HHP Care Model and Disease Management Webinar Series

Aducanumab: The Future of Alzheimer Disease Therapy?

Thursday, August 12, 2021
5:30pm – 6:30pm

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Moderator

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Medical Director, *Hawai‘i Health Partners*
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- You have been automatically muted.
  You cannot unmute yourself.
- You will be able to submit questions via the Q&A section.
  - Due to time constraints, any unanswered questions will be addressed this week and posted on the HHP website
- A recording of the meeting will be available tomorrow on the HHP website and intranet.

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INTERPROFESSIONAL CONTINUING EDUCATION

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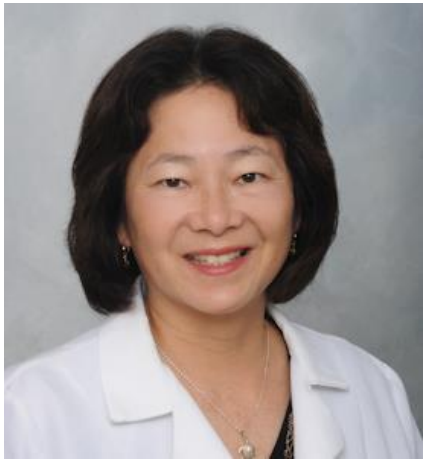
Aducanumab: The Future of Alzheimer Disease Therapy?

Huidy Shu, MD, PhD

Neurologist, Pali Momi Medical Center, Hawai‘i Pacific Health

Chief of Medical Subspecialties
Hawai‘i Pacific Health Medical Group



Dawn Minaai, MD
Geriatrics, Palliative and Hospice Care, Hawai‘i Pacific Health Medical Group

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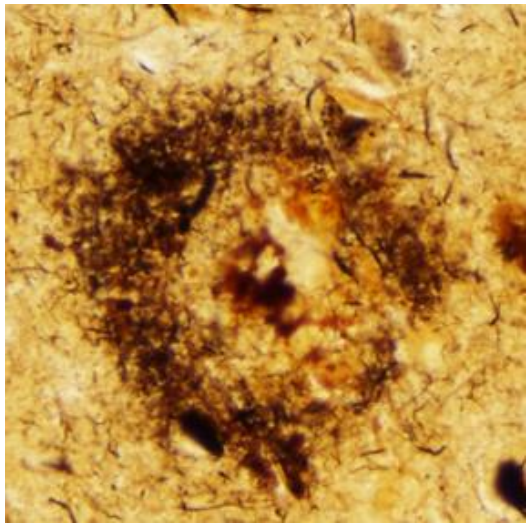
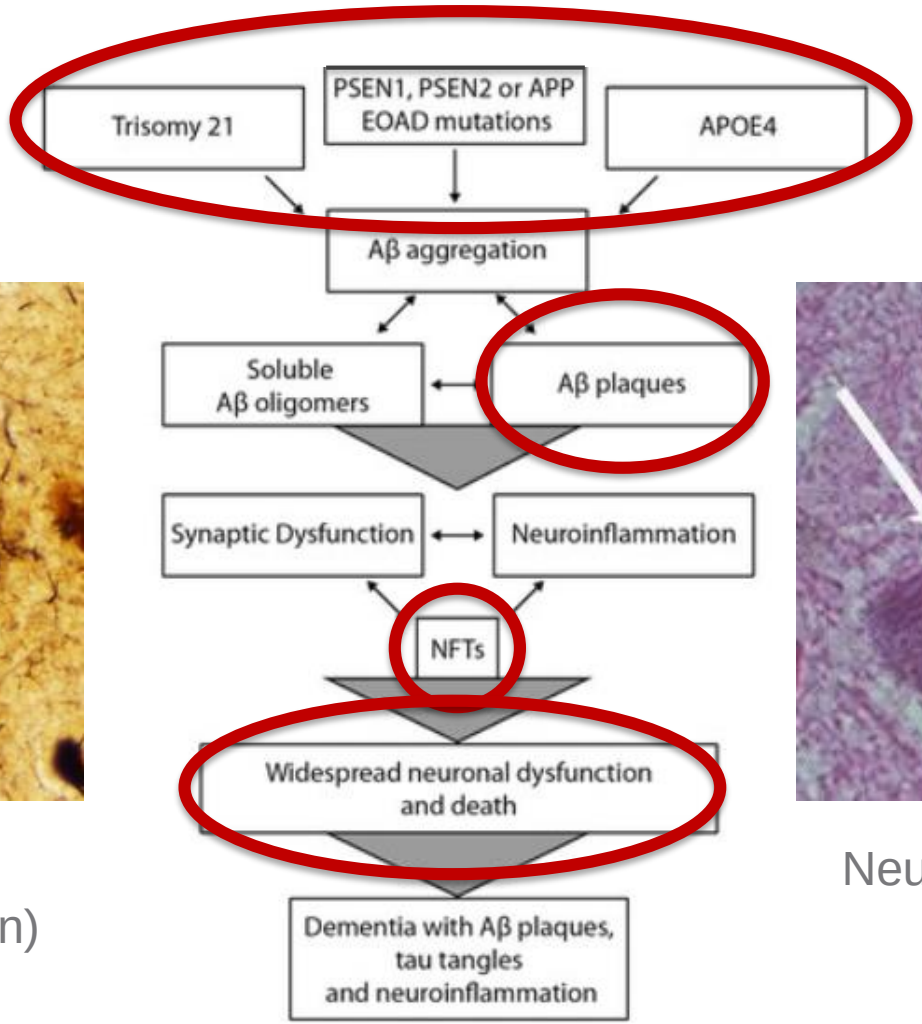
Current Drug Options for Alzheimer Disease and Related Behaviors

