences dementia passes through MCI

When you prevent new cases of MCI, you are preventing new cases of dementia

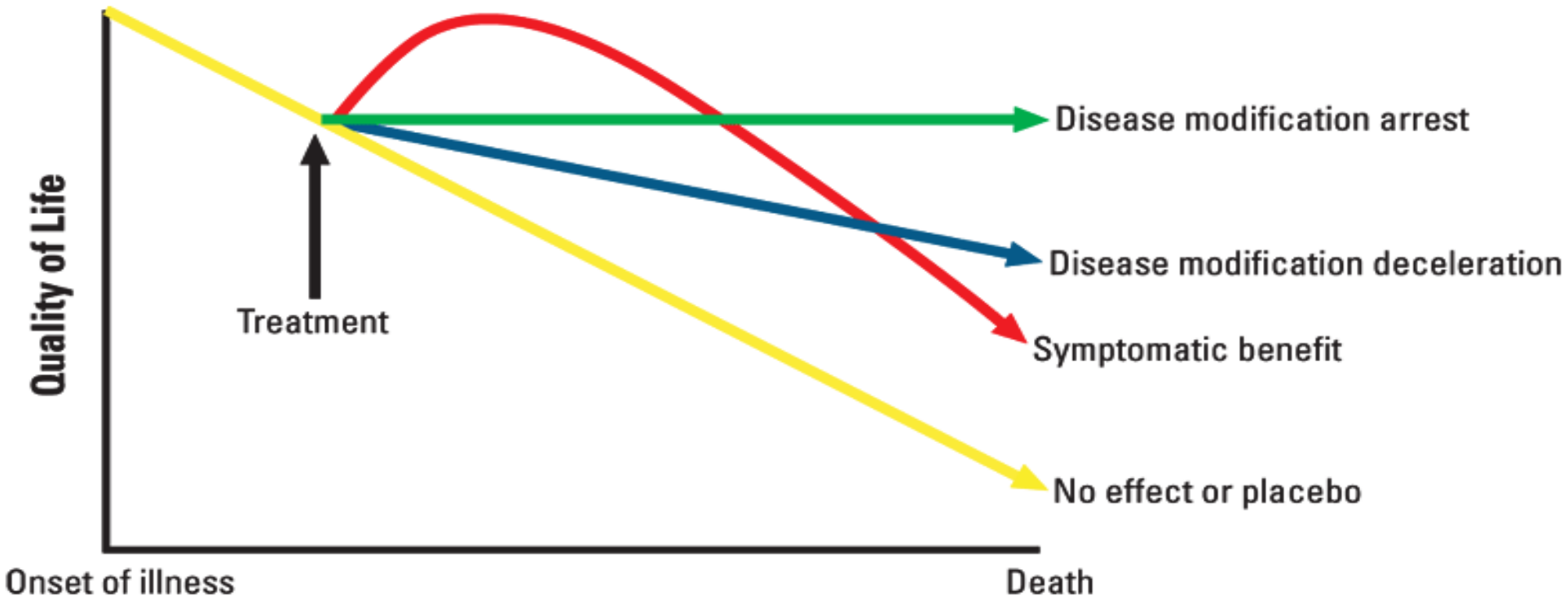


	Stage 0	Clinical Stage 1	Clinical Stage 2	Clinical Stage 3	Clinical Stages 4–6
Initial biological stage (A)	X	1A	2A	3A	4-6A
Early biological stage (B)	X	1B	2B	3B	4-6B
Intermediate biological stage (C)	X	1C	2C	3C	4-6C
Advanced biological stage (D)	X	1D	2D	3D	4-6D

Terapia sintomatica vs «modificante il decorso»

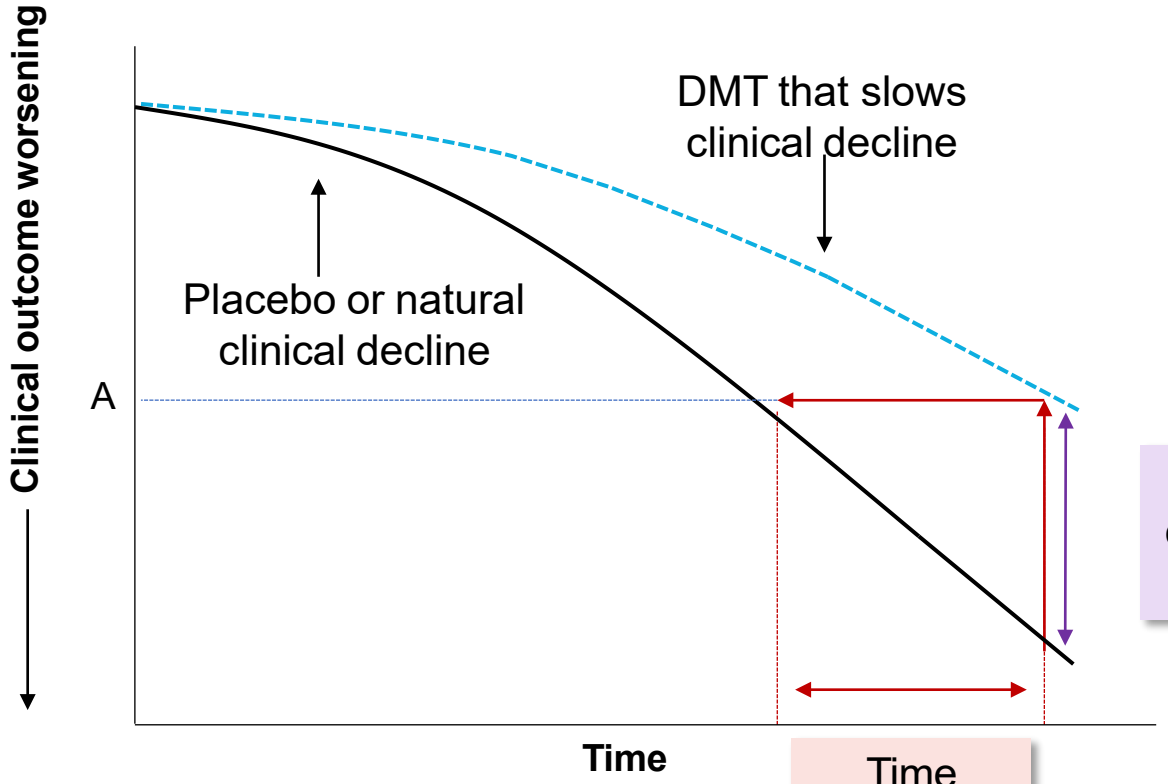
FIGURE

DISEASE MODIFICATION VERSUS SYMPTOMATIC BENEFIT IN THE TREATMENT OF ALZHEIMER'S DISEASE



Kennedy GJ. *Primary Psychiatry*. Vol 14, No 11. 2007.

Quale obiettivo?



