
New Drug Treatments for Alzheimer's Type Dementia
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Lessons in Dementia Series
Humboldt Senior Resource Center

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Dementia Definition

- "Dementia" is a general term for when a person has developed difficulties with reasoning, judgment, and memory
- People who have dementia usually have some memory loss as well as difficulty in at least one other area (speaking or writing coherently, recognizing familiar surroundings, planning and carrying out complex or multi-step tasks)
- In order to be considered dementia these issues **must be severe enough to interfere with a person's independence and daily activities**
- Dementia can be caused by several diseases that affect the brain. The most common cause is Alzheimer disease, it is present in approximately 60-80% of all cases of dementia
- Other diseases effecting the brain (such as vascular disease, Parkinson's or Lewy Body Dementia) may be present as well, these “mixed dementias” become more common as a person gets older

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What is Alzheimer's Disease?

- Neurodegenerative disorder (brain disease) that effects memory, thinking and behavior
- Progressive disease meaning it gets worse over time, highly variable in expression of symptoms and rate of progression
- On average, a person with Alzheimer's lives 4-8 years after diagnosis, but can live as long as 20 years
- Currently the 7th leading cause of death in the United States
- First described In 1906, German physician Dr. Alois Alzheimer who dissected the brain of a patient with profound memory loss and described the microscopic changes he observed in that patient's brain tissue
- These microscopic changes were later characterized as the "plaques and tangles" that cause Alzheimer's

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Plaques and Tangles

- Microscopic changes in the brain (formation of plaques and tangles) begin long before the first signs of memory loss
- **Beta Amyloid Plaques** are deposits of a protein fragment that build up in the spaces between nerve cells of the brain. Plaques around a neuron causes them to die, by preventing normal signaling between cells and by triggering an immune response in the immediate area
- **Tau Tangles** are twisted proteins that build up inside neurons. Tangles form inside of neurons and interfere with the cellular machinery used to create and recycle proteins, which ultimately kills the cell
- Plaques and tangles occur as we age, even in healthy brains without dementia but are present in much higher numbers in the brains of people with Alzheimer's

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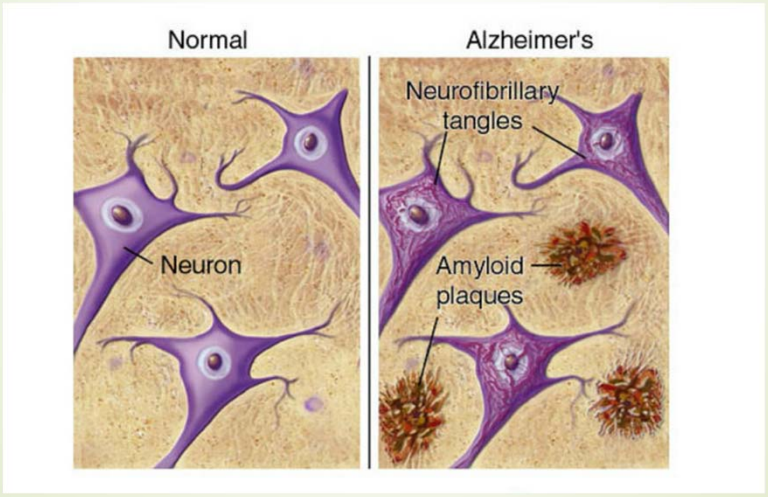
Both Amyloid Plaques and Tau Tangles damage neurons, over time this leads to atrophy (shrinking) of the brain



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Diagnosis of Plaques and Tangles

- It used to only be possible to see plaques and tangles by microscopic examination of brain tissue performed on autopsy
- We now have sophisticated imaging (**PET scans**) and tests for specific proteins in the cerebral spinal fluid and blood (**Biomarkers**) that can detect plaques and tangles on living patients, often a decade before the first symptoms of memory loss occur
- These are currently being used in research centers but are not commonly used in everyday primary care, there is not wide spread agreement on what levels are diagnostic i.e. "cut off values"
- Great deal of controversy on what role these scans and biomarkers should play in common clinical diagnosis of Alzheimer's as well as a lot of disagreement on whether individuals would want to know about the diagnosis sometimes years before symptoms may appear

