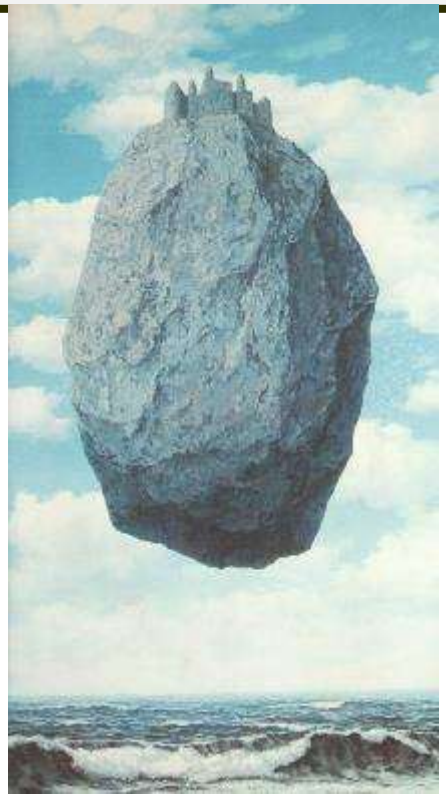
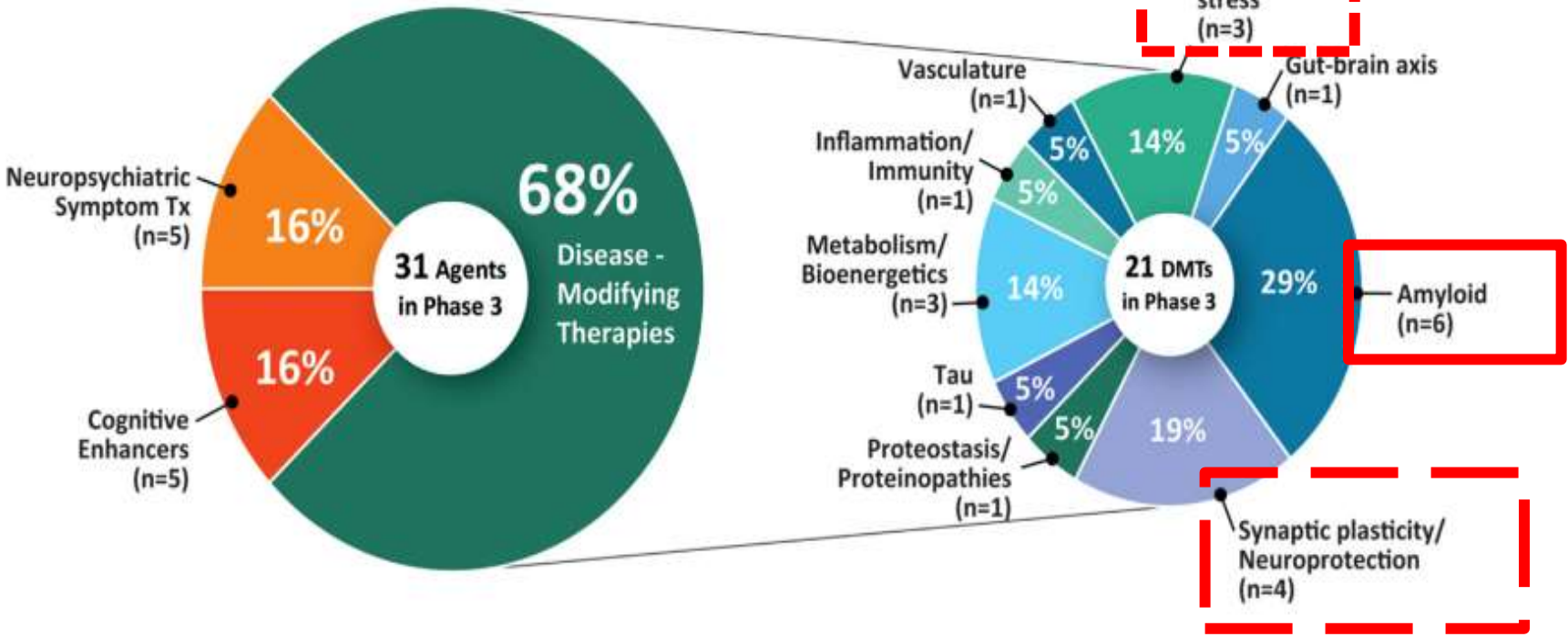
Update della terapia della Malattia di Alzheimer