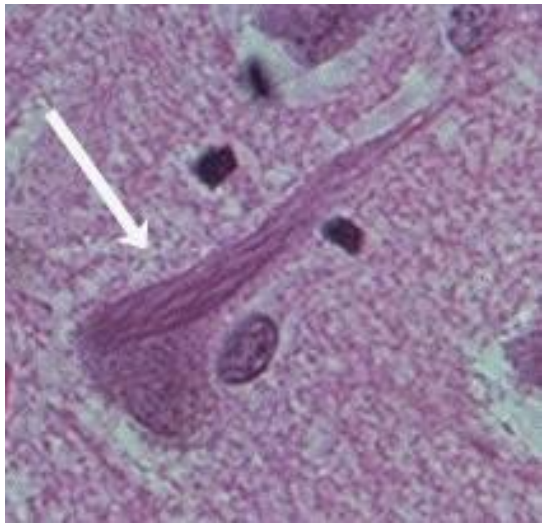
- Acetylcholinesterase Inhibitors
  - Donepezil
  - Rivastigmine
  - Galantamine
- NMDA Receptor Antagonist
  - Memantine
- SSRI / SNRI (off label)
- Dopamine Antagonist (off label/boxed warning)

The Amyloid Hypothesis of Alzheimer Disease



Amyloid Plaque
(Bielschowsky Stain)





Neurofibrillary Tangle
(H&E Stain)

Morris, G.P., Clark, I.A. & Vissel, B. Inconsistencies and Controversies Surrounding the Amyloid Hypothesis of Alzheimer's Disease. acta neuropathol commun 2, 135 (2014)

Aducanumab (Biogen)

- Human IgG1 monoclonal antibody
- Specific for conformational epitope on Aβ
- Binds only oligomeric Aβ, not monomers
- Phase 3 Clinical Trials were terminated in March 2019. Interim futility analyses showed they were unlikely to meet their primary end points.
- In October 2019, Biogen announced that it would file a Biologics License Application after detailed analysis showed positive results in the high-dose group from 1 of 2 trials.

Aducanumab (Biogen)

- In November 2020, FDA convened the Peripheral and Central Nervous System Drug Advisory Committee to review these trial data. This committee concluded that the data did **NOT** provide sufficient evidence of efficacy and it recommended against approval
- Approved by FDA for use in treating Alzheimer Disease on June 7, 2021, using the Accelerated Approval Pathway

ADUHELM (Aducanumab)

- Indications and Usage
  - Treatment of Mild Cognitive Impairment or Mild Dementia due to Alzheimer Disease
- Dosage and Administration

IV Infusion (q4 weeks)	Dosage (mg/kg)
1 and 2	1 mg/kg
3 and 4	3 mg/kg
5 and 6	6 mg/kg
7 +	10 mg/kg

Is This the Future of Alzheimer Disease Therapy?