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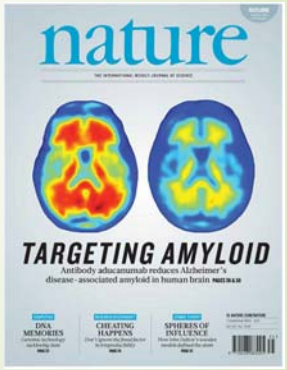
Aducanumab (Aduhelm™)

- There have been several drug trials exploring **Monoclonal Antibodies** (-mab drugs) that target and destroy beta amyloid, but the first widely successful trail was in 2016 with Aducanumab
- This generated a huge amount of excitement
- Drug had been shown to reduce amyloid plaques
- Question remained if reduction in amyloid would result in reduction in symptoms of Alzheimer's

Answering this question was the goal of two large Scale drug trials called ENGAGE and EMERGE



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Emerge and Engage Trials
Who was enrolled?

- Involved 3285 patients at 348 sites in 20 different countries
- Enrolled patients had to have diagnosis of mild cognitive impairment or early stage Alzheimer's disease AND a positive amyloid PET scan
- Lots of exclusion criteria: did not enroll anyone over the age of 85, anyone with a number co-morbid conditions (such as heart disease) or people taking certain other drugs including anticoagulation. Study also included very few minorities, patients were overwhelmingly white
- Patients received either placebo, low dose or high dose Aducanumab
- Over 18 months patients received IV infusions (lasting about an hour) every 4 weeks

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Emerge and Engage Trials What did they test?

- Primary "endpoint" measured was Clinical Dementia Rating or CDR
- CDR is a 5-point scale used to characterize six domains of cognitive and functional performance: Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care
- Study specifically used "sum of boxes" which is a composite score of all six domains
- Secondary endpoints included other cognitive testing such as the mini mental status exam and biomarkers for amyloid and tau deposition

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CDR Example

SECTION 1: STANDARD CDR

	IMPAIRMENT				
Please enter scores below.	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
1. MEMORY __·__	No memory loss, or slight inconsistent forgetfulness.	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness.	Moderate memory loss, more marked for recent events; defect interferes with everyday activities.	Severe memory loss; only highly learned material retained; new material rapidly lost.	Severe memory loss; only fragments remain.
2. ORIENTATION __·__	Fully oriented.	Fully oriented except for slight difficulty with time relationships.	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere.	Severe difficulty with time relationships; usually disoriented to time, often to place.	Oriented to person only.

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Emerge and Engage Trials Results

- Studies were stopped early based on results of a futility analysis conducted by an independent data monitoring committee
- Basically fancy statistics showed drug was not working and that both studies were unlikely to meet their endpoints
- 7 months later, Biogen announced that when the studies were separated there was a statistically significant difference in the placebo vs high dose group in the EMERGE trial
- All groups had worsening of their CDR scores but the high dose group had a smaller change than the placebo group in the EMERGE trial
- All drug groups in both studies showed dramatic reduction in amount of beta amyloid plaques and some reduction of tau tangles