Annachiara Cagnin
Padova

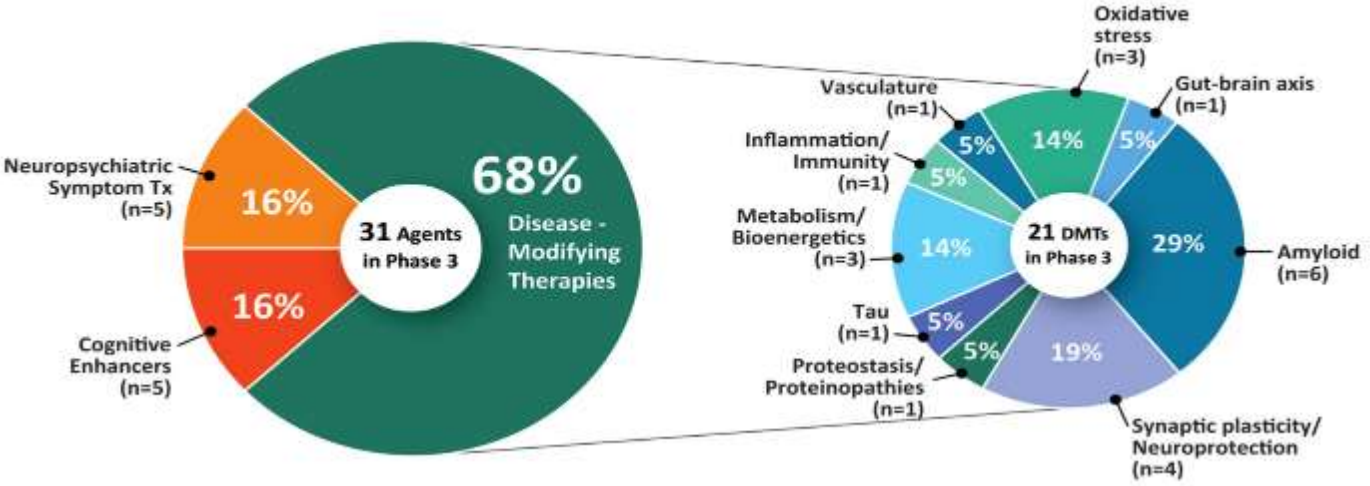
M-IT-00001966

2022 Pipeline

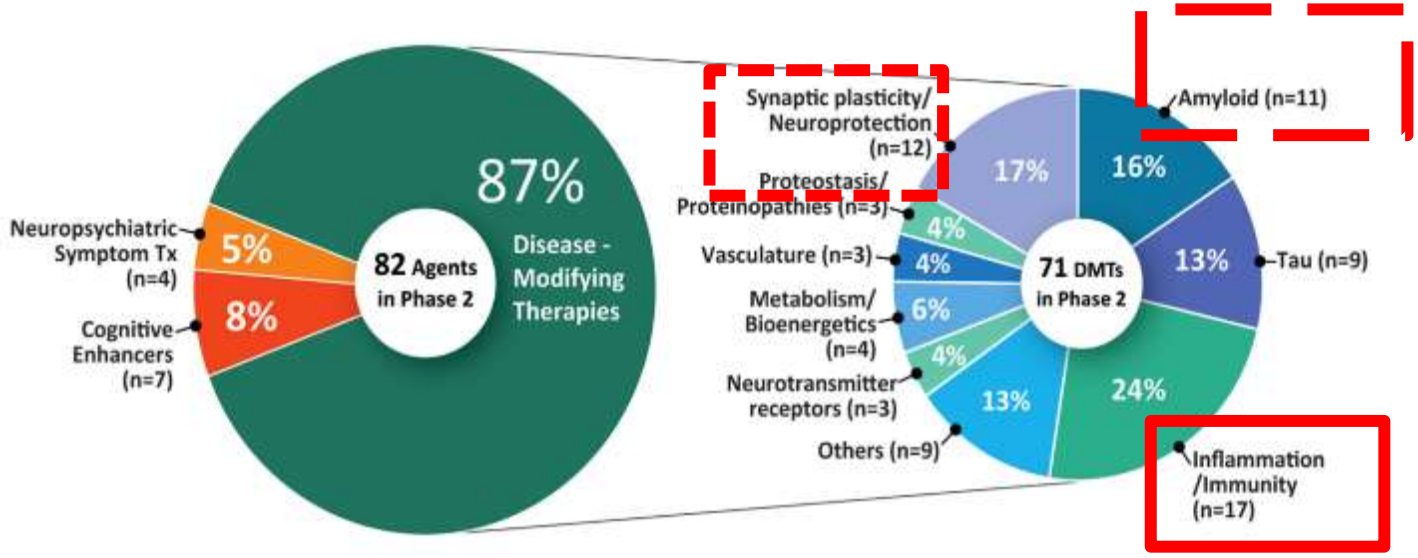


Cummings J, 2022

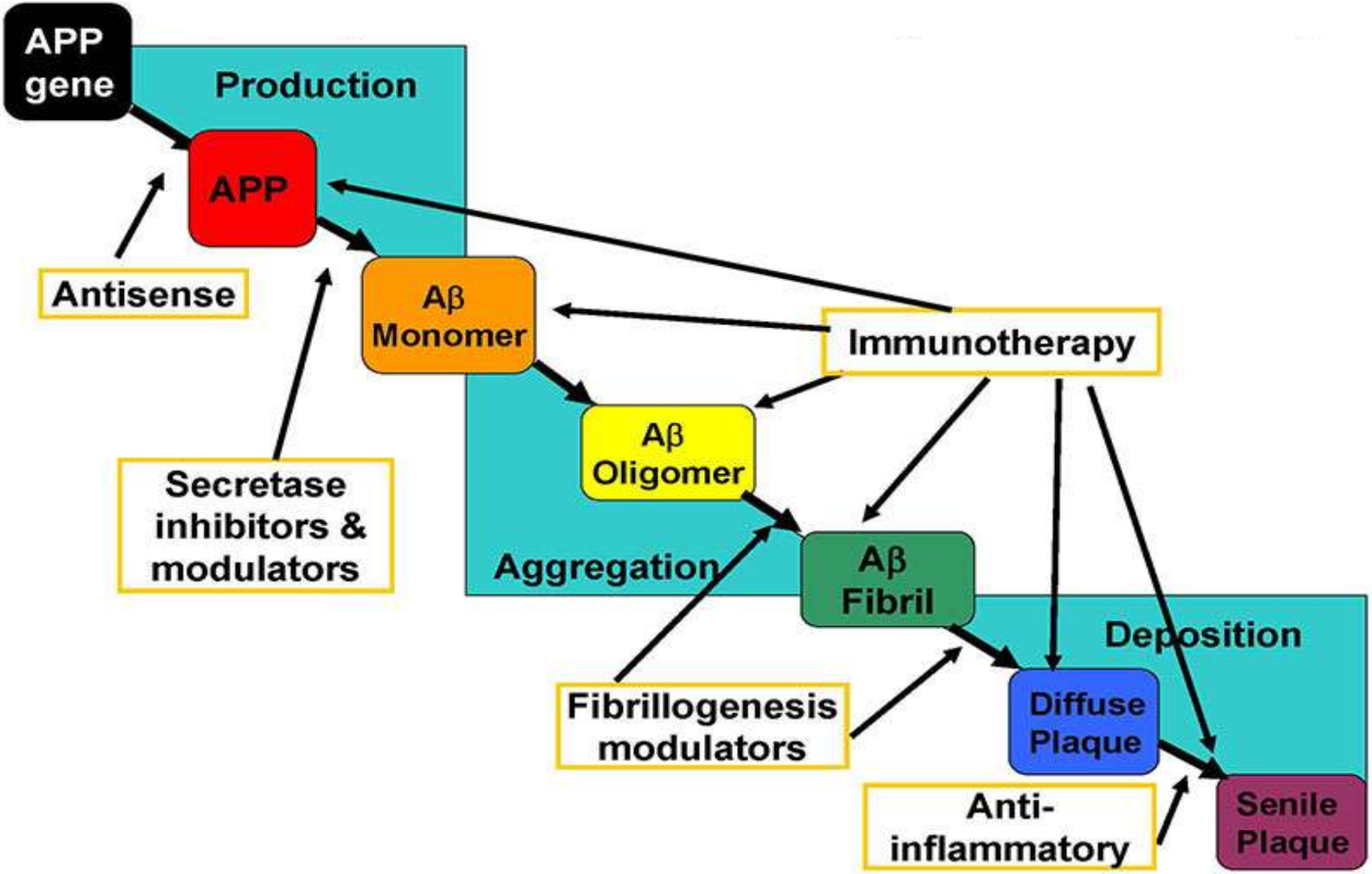
Phase 3



Phase 2



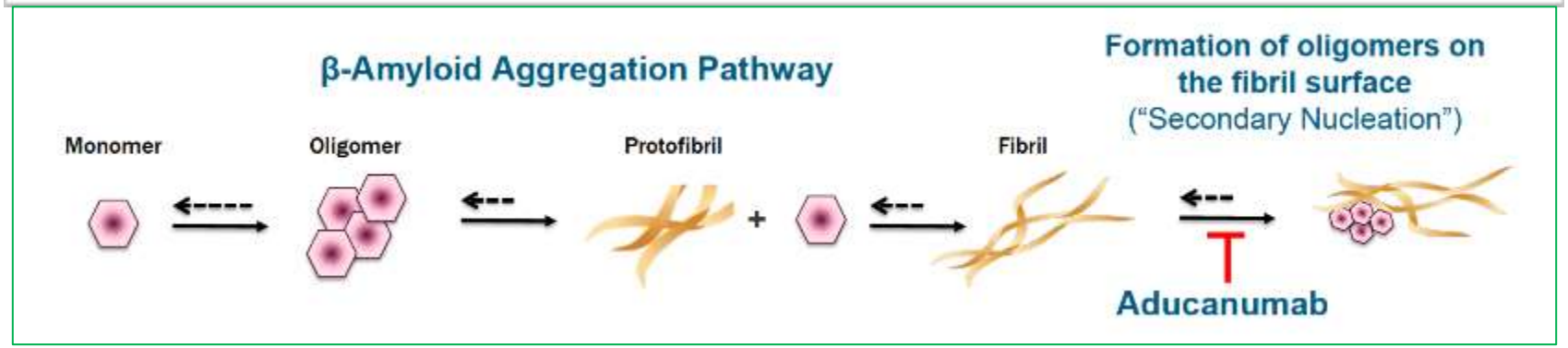
Cummings J, 2022

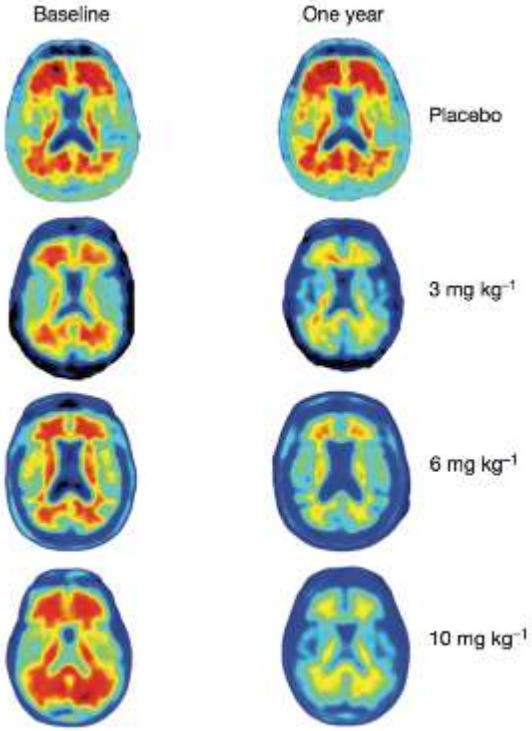

APP gene
Production
APP
Antisense
Aβ Monomer
Immunotherapy
Aβ Oligomer
Secretase inhibitors & modulators
Aggregation
Aβ Fibril
Deposition
Fibrillogenesis modulators
Diffuse Plaque
Anti-inflammatory
Senile Plaque