Aducanumab Phase 3 studies EMERGE and ENGAGE

Studies	Two identical,18-month, randomized, double-blind, placebo-controlled, Phase 3 studies
Geography/ sample size	3285 patients at 348 sites in 20 countries
Population	▪ Early Alzheimer's disease (MCI due to Alzheimer's disease + mild Alzheimer's disease dementia) • MMSE 24-30, CDR-G 0.5, RBANS ≤ 85, with confirmed amyloid pathology
Doses	▪ Two dosing regimens (low and high) and placebo; randomized 1:1:1
Primary endpoint	▪ CDR-SB at 18 months
Other endpoints	▪ Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI ▪ Sub-studies: amyloid PET, tau PET, CSF disease-related biomarkers

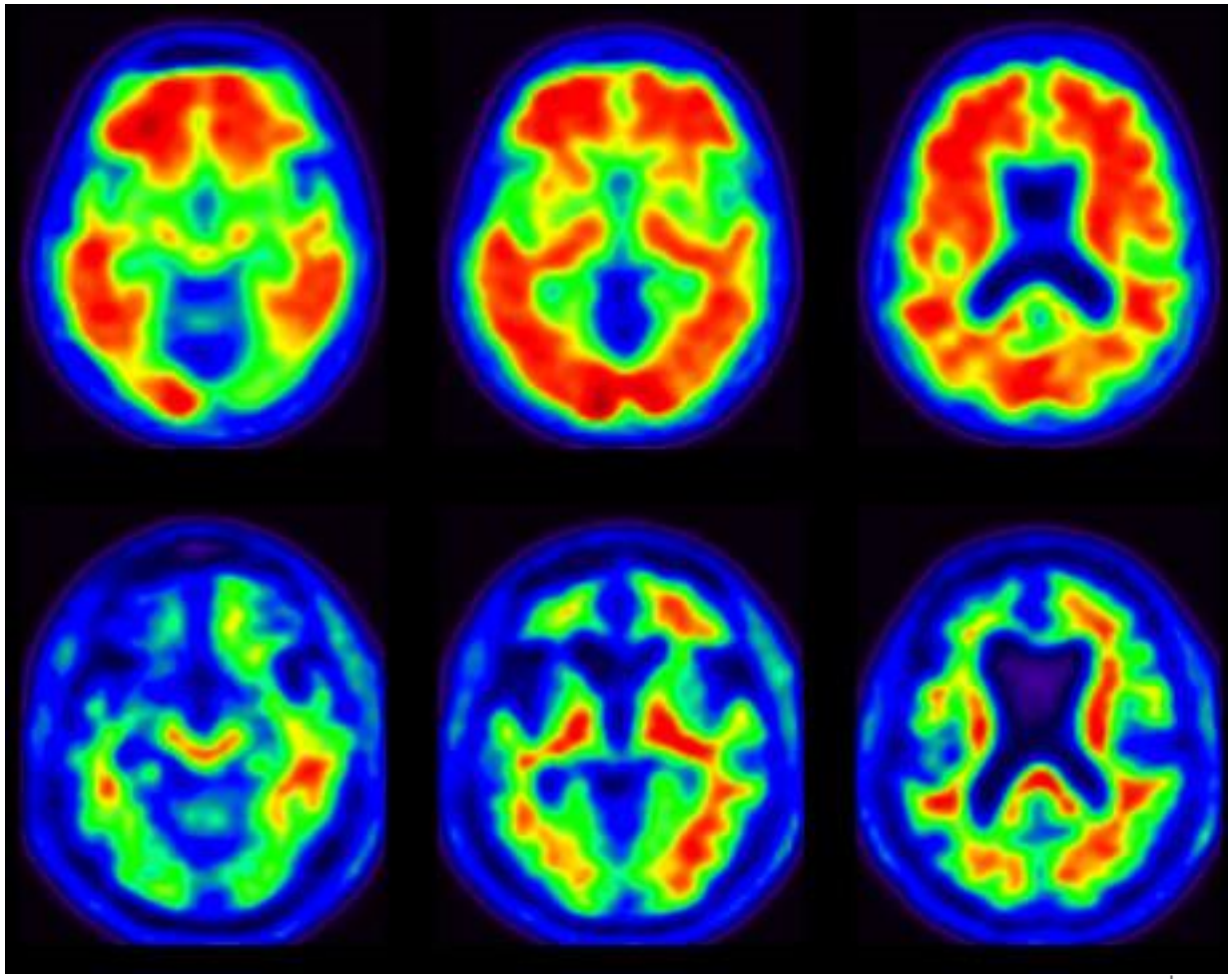
Countries with active sites included:
Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Poland, Portugal, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States

1. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02477800. Accessed November 2019; ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02484547. Accessed November 2019; Data on file.
ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron-emission tomography; RBANS, Repeatable Battery for Assessment of Neuropsychological Status.