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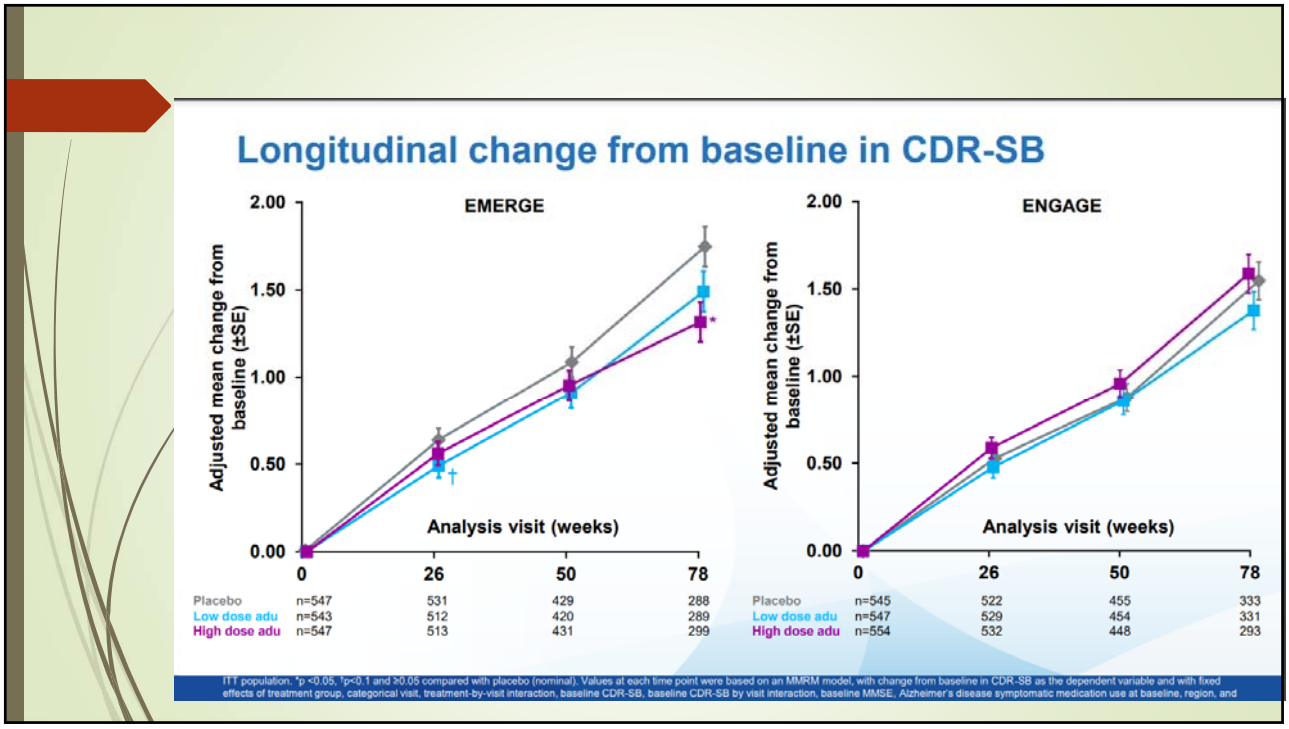
Longitudinal change from baseline in CDR-SB
EMERGE
Adjusted mean change from baseline (±SE)
2.00
1.50
1.00
0.50
0.00
Analysis visit (weeks)
0
26
50
78
Placebo n=547 531 429 288
Low dose adu n=543 512 420 289
High dose adu n=547 513 431 299
ENGAGE
Adjusted mean change from baseline (±SE)
Analysis visit (weeks)
Placebo n=545 522 455 333
Low dose adu n=547 529 454 331
High dose adu n=554 532 448 293
ITT population. *p <0.05, †p<0.1 and ≥0.05 compared with placebo (nominal). Values at each time point were based on an MMRM model, with change from baseline in CDR-SB as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at baseline, region, and

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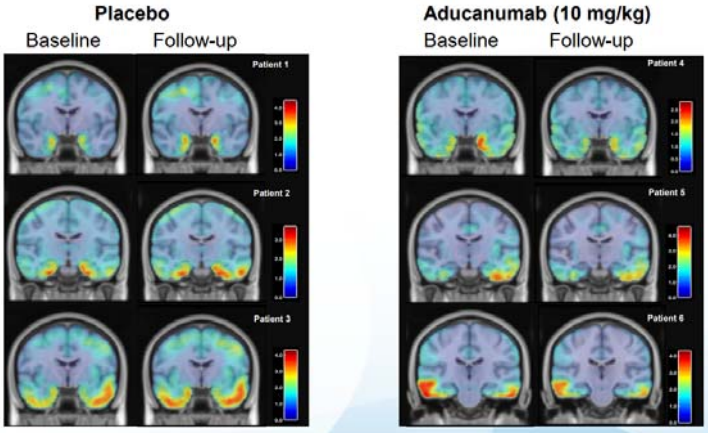
Tau deposition in representative patients