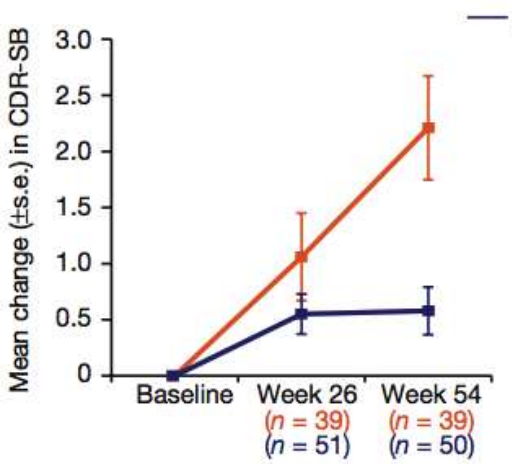
Accelerated FDA approval for the first anti-amyloid Mab

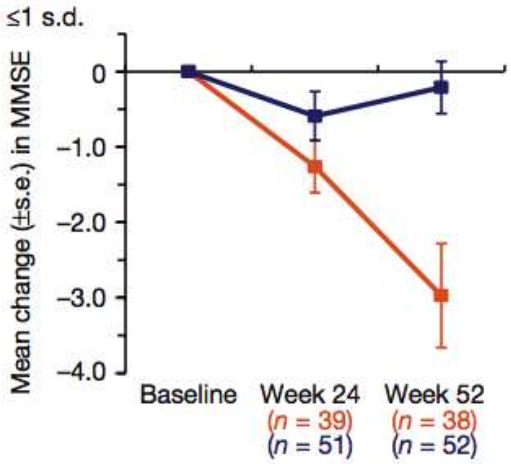
- Based on evidence of amyloid clearance by PET
- Request of real life phase IV trial
- Eligibility criteria, monitoring, recruiting centers under evaluation

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease







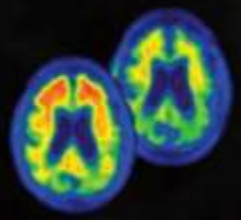


Nature, 2016

LA STRADA PER ADUCANUMAB

25 Marzo 2015

Analisi preliminari; conferenza AD/PD, Nizza, Francia



Aducanumab sembra ridurre le placche di proteina amiloide e rallentare il decadimento cognitivo

31 Agosto 2016

Risultati sulla proteina amiloide pubblicati sulla rivista Nature

Aducanumab mostra un effetto dose-dipendente nel ridurre le placche di proteina amiloide nei pazienti con Alzheimer

EMERGE
+
ENGAGE
-

21 Marzo 2019

Interruzione degli studi

Analisi cliniche: nessun beneficio per pazienti che assumono aducanumab. Tutti gli studi sono interrotti

22 Ottobre 2019

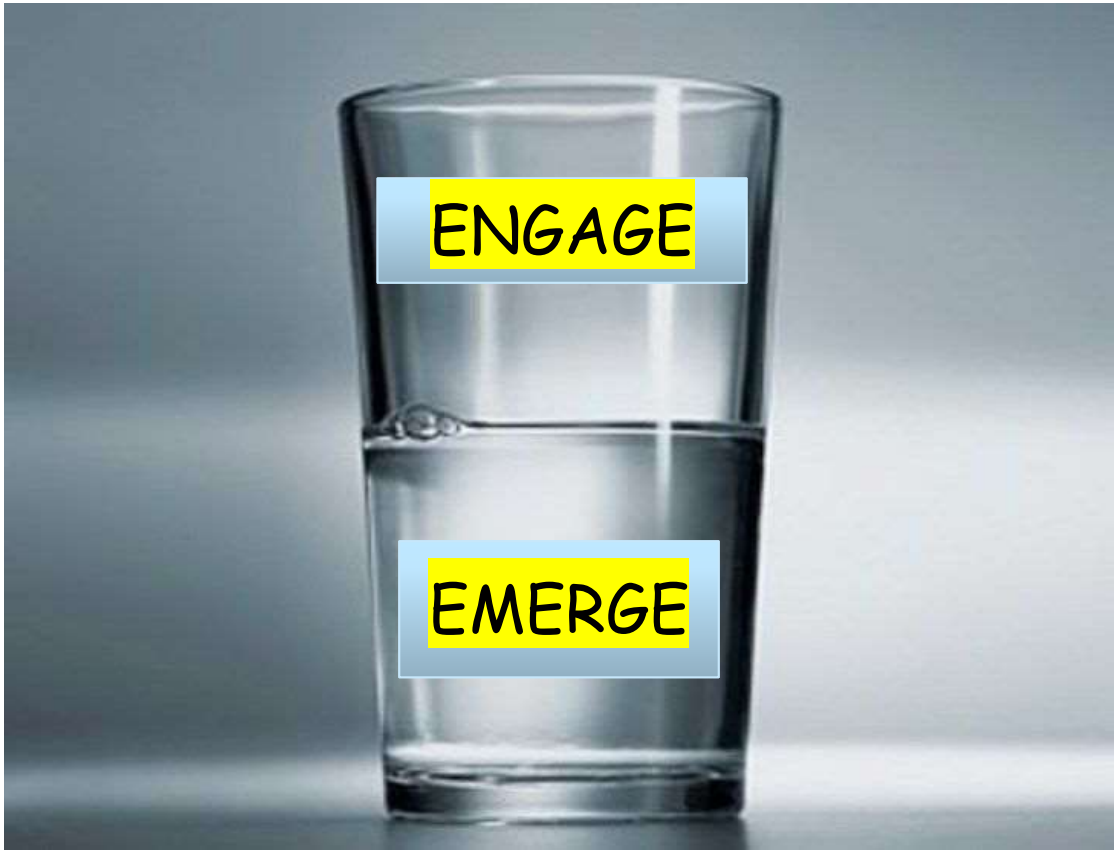
Nuove analisi; Richiesta approvazione farmaco

Nuove analisi: miglioramento clinico nei pazienti e riduzione proteina Tau. L'azienda fa richiesta di approvazione del farmaco