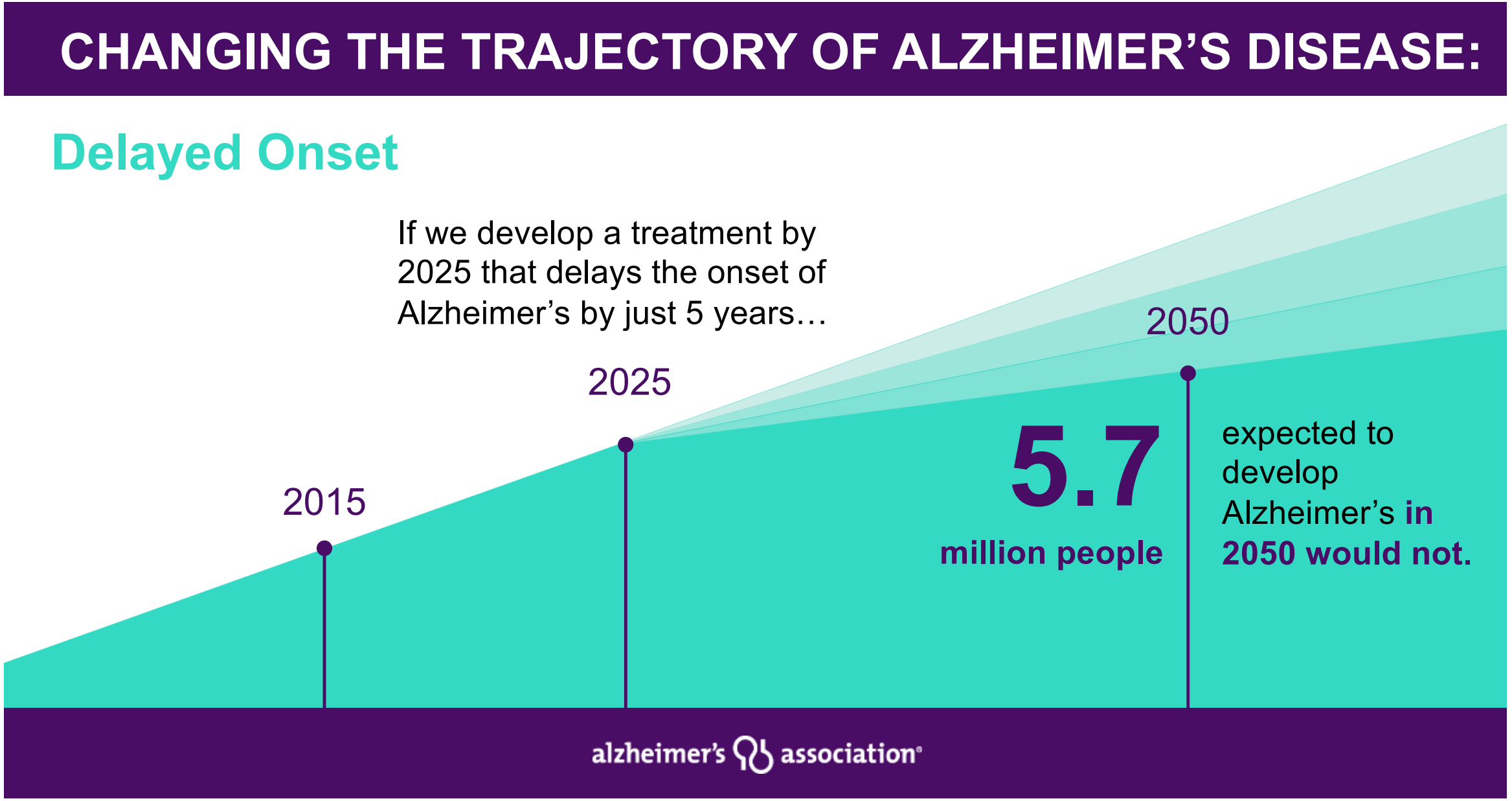
DMT effect on clinical outcome measure → Expressed as the *point difference* between treatment and placebo groups or *% slowing*

The time saving approach expresses treatment effect as *time saved* with treatment → Time saved with DMT

Dickson et al J Prev Alz Dis 2023;10:595-599

Abbreviations: DMT=disease-modifying therapy; iADRS=integrated Alzheimer's Disease Rating Scale

Quale obiettivo?



Outline

Criticità nello sviluppo dei DMT nella malattia di Alzheimer

Terapie attuali

I monoclonali… luci e ombre

Int J Geriatr Psychiatry 2017; **32**: 650–656

Anticholinergic effect on cognition (AEC) of drugs commonly used in older people

Delia Bishara[1,2,3], Daniel Harwood[2], Justin Sauer[2] and David M. Taylor[1,3]

Medication
Furosemide
Alprazolam
Quetiapine
Isosorbide
Risperidone
Trazodone
Olanzapine
Ranitidine
Quinidine
Warfarin
Codeine
Fentanyl
Morphine
Aripiprazole
Venlafaxine
Amitriptyline
Clozapine
Nortriptyline
Oxybutynin

Drugs with AEC score of 2	Drugs with AEC score of 3
Amantadine	Alimemazine (trimeprazine)
Chlorphenamine	Amitriptyline
Desipramine	Atropine
Dicycloverine (dicyclomine)	Benztropine
Dimenhydrinate	Chlorpromazine
Diphenhydramine	Clemastine
Disopyramide	Clomipramine
Levomepromazine (methotrimeprazine)	Clozapine
Olanzapine	Cyproheptadine
Paroxetine	Dothiepin
Pethidine	Doxepin
Pimozide	Hyoscine hydrobromide
Prochlorperazine	Imipramine
Promazine	Lofepramine
Propantheline	Nortriptyline
Quetiapine	Orphenadrine
Tolterodine	Oxybutynin
Trifluoperazine	Procyclidine
	Promethazine
	Trihexyphenidryl (benzhexol)
	Trimipramine

•*Si invecchia come si è vissuto*

Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective

Matthew Baumgart[a], Heather M. Snyder[b,*], Maria C. Carrillo[b], Sam Fazio[c], Hye Kim[a], Harry Johns[d]

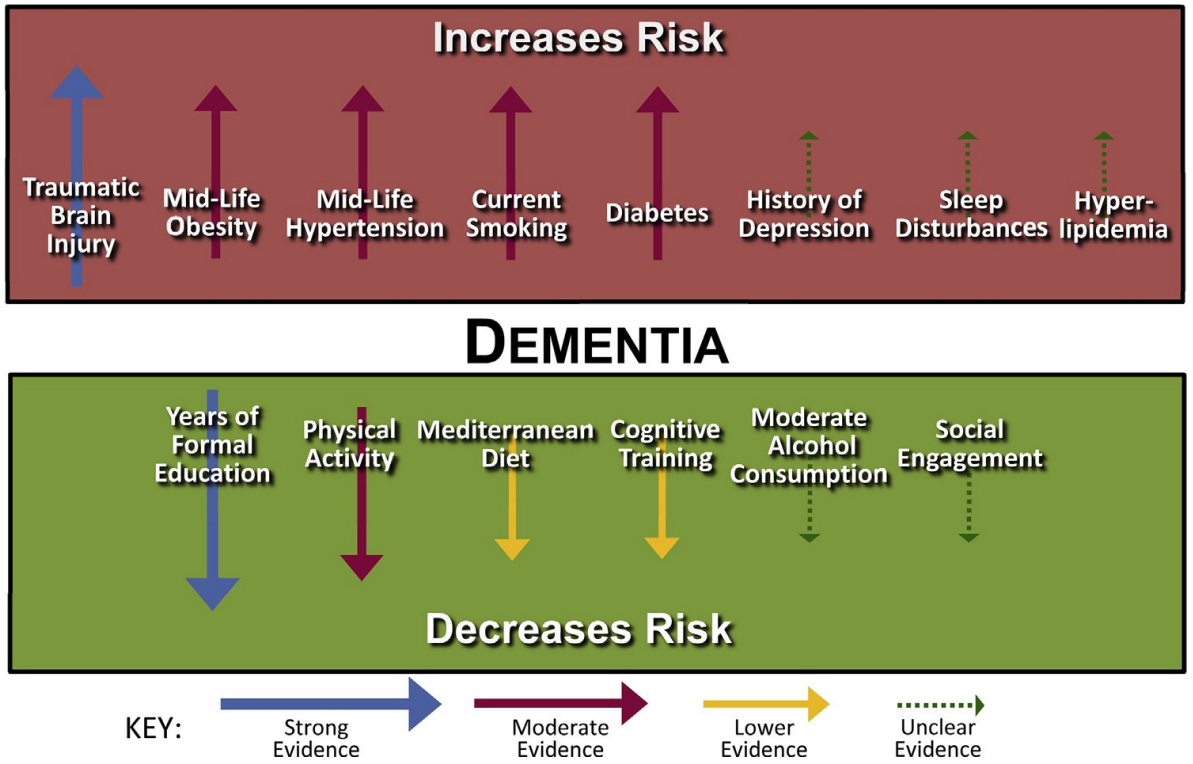


Fig. 2. Strength of evidence on risk factors for dementia.