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Side effects of Aducanumab

- Most significant side effect was Amyloid Related Imaging Abnormalities (ARIA) which occurred in about 40% of the patients in the high dose group
- ARIA was demonstrated on MRI and included cerebral edema (swelling in the brain) and cerebral mico-hemorrhage (tiny bleeds within the brain)
- Sometimes ARIA was asymptomatic (patients did not feel the effects) but it could also result in headache (47% of patients), confusion (15%), dizziness (11%) and nausea (8%)
- ARIA would resolve after stopping the drug but many patients required "pauses" in their treatments and serial MRI scans to monitor for ARIA, about 6% of patients with ARIA had to stop the drug all together
- It is unknown if ARIA has any long term effects

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FDA Approval

- Based on the post hock analysis of the EMERGE trail Biogen applied directly to the FDA for approval of Aducanumab
- In November 2020 the scientific advisory committee to the FDA recommended against approval of Aducanumab to treat the cognitive effects of Alzheimer's disease
- June 2020 FDA approved Aducanumab under the "accelerated approval" pathway: "approves a drug for a serious or life-threatening illness that may provide meaningful therapeutic benefit over existing treatments when the drug is shown to have an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients and there remains some uncertainty about the drug's clinical benefit"
- Importantly it was approved based on it's ability to clear amyloid (surrogate endpoint) not on evidence that it slowed progression of disease

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Controversy Around FDA Approval

- Aducanumab is very expensive, originally Biogen stated it would cost 56K$ per year but later revised the price to 28K$
- Three of the scientific advisory committee members that recommended against approval quit in protest after the FDA approved Aducanumab
- Biogen worked closely with the FDA in post hock data analysis, many thought this was too close and that FDA needed greater distance from drug companies
- Medicare has stated only patients enrolled in clinical trials will be eligible for Aducanumab, prompting criticism from the Alzheimer's Association

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Lecanemab (Leqembi™)

- Sponsored by Japanese company Eisai in partnership with Biogen, also a MAB targeting amyloid (but a different form of amyloid)
- Trial enrolled 1795 patients aged 50-90 years with MCI or early stage Alzheimer's with confirmed amyloid pathology
- Study over 18 months, IV infusions (lasting about an hour) every 2 weeks
- Again looked at CDR-SB scale as primary end point
- Also looked at amyloid and tau deposition as well as several other cognitive tests and measures of activities of daily living

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Differences Between Aducanumab and Lecanemab

- Lecanemab targets amyloid when it is soluble in the blood while Aducanumab targets amyloid that is already adhered to vessel walls
- Published study in peer reviewed journal (NJEM) rather than going directly to FDA with the data
- Patients had to have confirmed amyloid pathology but could use PET scans OR CSF studies which are much cheaper and more widely available
- Although still underrepresented the study attempted to include more minority groups

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Result of Lecanemab Trial

- Statistically significant reduction in the change of CDR-SB scores, overall a 27% reduction in change of scores
- Some people responded more or less to the drug but the average difference between placebo group and drug group was about 0.45 points out of an18 point scale
- Significant reduction in amyloid plaques
- Importantly also showed IMPROVED scores on quality of life questionnaires for both patients and caregivers