PET Imaging Confirms Amyloid Pathology

Amyloid +

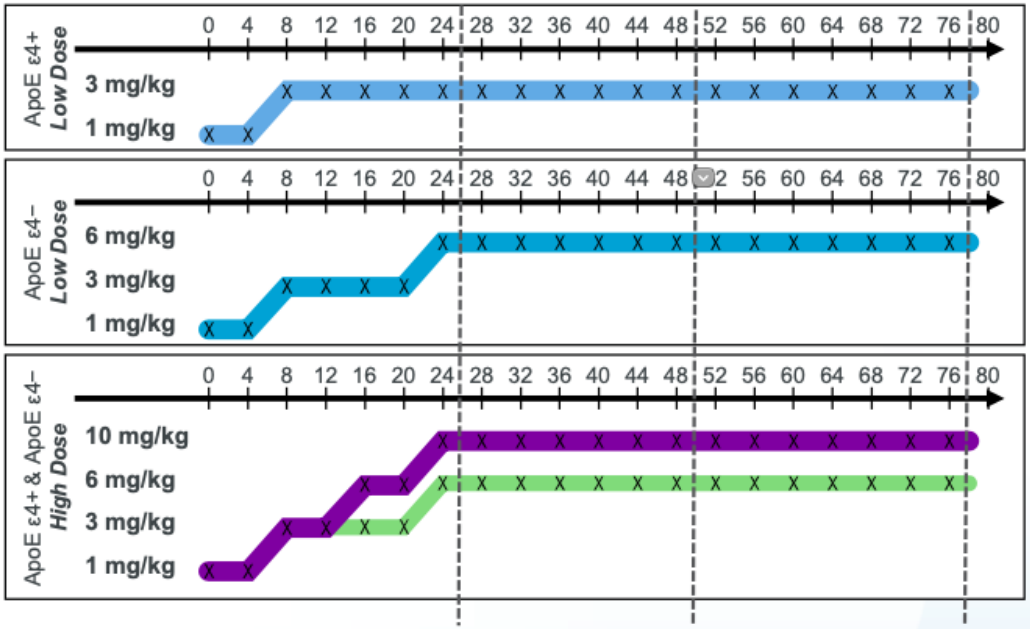
Amyloid -



https://www.ideas-study.org/2015/07/30/qa-alzheimers-disease-and-amyloid-pet-imaging/

EMERGE and ENGAGE: Dose regimen

Early enrolled patients in the high dose arm received a lower dose



Expected # of 10 mg/kg in high dose group

***by Week 26*: 1 dose**

***by Week 50*: 7 doses**

***by Week 78*: 14 doses**

Median <u>cumulative</u> dose at Week 78

56 mg/kg	**<u>Low dose</u>** • Titrated to 3 or 6 mg/kg • Maintained throughout study
98 mg/kg	
116 mg/kg (pre-PV4)	**<u>High dose</u>** • Titrated to 6 or 10 mg/kg in Protocol Versions 1-3 • Titrated to 10 mg/kg in Protocol Version 4 and higher
153 mg/kg (post-PV4)	

ApoE, apolipoprotein E; PV3, Protocol Version 3; PV4, Protocol Version 4.