Clinical practice with anti-dementia drugs: A revised (third) consensus statement from the British Association for Psychopharmacology

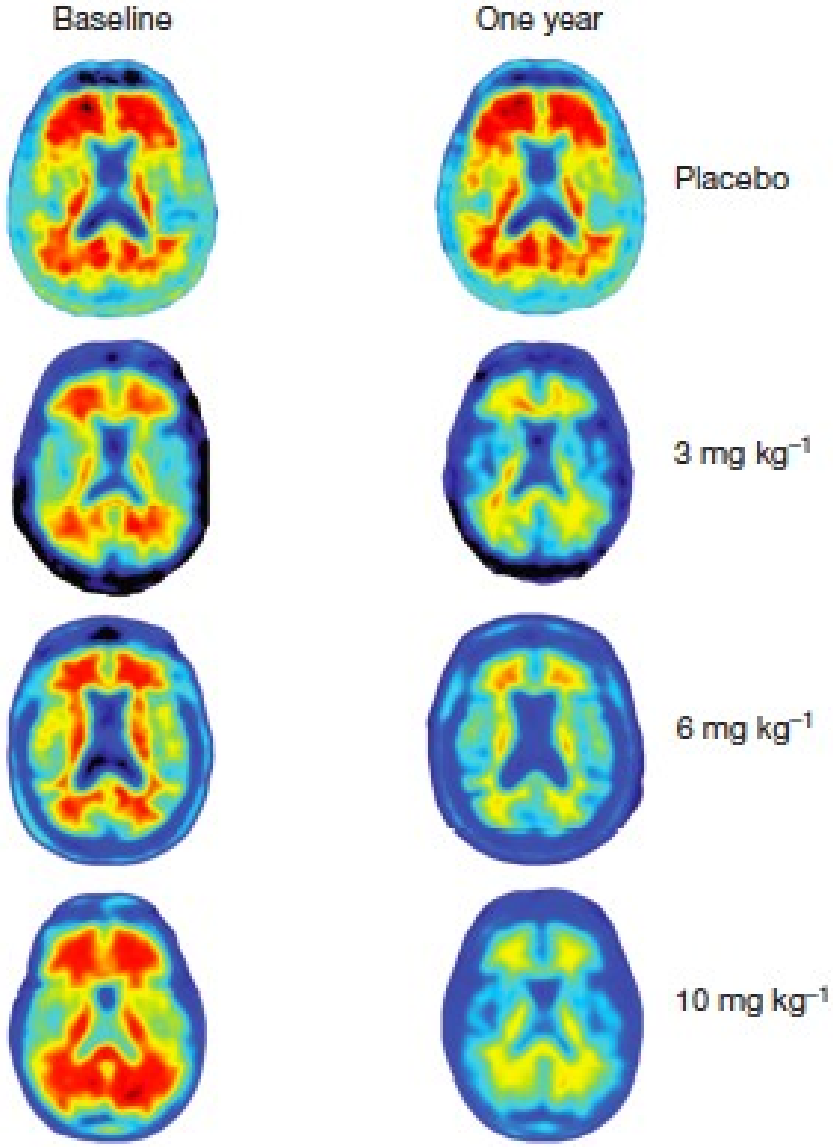
Journal of Psychopharmacology
2017, Vol. 31(2) 147–168

Table 3. Summary box: Alzheimer's disease.

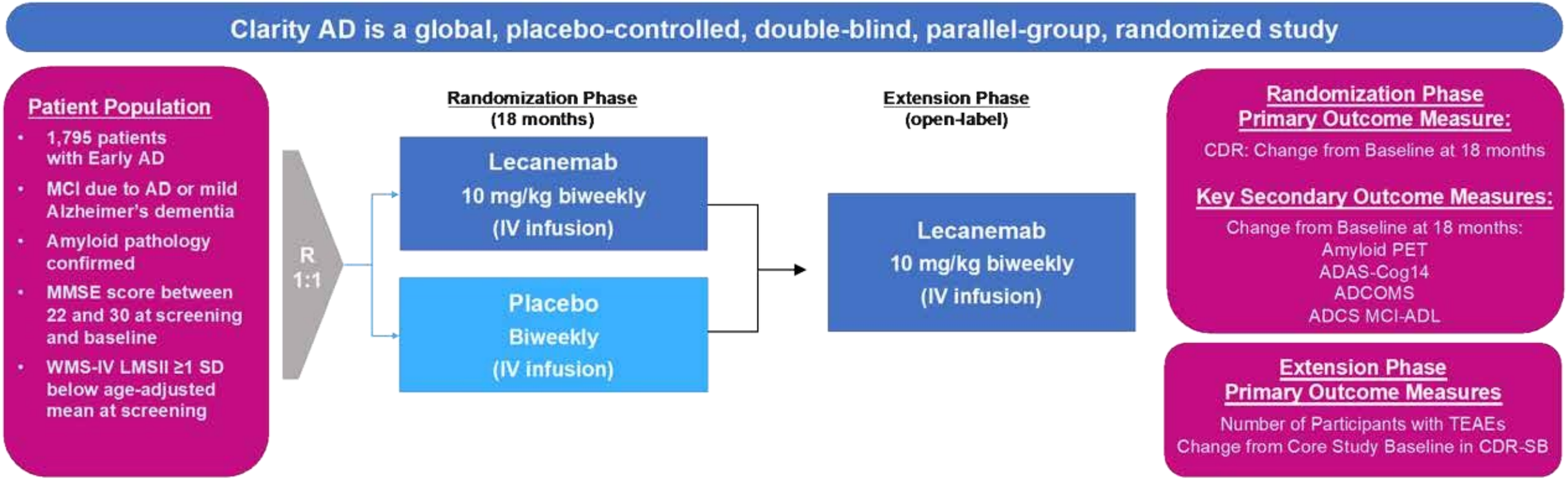
Intervention	Level of evidence	Recommendation
Treatment with cholinesterase inhibitors and memantine	There is type I evidence for the efficacy of cholinesterase inhibitors in the treatment of mild to severe Alzheimer's disease.	A
	There is type I evidence for memantine in moderate to severe Alzheimer's disease.	A
	There is type I evidence that cholinesterase inhibitors should not be stopped just because the point of severe dementia has been reached.	A
Switching between cholinesterase inhibitors	There is type II evidence to support the switching of one cholinesterase inhibitor to another if the first is not tolerated or effective.	B
Combination therapy	There is type I evidence for adding memantine to a cholinesterase inhibitor.	B

DEPOSITO AMILOIDEO

Amiloide… dal microscopio alle immagini PET



Clarity AD Study Design



Randomization stratified according to:

- Clinical subgroup (MCI due to AD or mild AD dementia)
- Presence or absence of ongoing approved AD treatment (eg, acetylcholinesterase inhibitors, memantine, or both)
- ApoE4 status (ie, carriers or non-carriers)
- Geographical region

Diverse patient population

- Eligibility Criteria
- Site selection
- Community outreach
- Decentralized activities