FASE I FASE III FUTILITY STOP

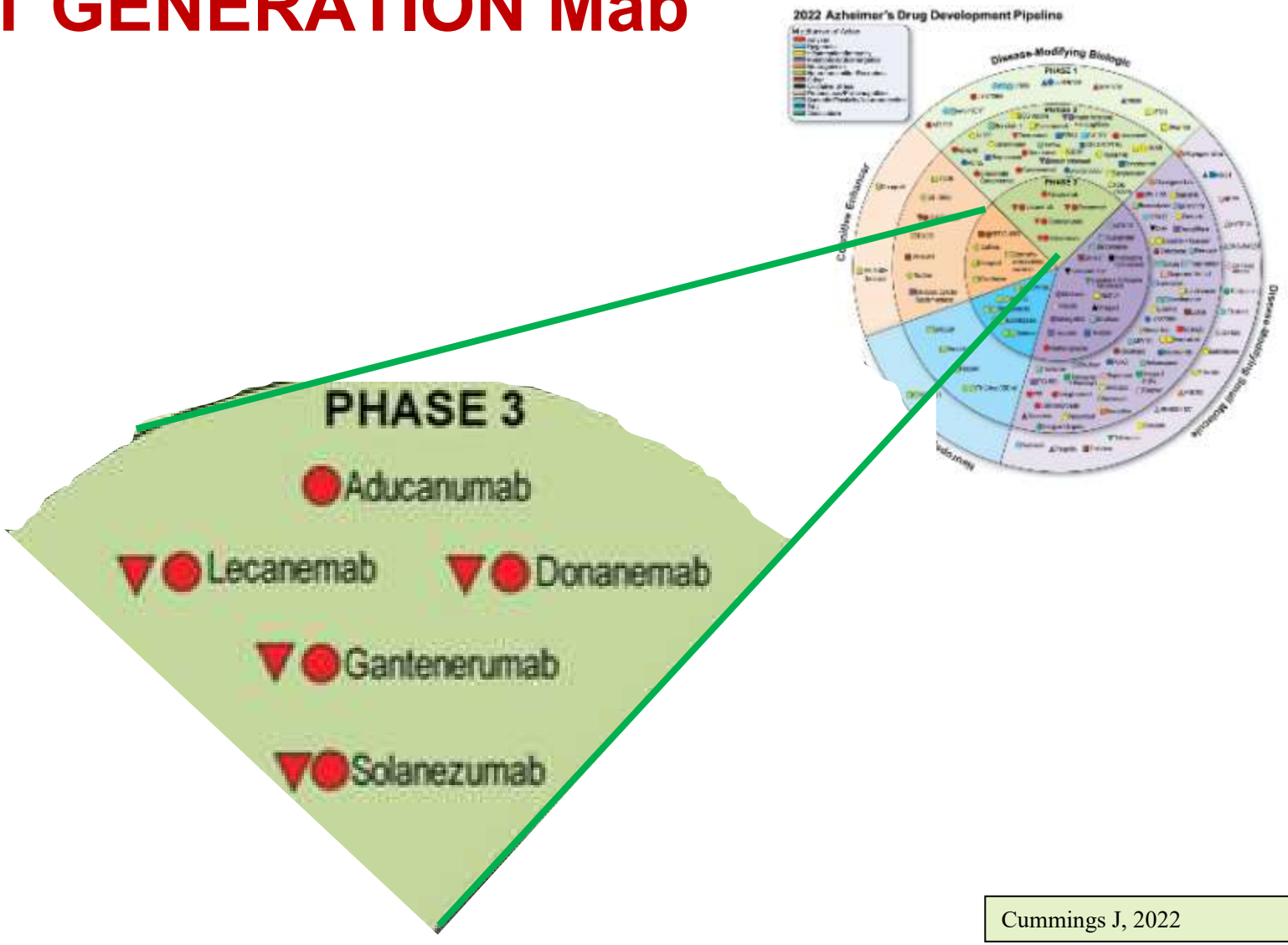
Target engagement!
Changes of Amyloid and tau

Negative trial
Low total exposure
(dose and time)



Positive trial: CDR, MMSE, NPI, Functional
High dose, 2/3 APOE4, ARIA 1/3
Meglio: > 70 yrs, M>F, Mild

NEXT GENERATION Mab



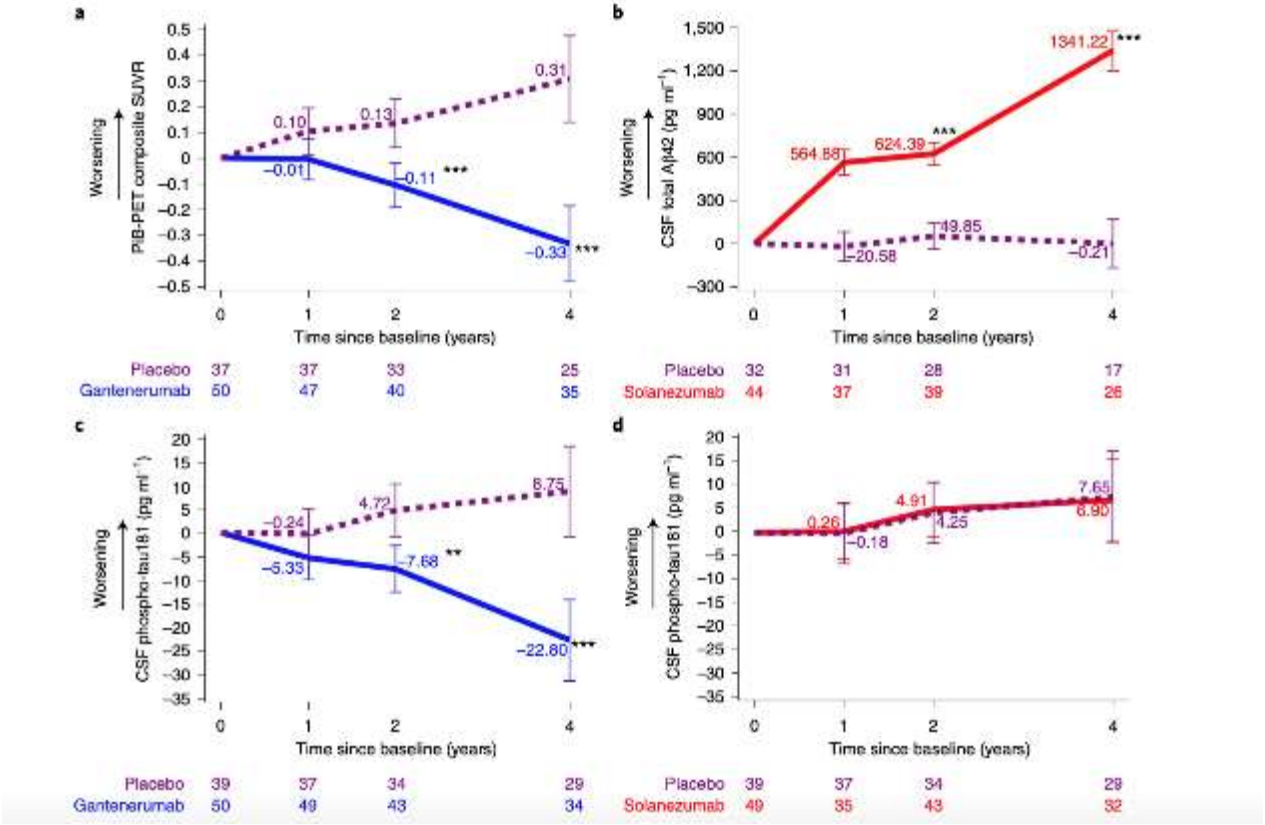
Cummings J, 2022

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01369-8

A trial of gantenerumab or solanezumab in dominantly inherited Alzheimer's disease