Clinical Dementia Rating- Sum of Boxes

Clinical dementia rating (CDR): 0, 0.5, 1, 2, 3

Impairment	None (0)	Questionable (0.5)	Mild (1)	Moderate (2)	Severe (3)
Memory	No memory loss or slight inconstant forgetfulness	Consistent slight forgetfulness; partial recollection of events	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
Orientation	Fully oriented	Fully oriented or 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 in time, often to place	Oriented to person only
Judgment and problem	Solves everyday problems and handles business and financial affairs well; judgment good in relation to past performance	Slight impairment to solving problems, similarities, differences	Moderate difficulty in handling problems, similarities, differences; social judgment usually maintained	Severely impaired in handling problems, similarities, differences; social judgment usually impaired	Unable to make judgments or solve problems
Community affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside of home; appears well enough to be taken to functions outside of family home	No pretense of independent function outside of home; appears too ill to be taken to functions outside a family home
Home and hobbies	Life at home, hobbies, intellectual interests well maintained	Life at home, hobbies, intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal care	Fully capable of self care	Fully capable of self care	Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impaired due to other factors.

EMERGE and ENGAGE Primary Endpoints

All Patients Included

EMERGE	Placebo decline (n=548)	Low dose (n=543)	High dose (n=547)
		diff vs. placebo, (%)[c]	diff vs. placebo (%)[c]
CDR-SB	1.74	**-0.26** (-15%)	**-0.39** (-22%)

ENGAGE	Placebo decline (n=545)	Low dose (n=547)	High dose (n=555)
CDR-SB	1.56	**-0.18** (-12%)	**0.03** (2%)

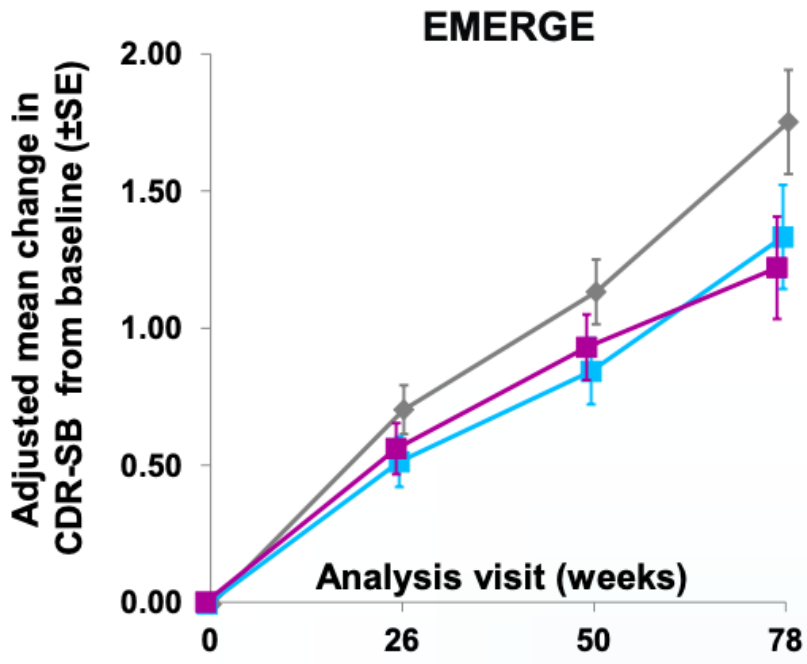
Dosing Protocol 4 Only

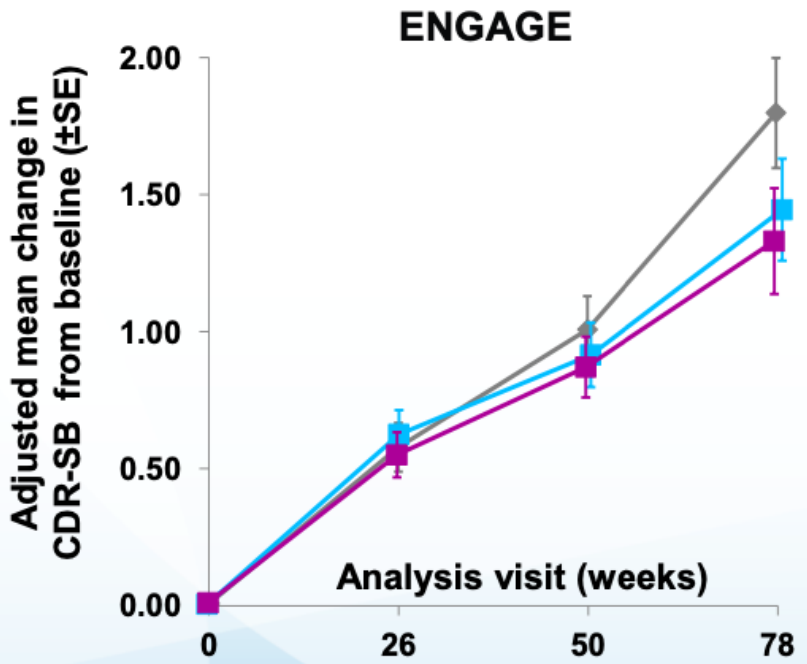
Placebo decline (n=304)	Low dose (n=295)	High dose (n=288)
	diff vs. placebo (%)[c]	diff vs. placebo (%)[c]
1.76	**-0.42** (-24%)	**-0.53** (-30%)