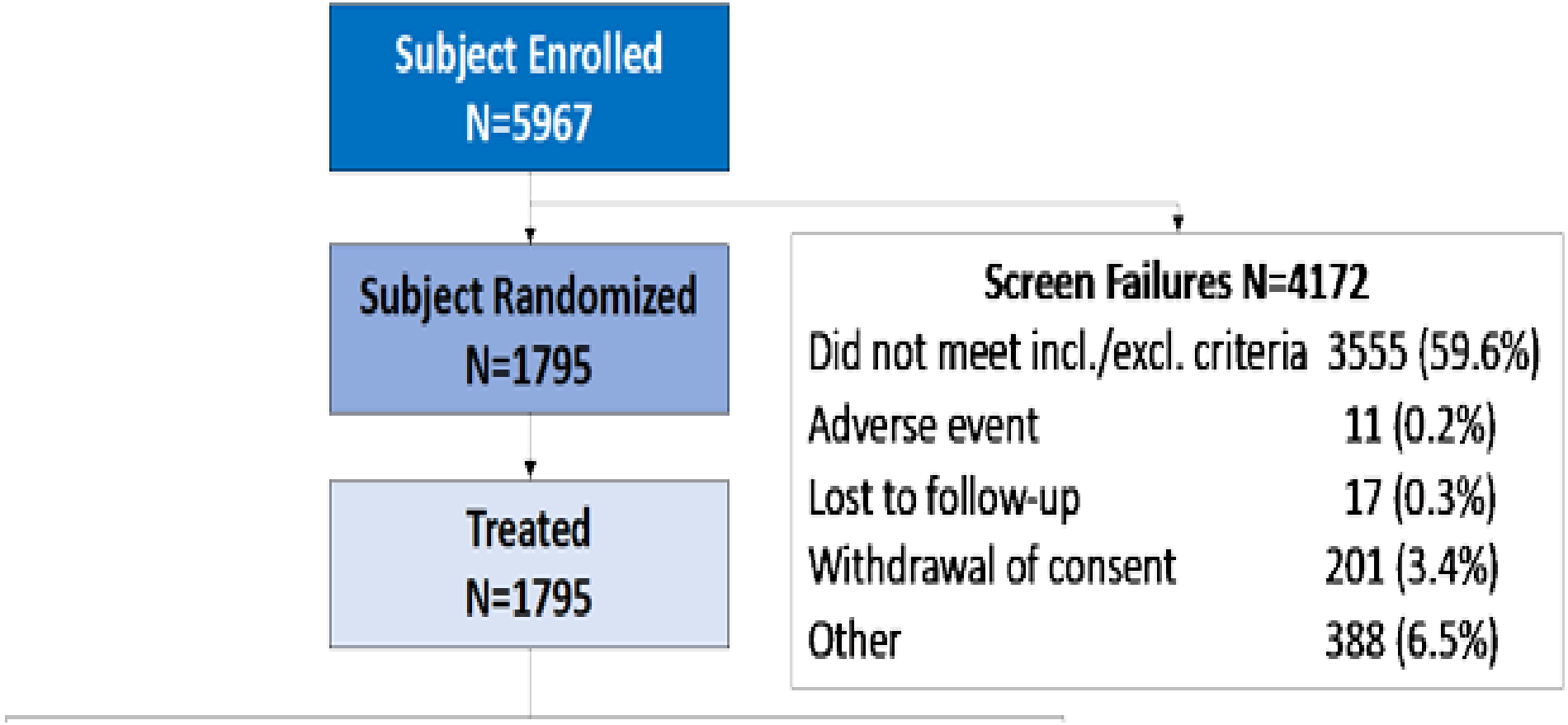
Optional longitudinal sub-studies

- Amyloid burden (amyloid PET; n=716)
- Brain tau pathology (tau PET; n=257)
- CSF biomarkers of neurodegeneration (n=281)
- Subcutaneous formulation (OLE)

AD, Alzheimer's disease; ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ApoE4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating-sum of boxes; CSF, cerebrospinal fluid; IV, intravenous; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; OLE, open-label extension; PET, positron emission tomography; SD, standard deviation; TEAEs, treatment emergent adverse events; WMS-IV LMSII, Wechsler Memory Scale IV-Logical Memory (subscale) II.

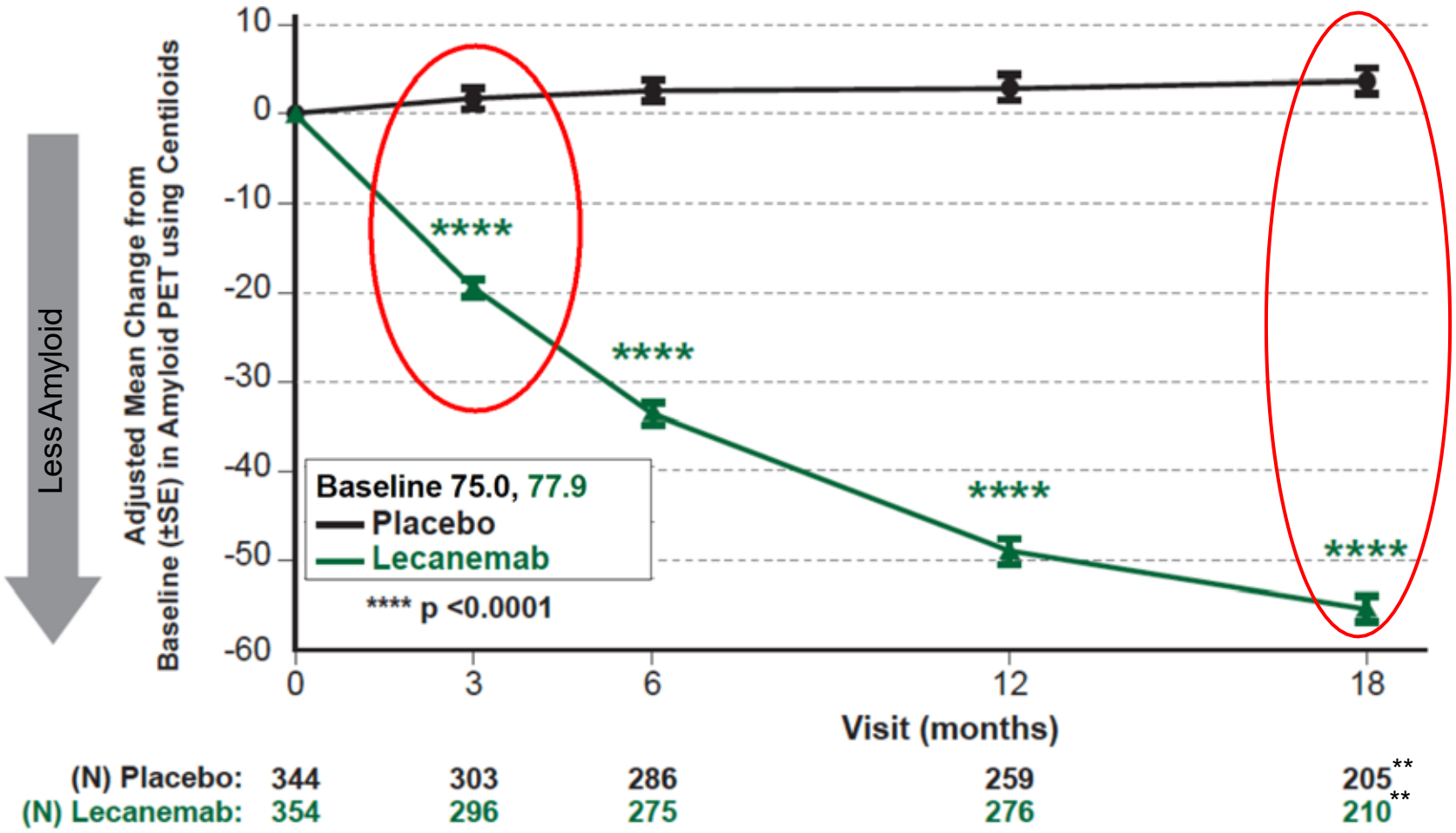
Clarity AD

Subject Disposition and Analyses Populations



Amyloid PET:

Lecanemab Significantly Reduced Fibrillar Amyloid Burden at All Time Points Beginning at 3 Months



Mean <30 Centiloids for lecanemab at 18 months*

Difference of -59.1 Centiloids at 18 months

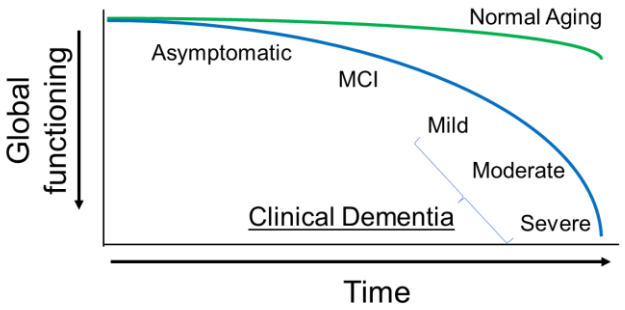
*After 18 months of treatment, the average amyloid level was 23 Centiloids in the lecanemab treatment group in the amyloid PET substudy, which is below the threshold for amyloid positivity of approximately 30 Centiloids above which participants are considered to have elevated brain amyloid.

** 73 subjects were not included at 18 months (per Statistical analysis plan) since their PET assessments were performed after receiving lecanemab in the extension phase.

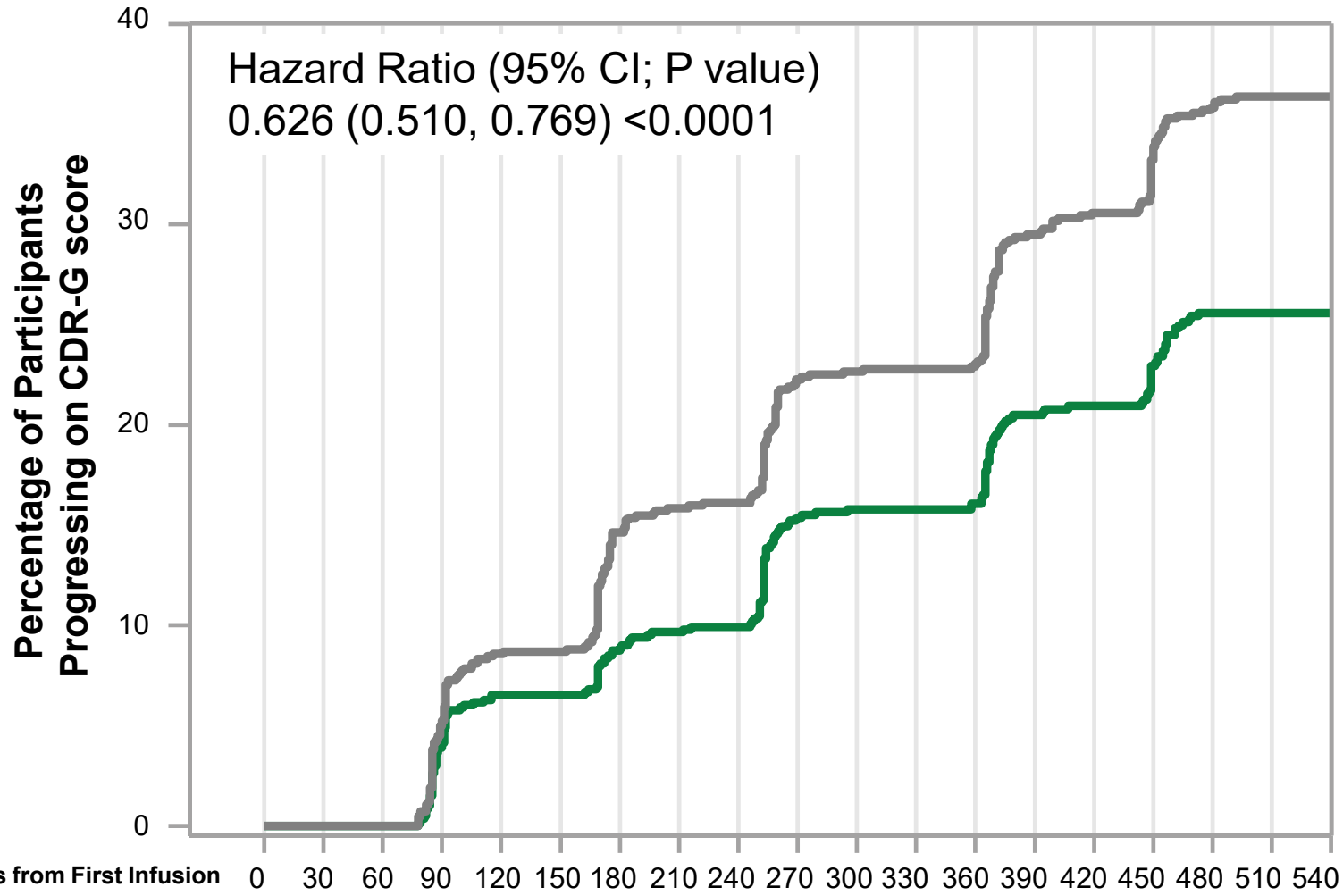
Note: Based on pharmacodynamic analysis population (amyloid PET substudy population). Adjusted mean change from baseline, standard error (SE) and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.
PET: positron emission tomography. SE, standard error.

Risk of Progression

Combined Tau population



Modified from Sperling, A (2011). Alzheimer's & Dementia, 7, 280–292. https://doi.org/10.1016/j.jalz.2011.03.003