nature medicine

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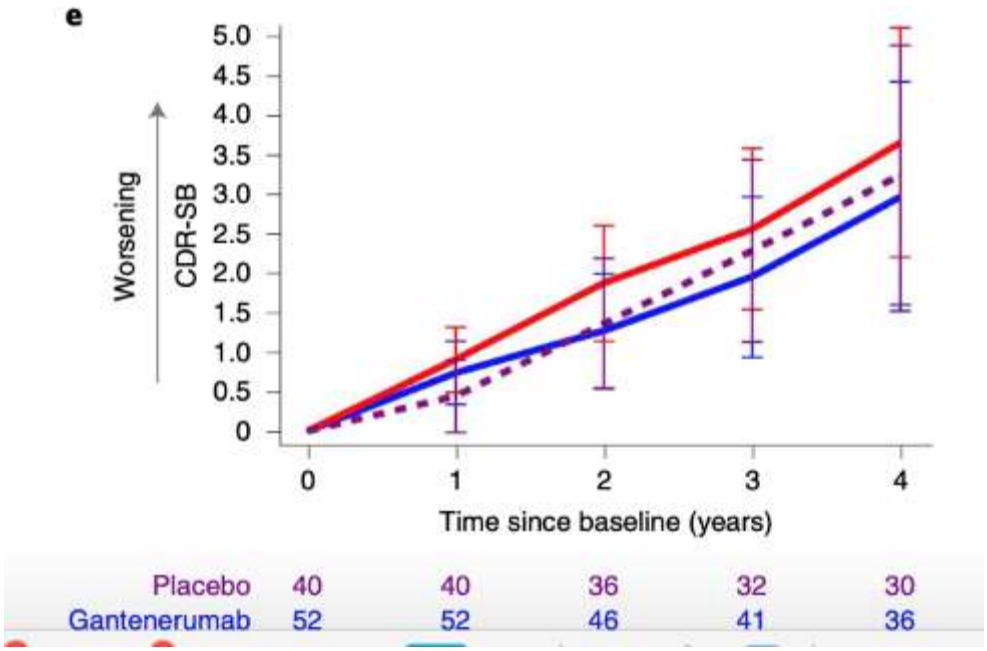
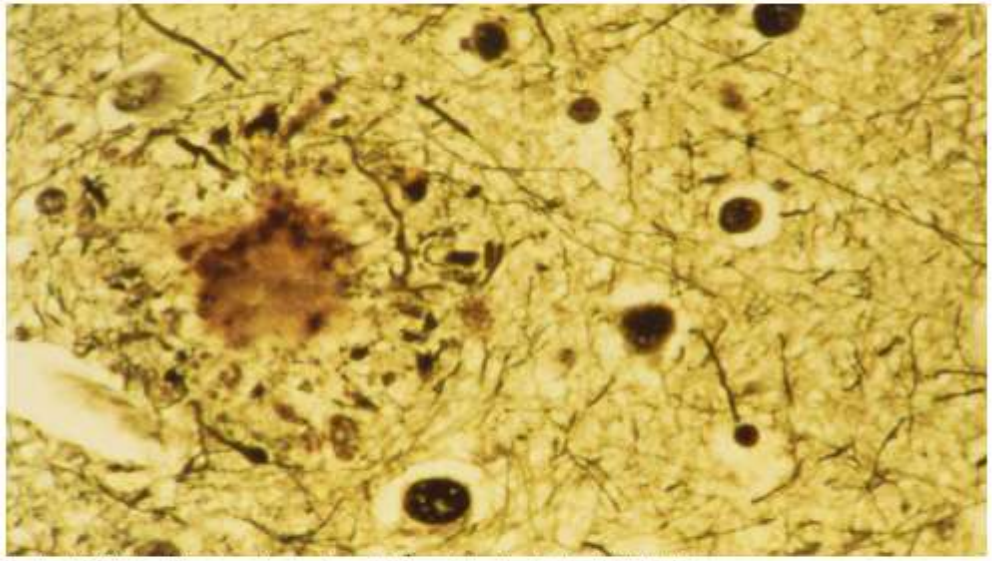


Nature | Vol 610 | 6 October 2022 |

The world this week

News in focus



People with Alzheimer's disease usually develop protein plaques (circular splotch on left) in their brains.

ALZHEIMER'S DRUG SLOWS MENTAL DECLINE IN TRIAL — BUT IS IT A BREAKTHROUGH?

Researchers are cautiously optimistic after companies announce positive results for lecanemab.

Lecanemab

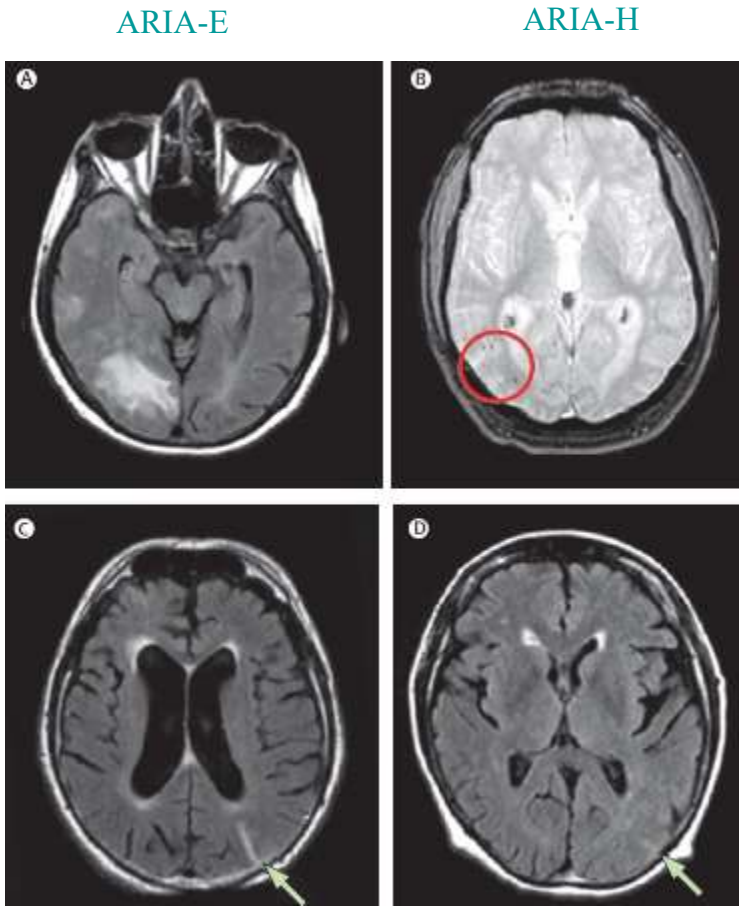
1/2weeks
18 months

27% better CDR
20% ARIA

Accelerated approval (FDA January)