Placebo decline (n=247)	Low dose (n=261)	High dose (n=282)
1.79	**-0.35** (-20%)	**-0.48** (-27%)

[a]MMRM model was fitted separately for pre- and post-Protocol Version 4 set; [b]Patients who consented to PV4 or higher version prior to Week 16 in ITT population; [c]Difference vs placebo at Week 78. Negative percentage means less progression in the treated arm; N denotes the number of all randomized and dosed patients that were included in the ITT analysis.
CDR-SB, Clinical Dementia Rating–Sum of Boxes; ITT, intent to treat.

EMERGE and ENGAGE Dosing Protocol 4 Results



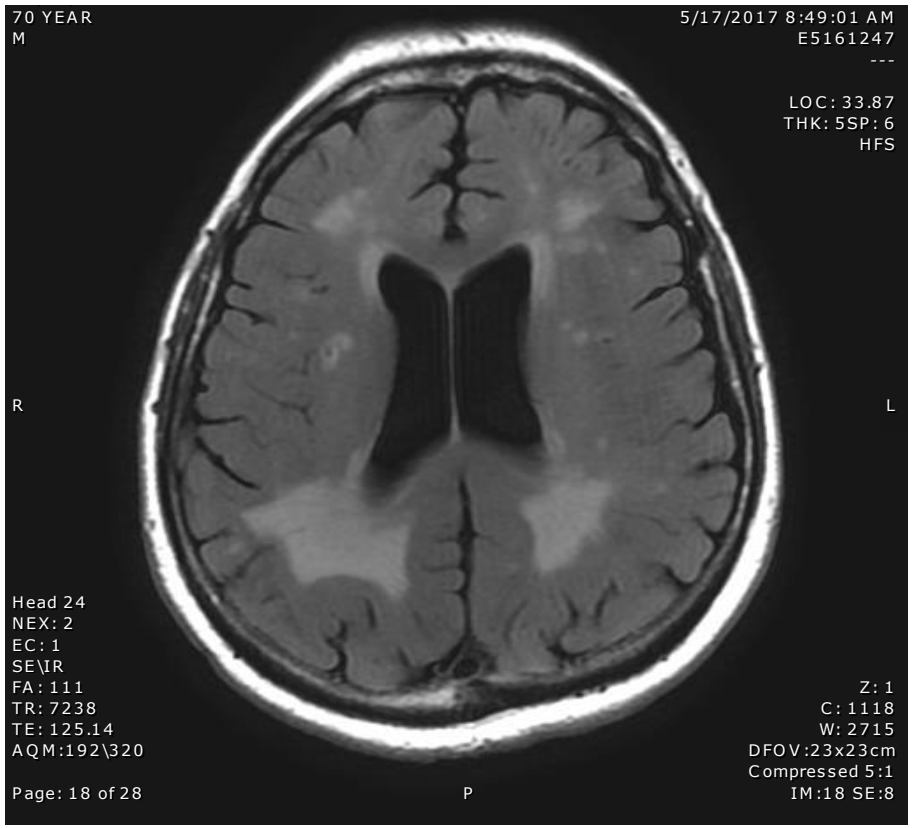


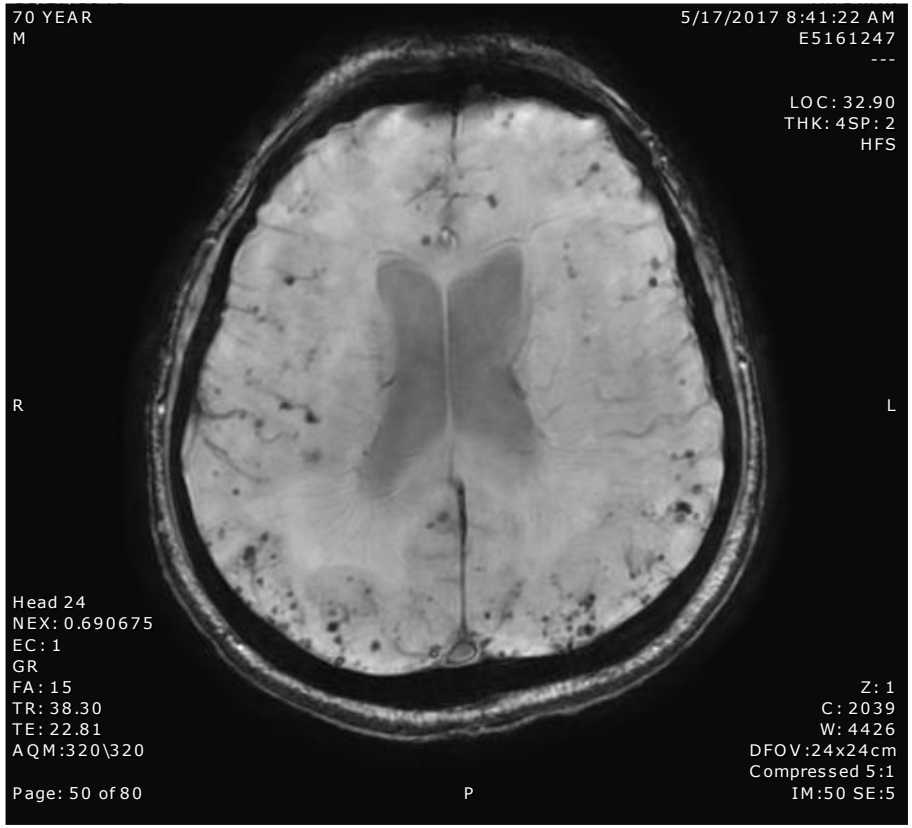
[a]MMRM model was fitted separately for pre- and post-Protocol Version 4 set; [b]Patients who consented to PV4 or higher version prior to Week 16 in ITT population.
CDR-SB, Clinical Dementia Rating–Sum of Boxes; PV4, Protocol Version 4; SE, standard error.

Clinical results of EMERGE (All Patients)

Endpoint at Week 78	ADUHELM High Dose	Placebo
CDR-SB		
-Mean Baseline	2.51	2.47
-Change from baseline	1.35 **(-22%)** p= 0.0120	1.74
MMSE		
-Mean Baseline	26.3	26.4