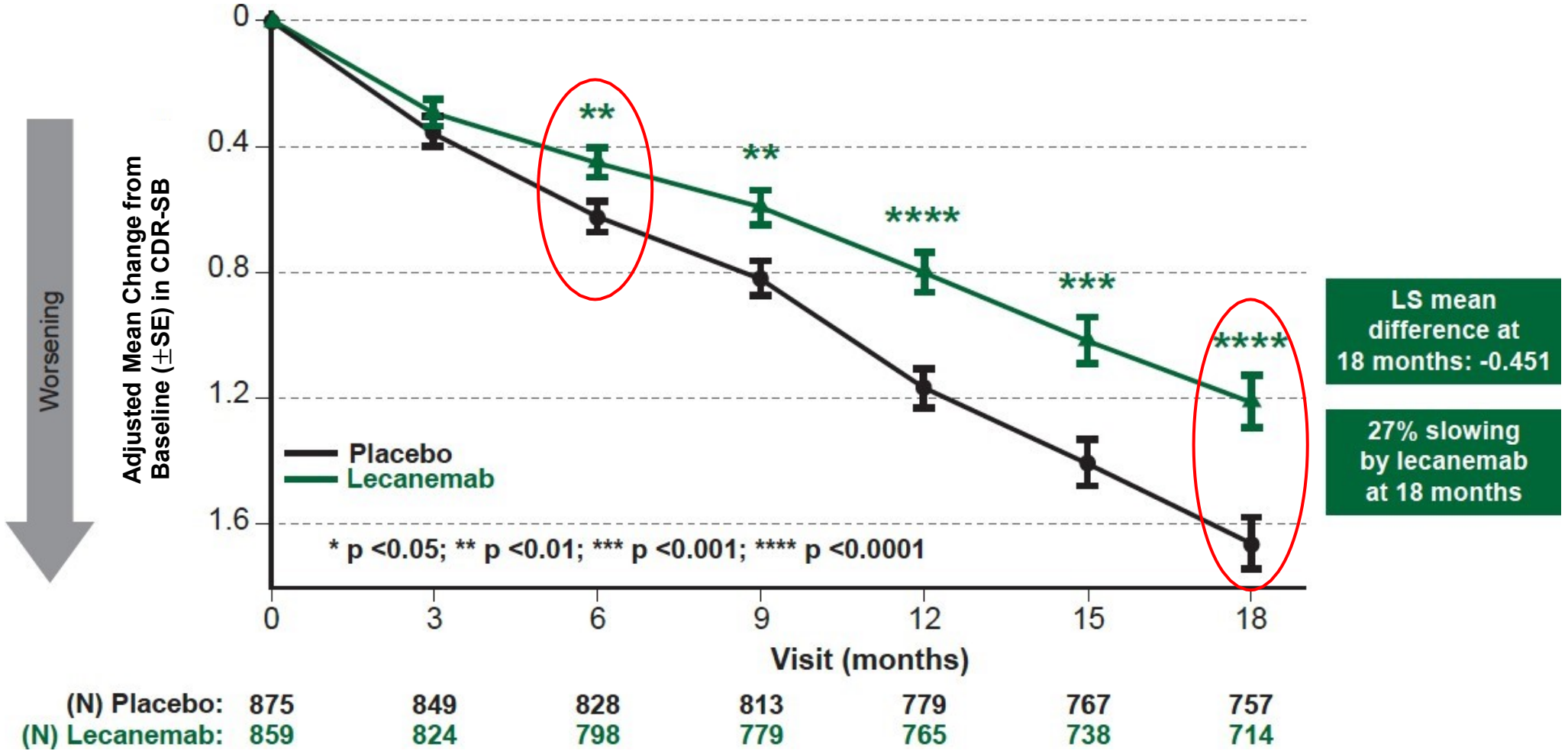


37.4% lower risk of progression over 76 weeks

Definition of event: an increase from baseline in CDR-G score at two consecutive visits. Hazard ratio and P-value were generated using a Cox proportional hazards model adjusted for baseline age, baseline value, and baseline acetylcholinesterase inhibitor/memantine use and stratified by pooled investigator and baseline tau level. Abbreviations: CDR-G=Clinical Dementia Rating-Global Scale; CI=confidence interval; MCI=mild cognitive impairment; N=number of participants; SE=standard error

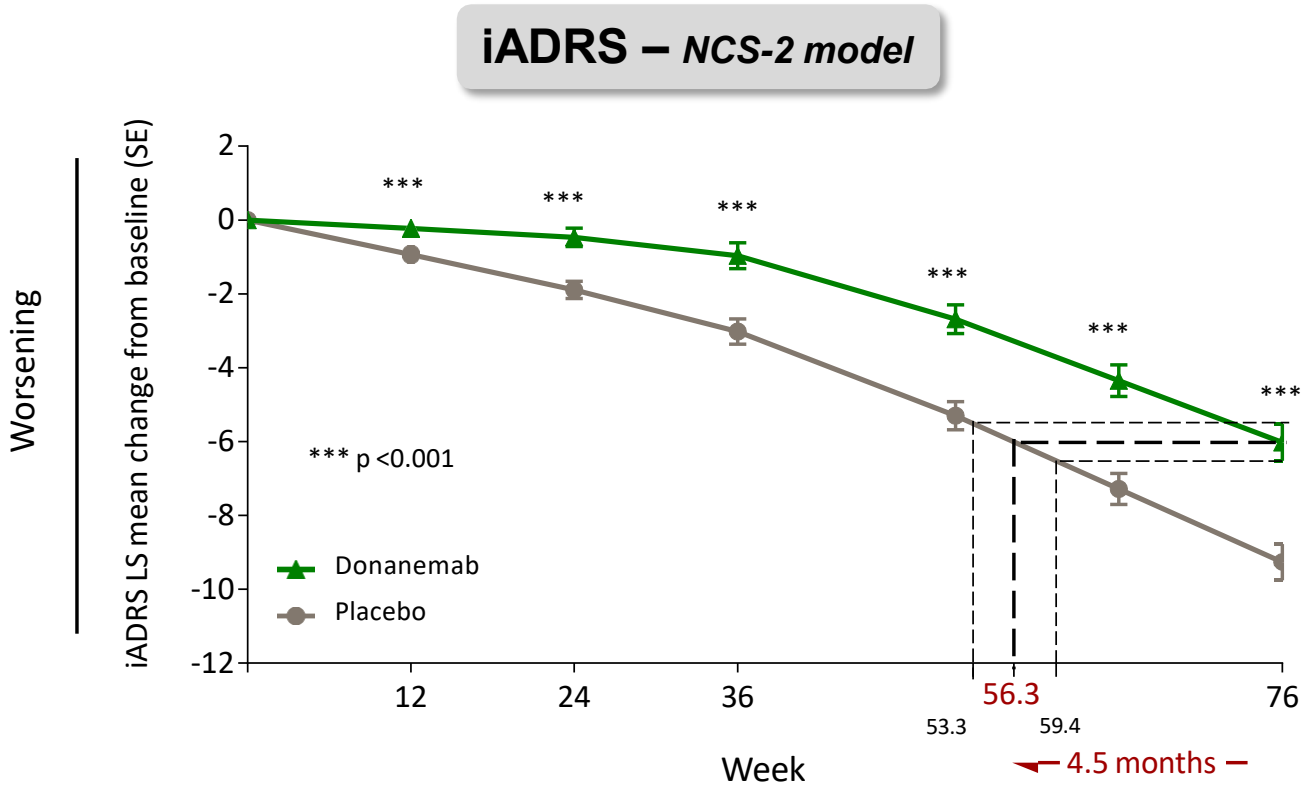
Clarity AD Primary Endpoint: CDR-SB

Lecanemab Significantly Slowed Disease Progression on CDR-SB by 27% at 18 Months and at All Time Points Beginning at 6 Months

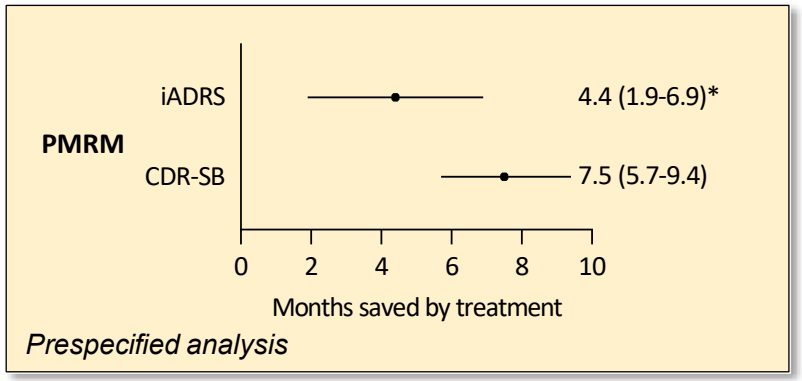


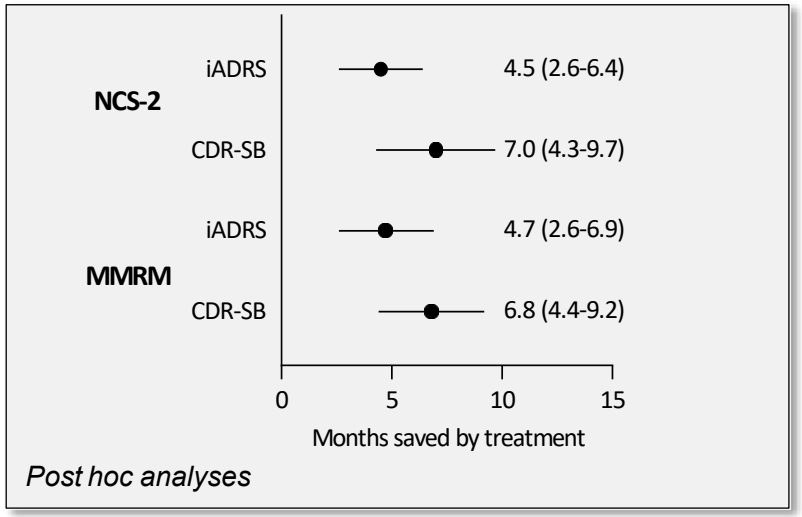
Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.
CDR-SB, Clinical Dementia Rating, sum of boxes; LS, least squares; SE, standard error.