CLARITY AD PHASE 3 TRIAL

ARIA
Amyloid Related Imaging Abnormalities



Lancet Neurol, 2012

ARIA-E: 17%

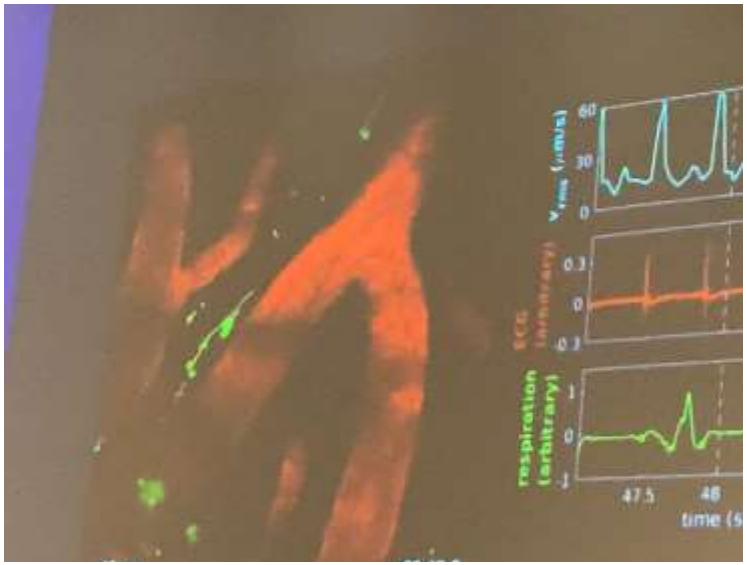
78%
No symptoms

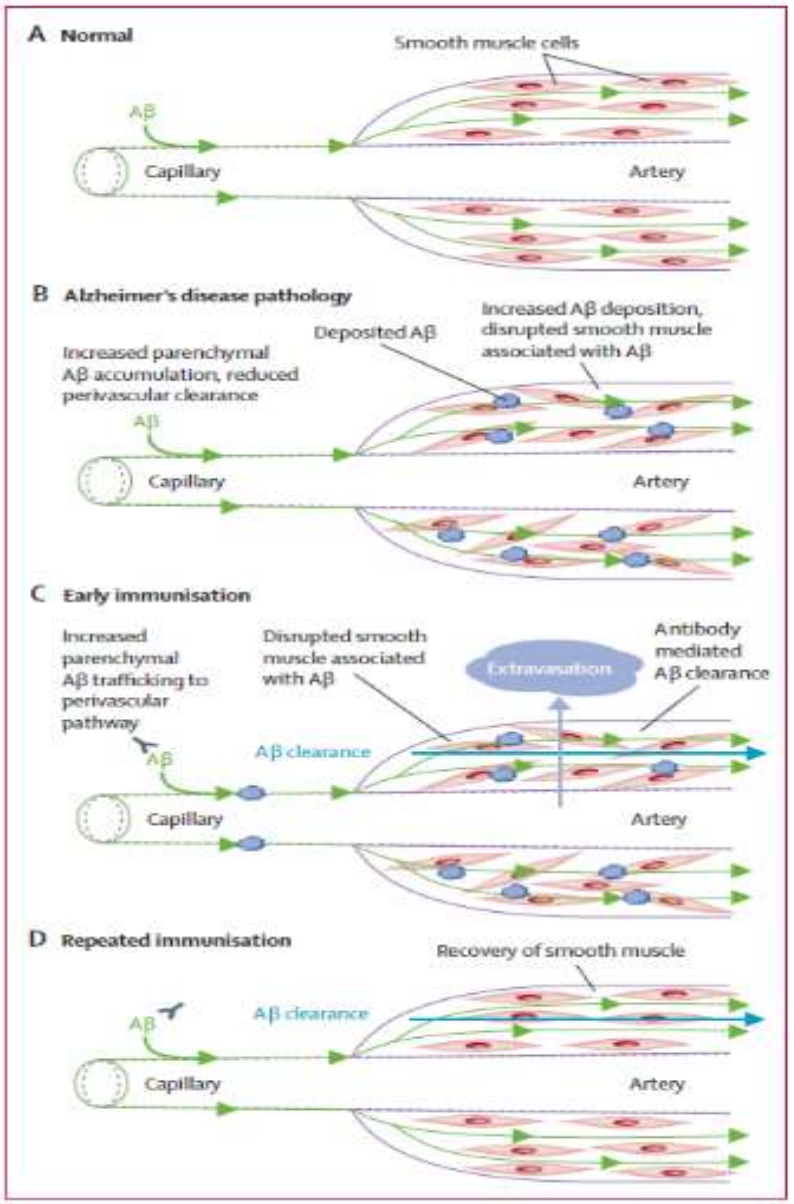
22%
Headache
Confusion
Psychosis

ARIA-H: <10%

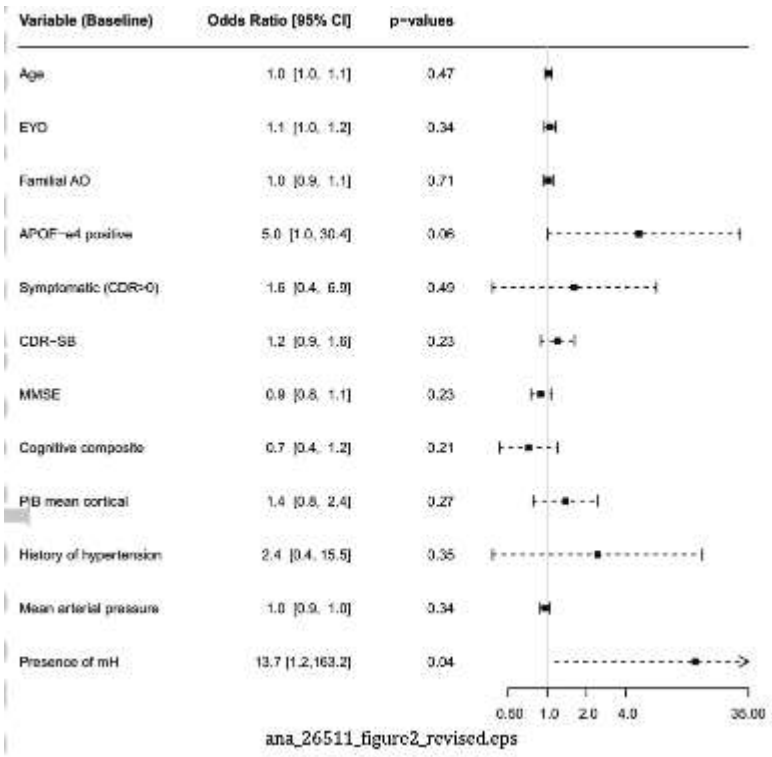
Dose dependent
APOEε4 dependent

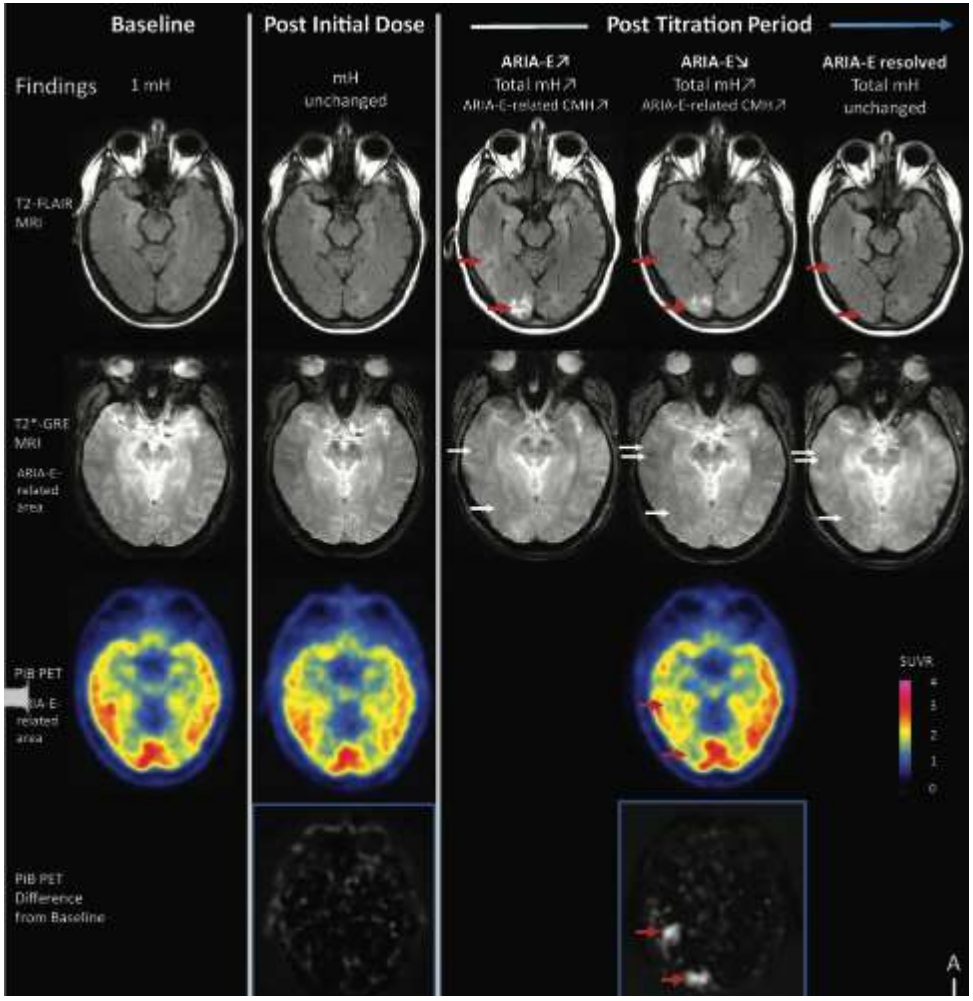
Interstitial fluid flow





Amyloid-related imaging abnormalities in the DIAN-TU-001 trial of gantenerumab and solanezumab: lessons from a trial in dominantly inherited Alzheimer disease