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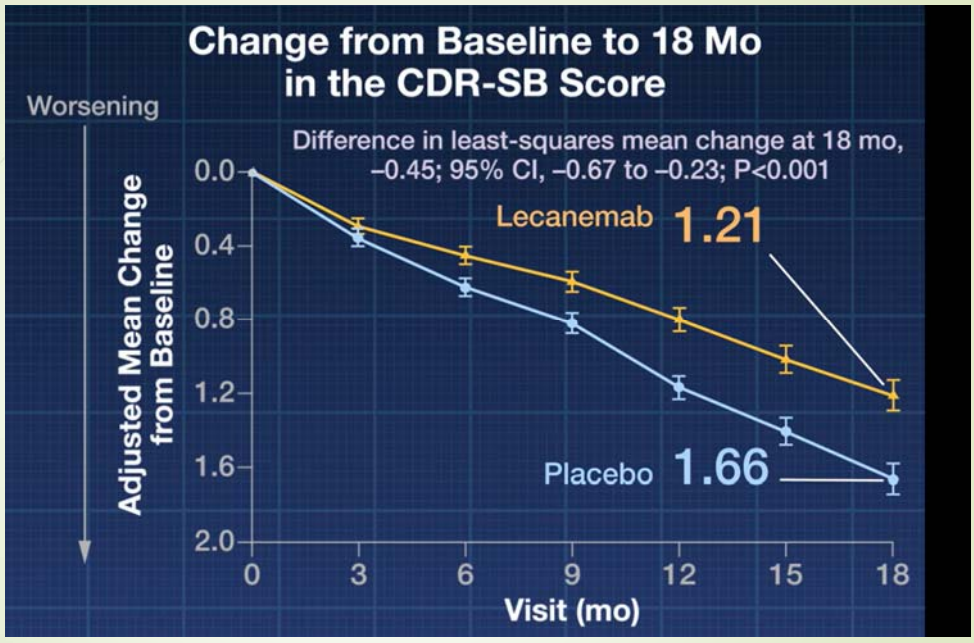
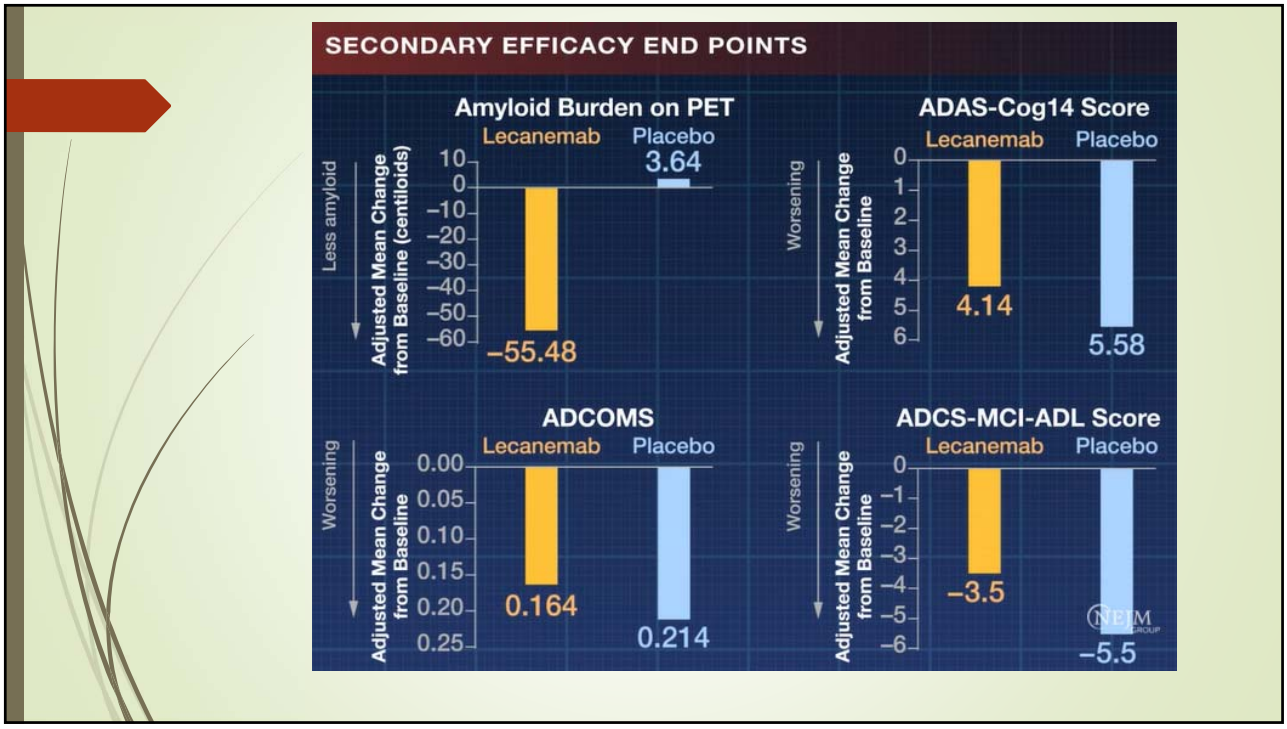