Phase 3 TRAILBLAZER-ALZ 2: Time Saved with Donanemab (low-medium tau population)



Across statistical approaches and outcome measures, donanemab treatment resulted in 4.4 – 7.5 months *saved* (i.e., delay in clinical decline) at 18 months





PMRM proportionality of time slowing was valid and utilized for CDR-SB, but not utilized for iADRS
*mean (95% confidence interval)

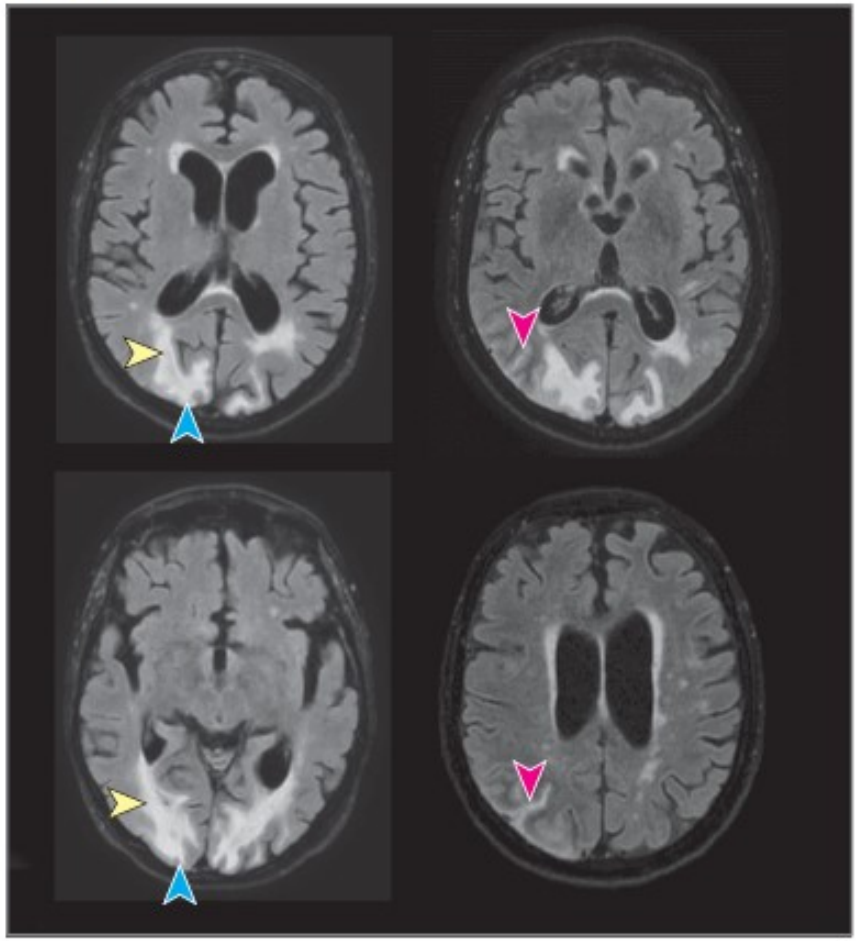
Abbreviations: CDR-SB=Clinical Dementia Rating-Sum of Boxes; iADRS=integrated Alzheimer's Disease Rating Scale; MMRM=mixed model repeated measures; LS=least sum of squares; NCS-2=Natural cubic spline model with 2 degrees of freedom; PMRM=Progression Model for Repeated Measures; SE=standard error

JAMA Neurology | Review

Amyloid-Related Imaging Abnormalities and β-Amyloid-Targeting Antibodies
A Systematic Review

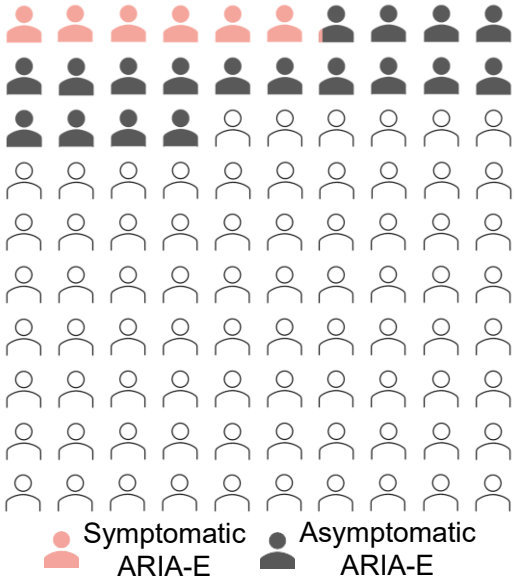
Massimo Filippi, MD; Giordano Cecchetti, MD; Edoardo Gioele Spinelli, MD; Paolo Vezzulli, MD; Andrea Falini, MD; Federica Agosta, MD, PhD

A ARIA-E



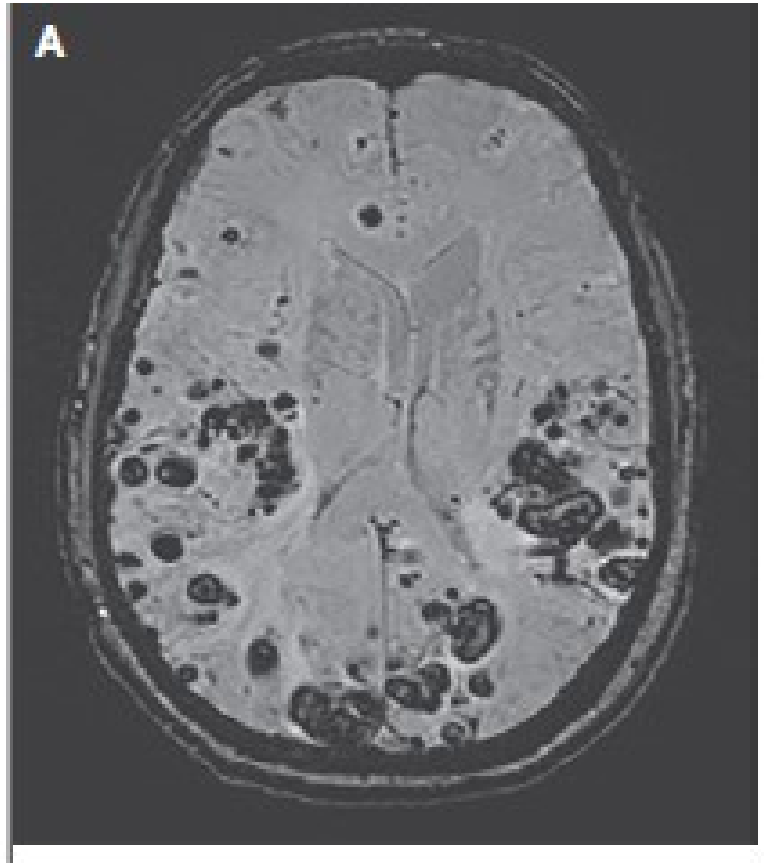
Characteristic	ARIA-E
Primary MRI features	FLAIR hyperintense
	DWI negative
	No contrast enhancement
Nature of leakage products	Proteinaceous fluids
Location of increased vascular permeability	Parenchyma: vasogenic edema (parenchymal hyperintensities and gyral swelling)
	Leptomeninges: sulcal effusion/exudate (sulcal hyperintensities)
	Frequently unilateral, involving occipital, frontal, and temporal regions
Evaluation of severity	Barkhof MRI severity scale[7]
	3-Point and 5-point scales[8,9]