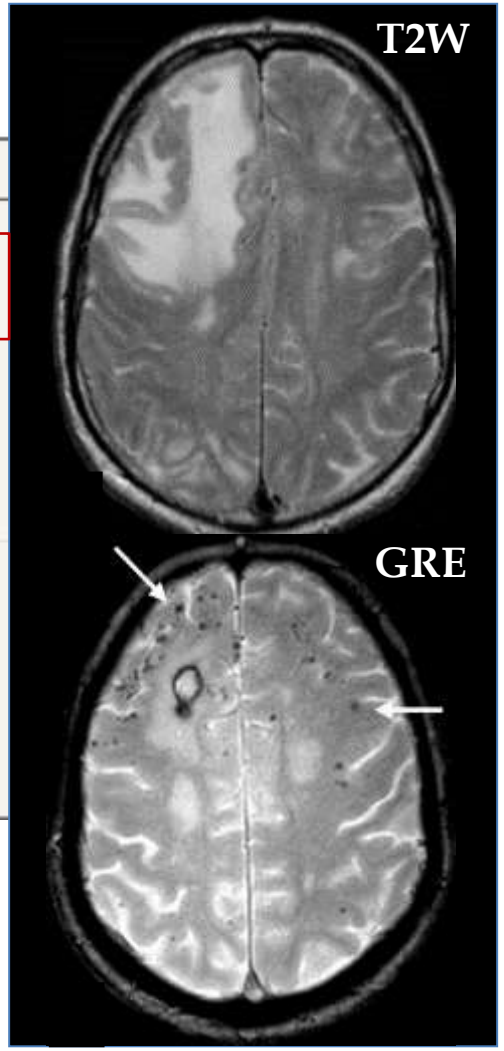




CAA – RI = ARIA spontanea

Table 1. Criteria for the Diagnosis of CAA-ri

Diagnosis	Criteria
Probable CAA-ri	1. Age ≥40 y 2. Presence of ≥1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute ICH 3. MRI shows unifocal or multifocal WMH lesions (corticosubcortical or deep) that are asymmetric and extend to the immediately subcortical white matter; the asymmetry is not due to past ICH 4. Presence of ≥1 of the following corticosubcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis[8] 5. Absence of neoplastic, infectious, or other cause
Possible CAA-ri	1. Age ≥40 y 2. Presence of ≥1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute ICH 3. MRI shows WMH lesions that extend to the immediately subcortical white matter 4. Presence of ≥1 of the following corticosubcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis[8] 5. Absence of neoplastic, infectious, or other cause



iperintensità FLAIR sostanza bianca focali/confluenti asimmetriche

Aβ vasale → risposta infiammatoria

1. forma **vasculitica** (angite transmurale)
2. forma **non vasculitica** (infiltrato perivascolare)

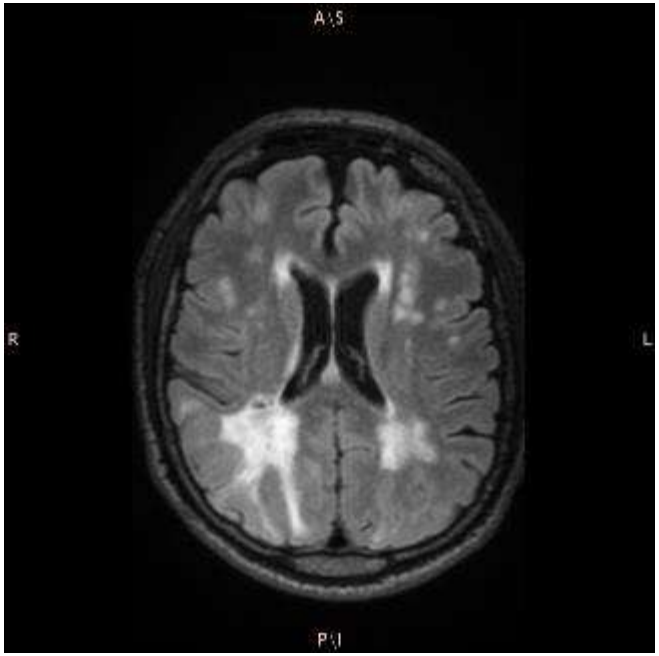
Chung KK et al. JNNP 2011; Auriel Jama Neurol 2015

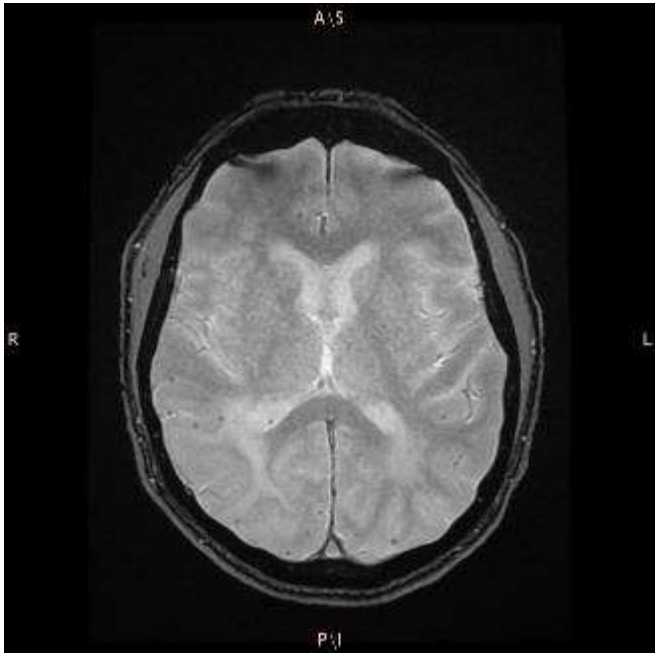
CASE 1

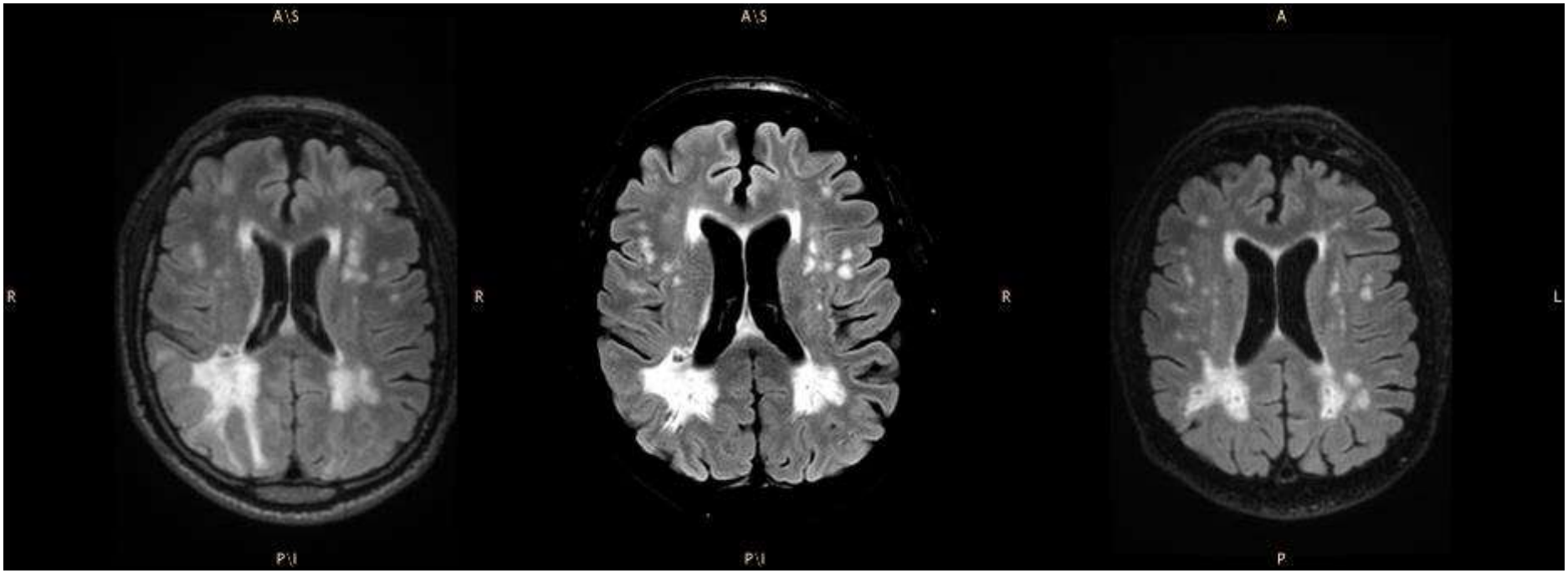
M, 74 anni.