Change from Baseline to 18 Mo
in the CDR-SB Score
Worsening
Adjusted Mean Change from Baseline
Difference in least-squares mean change at 18 mo,
–0.45; 95% CI, –0.67 to –0.23; P<0.001
Lecanemab 1.21
Placebo 1.66
0.0
0.4
0.8
1.2
1.6
2.0
0
3
6
9
12
15
18
Visit (mo)

20


SECONDARY EFFICACY END POINTS
Amyloid Burden on PET
Lecanemab
Placebo
Less amyloid
Adjusted Mean Change from Baseline (centiloids)
10
0
−10
−20
−30
−40
−50
−60
3.64
−55.48
ADAS-Cog14 Score
Lecanemab
Placebo
Worsening
Adjusted Mean Change from Baseline
0
1
2
3
4
5
6
4.14
5.58
ADCOMS
Lecanemab
Placebo
Worsening
Adjusted Mean Change from Baseline
0.00
0.05
0.10
0.15
0.20
0.25
0.164
0.214
ADCS-MCI-ADL Score
Lecanemab
Placebo
Worsening
Adjusted Mean Change from Baseline
0
−1
−2
−3
−4
−5
−6
−3.5
−5.5
NEJM GROUP

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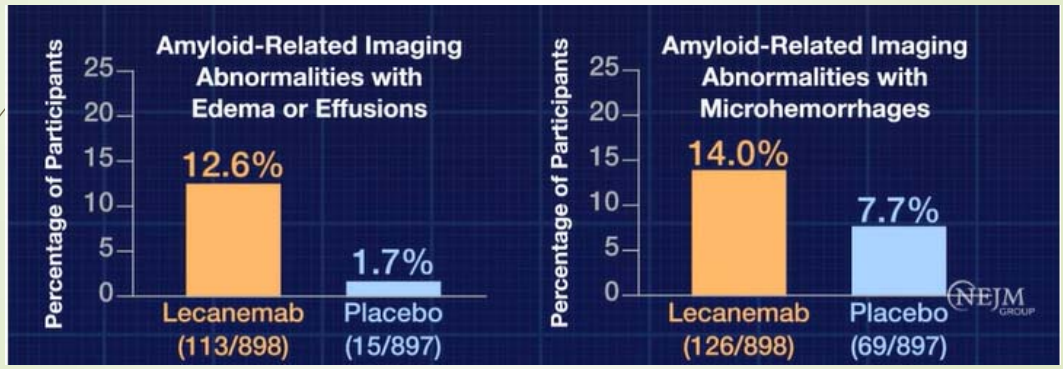
ARIA is a side effect but much less common than in Aducanumab



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Other Risks

- There were two deaths in the Lecanemab trial that MAY have been related to the drug causing bleeding in the brain, both of these patients were receiving high dose IV anticoagulation, one for treatment of a stroke another for a heart attack
- It is possible this drug increases the risk of hemorrhage in the brain but it is hard to know for sure as high dose IV anticoagulation can cause fatal brain bleeds in patients not taking Lecanemab
- Likely will require retrospective safety monitoring to determine if Lecanemab increases bleeding risk

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FDA Approval of Lecanemab

- Received the F.D.A.'s accelerated approval on January 6th 2023
- Eisai has submitted an application for the F.D.A.'s full approval based on these trial results; if the company gets it, Medicaid, Medicare, and some private insurers will pay for the drug
- Expected to be around 26k$ a year

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Summary

- Amyloid MAB drugs are very effective at removing plaques from the brain
- They likely have a mild effect on preserving cognitive function and therefore may be beneficial for some patients in very early stages of the disease
- They have definite risks and warrant an in depth discussion with a specialist about whether you have certain risk factors for side effects (such as APOE 4 status)
- This is a rapidly developing field with many studies in the works, we will likely know much more about the pathophysiology of Alzheimer's disease in the next 5-10 years

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