24% of donanemab-treated participants experienced ARIA-E



CORRESPONDENCE

Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke



A 65-year-old patient who was homozygous for the *APOE* ε4 allele and was in the early stages of cognitive decline presented to an emergency department 30 minutes after the acute onset of aphasia and left gaze preference due to an ischemic stroke. The patient had participated in the randomized phase of the trial of lecanemab, during which the treatment assignment is not known, followed by participation in the open-label phase, in which three intravenous

The patient had no contraindications to thrombolysis (blood pressure, 163/84 mm Hg; platelet count, 256×10^3 per microliter; international normalized ratio, 1.0; fibrinogen level, 304 milligrams per deciliter) and was within the conventional time window for thrombolysis. After intravenous administration of an 8-mg t-PA bolus and 50 minutes into the t-PA infusion (when 65.7 mg of the total dose of 76 mg had been administered), hypertension suddenly developed (blood pressure, 250/111 mm Hg) and the t-PA infusion was stopped. A CT scan showed extensive, multifocal intraparenchymal hemorrhages. There was no systemic bleeding.

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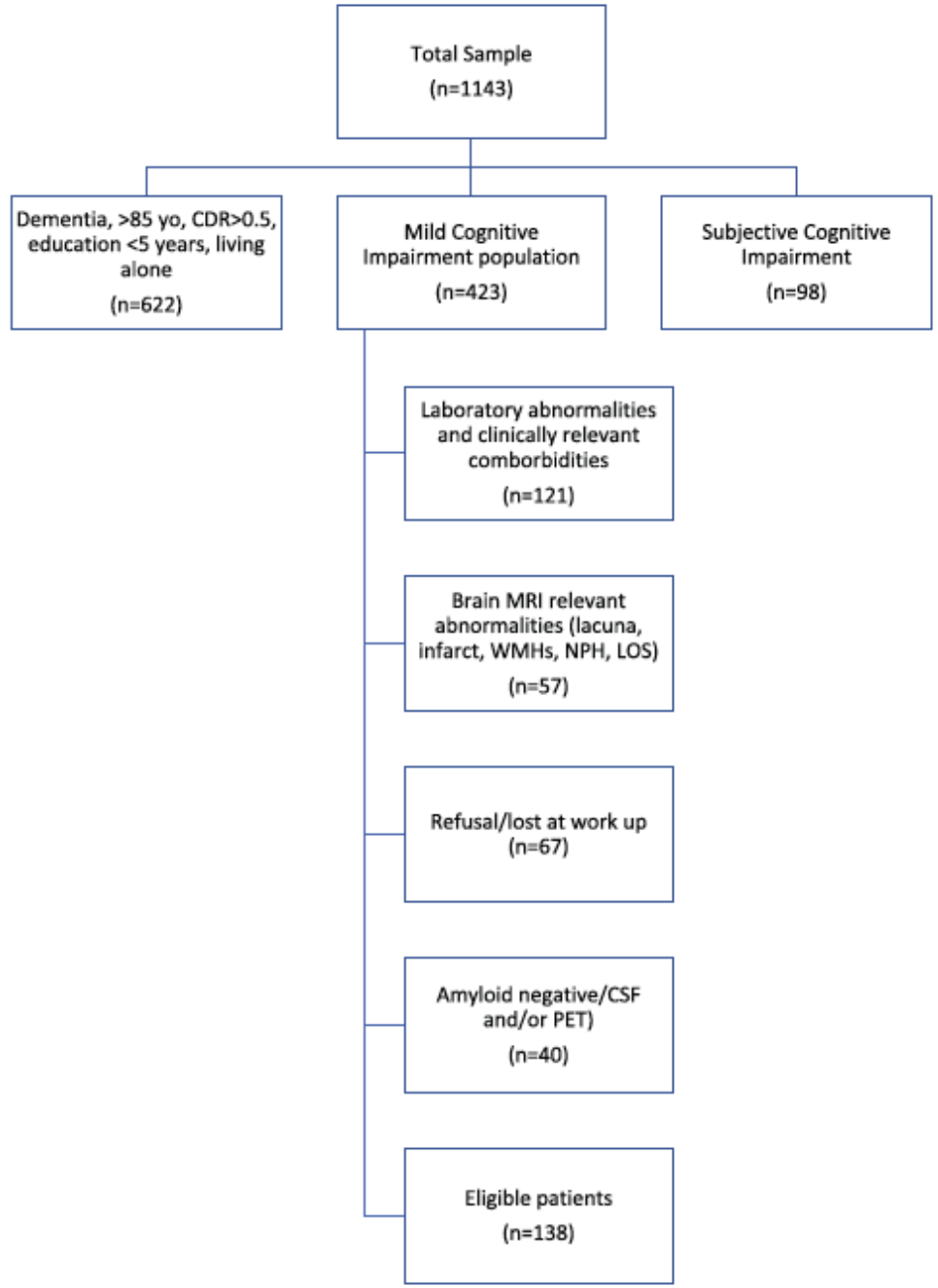
DOI: 10.1111/jgs.17530

Journal of the American Geriatrics Society

LETTERS TO THE EDITOR

RESEARCH

"Real-world" eligibility for aducanumab depends on clinical setting and patients' journey



J Prev Alz Dis 2023;3(10):362-377
Published online March 27, 2023, http://dx.doi.org/10.14283/jpad.2023.30

Review

Lecanemab: Appropriate Use Recommendations

J. Cummings[1], L. Apostolova[2], G.D. Rabinovici[3], A. Atri[4], P. Aisen[5], S. Greenberg[6], S. Hendrix[7], D. Selkoe[8], M. Weiner[9], R.C. Petersen[10], S. Salloway[11], For the Alzheimer's Disease and Related Disorders Therapeutics Work Group

Table 11. Resources needed by a clinician or medical center for the safe and effective use of lecanemab

• Clinician skilled in the assessment of cognition to identify individuals with mild cognitive impairment or mild dementia due to Alzheimer's disease
• MRI available for baseline assessment of cerebrovascular pathology and for monitoring of amyloid related imaging abnormalities (ARIA)
• Radiologists, neurologists, or other clinicians expert in the identification and interpretation of cerebrovascular lesions and ARIA
• Amyloid positron emission tomography or lumbar puncture capability to determine the amyloid status of treatment candidates
• Radiologists, nuclear medicine specialists, neurologists, or other specialists skilled in the interpretation of amyloid imaging or neurologist, radiologists, or other clinicians skilled in the conduct of lumbar puncture
• Apolipoprotein E genotyping resources
• Genetic expertise to counsel patients on the implications of apolipoprotein E genotyping
• Expertise in communicating with patients and care partners regarding anticipated benefits, potential harm, and requirements for administration and monitoring while on lecanemab
• Infusion settings that can be made available every two weeks to patients receiving therapy
• Knowledgeable staff at infusion sites capable of recognizing and managing infusion reactions
• Communication channels established between experts interpreting MRIs and clinicians treating patients with lecanemab
• Communication channels established between clinicians treating patients with lecanemab and the patient and care partner
• Availability of hospital resources including intensive care unit
• Expertise in the management of seizures and status epilepticus for patients with severe or serious ARIA
• Protocol with standard operating procedures for management of serious and severe ARIA

Take home message

Terapia giusta… per il paziente giusto

Necessità di un approccio integrato

Il coraggio della prudenza…