Settembre 2017: intervento chirurgico per diverticolite, episodio di delirium post operatorio. Al domicilio comparsa di deficit mnesici, attentivi e visuospaziali, instabilità della marcia

Marzo 2018: RMN cerebrale in altra sede: **«alterazioni ischemiche croniche dei centri semiovali»**







Marzo 2018 Maggio 2018 Novembre 2019

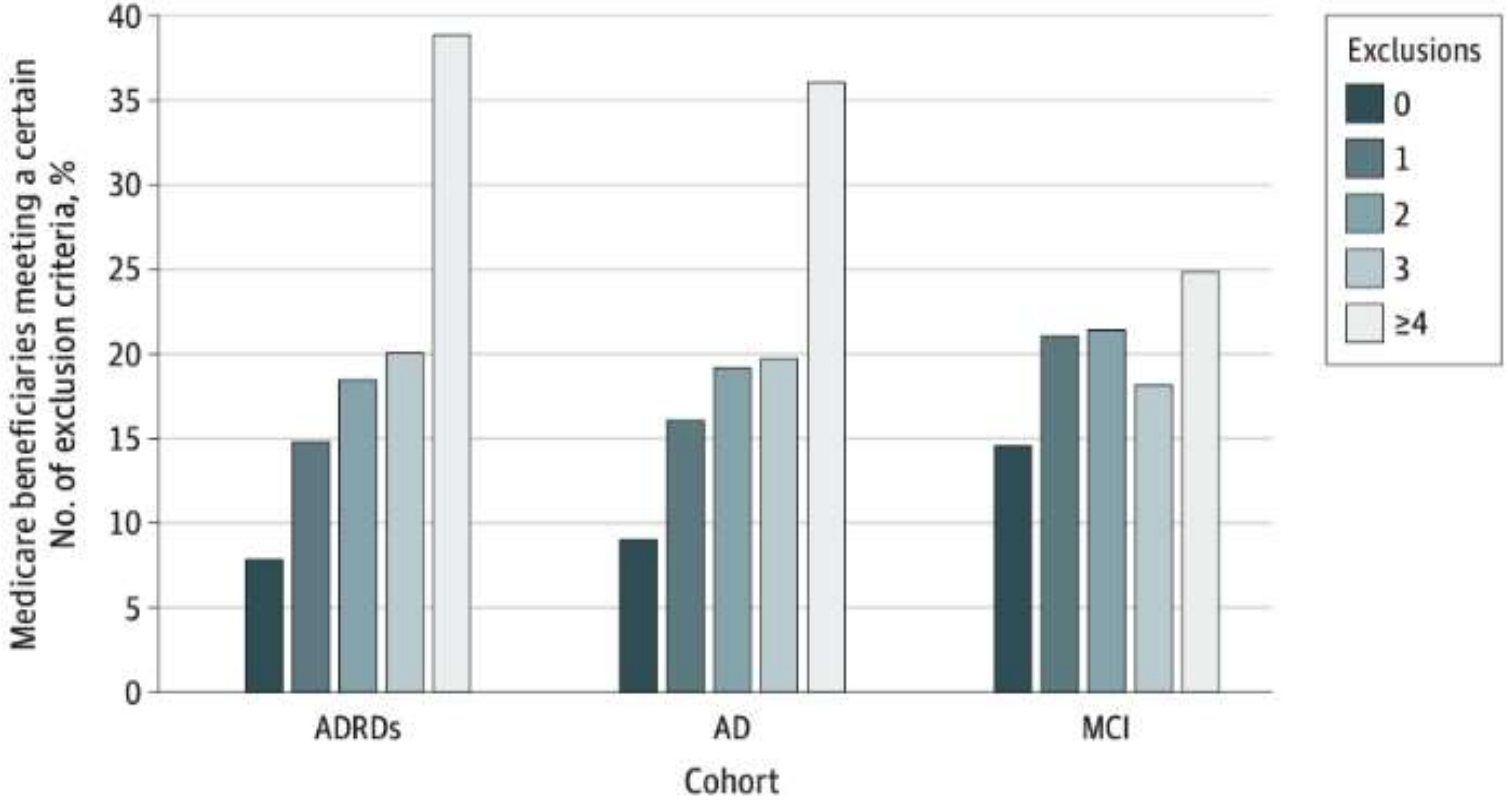
BOLI EV decalàge per os

Possible eligible patients exclusion criteria

- **Past history of seizures or autoimmune disorders**
- **Anticoagulation or bleeding disorders, unstable cardiovascular conditions**
- **MRI evidence of**
  - Acute/subacute hemorrghages
  - >4 microbleeds /1 macrobleed
  - Cortical infarction >1.5 cm
  - 1 lacunar infarction > 1.5 cm
  - >1 CSS
  - Diffuse WM disease

AUR; Cummings J, 2022

Estimates of exclusion criteria impact



Jama 2021

Other uncertainties

- Cognitive monitoring: which instruments
- Is it possible to stop after a certain amount of amyloid is removed?
- What to do with disease progression?
- Biomarker assessment needs to be re-tested as surrogate information of drug effect?

Clinical organization

Table 4. Patient care can be optimized by development of a triage strategy for evaluation and management of patients with symptoms and signs of severe ARIA. The plan will vary to accommodate clinical judgement as well as institutional resources and circumstances but will typically include these elements

• Referral of patient to emergency department for thorough assessment of suspected/known ARIA
• Brain MRI without contrast enhancement if not already obtained (FLAIR, T2*-GRE or SWI, and DWI sequences)
• MRI review by a reader proficient in detection of ARIA (preferably with access to past MRIs for comparison) and rapid communication between MRI reader and clinicians responsible for patient's aducanumab treatment and AD care
• Discontinuation of anti-amyloid therapy
• Consultation by a neurologist, preferably a vascular neurologist with experience in management of ARIA-like syndromes
• Admittance to hospital ward for close neurologic monitoring and tiered level of monitoring and management
• Admit or transfer to a stroke care unit or neurological intensive care unit if warranted
• Protocols for, when warranted: o Early initiation of treatment with intravenous methylprednisolone 1 g/day for 5 days o Conducting electroencephalography to detect epileptiform activity o Treatment with anticonvulsants for seizure management or prophylaxis if electroencephalography suggests they are indicated o Consideration of additional immunosuppressive treatment if not responding to methylprednisolone after 5 days of treatment o Plan transition to oral steroid treatment and taper as outpatient
• Support and communicate with patient and family members/care partners throughout the event with informed patient-centered decision making

AUR; Cummings J, 2022

“We presently are woefully unprepared to incorporate any truly effective therapy into clinical practice”

«Clinics will need new resources and training to enable them to diagnose and treat patients»

John Morris

Washington University