-Change from baseline	-2.7 **(-18%)** p = 0.0493	-3.3
ADAS-COG		
-Mean Baseline	22.246	21.867
-Change from baseline	3.763 **(-27%)** p = 0.0097	5.162
ADCS-ADL-MCI		
-Mean Baseline	42.5	42.6
-Change from baseline	-2.5 **(-40%)** p = 0.0006	-4.3
NPI-10		
-Mean Baseline	4.5	4.3
-Change from baseline	0.2 **(-87%)** p = 0.0215	1.5

Amyloid Related Imaging Abnormalities - ARIA-E and ARIA-H





ARIA Occurred in 41% of High-Dose Patients

-Symptomatic in 24% (headache, confusion, dizziness)

-Symptoms resolve in 88% period during observation

	EMERGE			ENGAGE		
	Placebo (n=547)	Low dose (n=544)	High dose (n=547)	Placebo (n=541)	Low dose (n=548)	High dose (n=558)
Patients with any event, n (%)	**476** (87.0)	**477** (87.7)	**505** (92.3)	**465** (86.0)	**491** (89.6)	**500** (89.6)
ARIA-E (%)	**12** (2.2)	**140** (25.7)	**186** (34.0)	**16** (3.0)	**139** (25.4)	**198** (35.5)
Headache (%)	**83** (15.2)	**106** (19.5)	**106** (19.4)	**81** (15.0)	**98** (17.9)	**114** (20.4)
ARIA-H, microhemorrhage (%)	**38** (6.9)	**88** (16.2)	**102** (18.6)	**31** (5.7)	**85** (15.5)	**98** (17.6)
Nasopharyngitis (%)	**90** (16.5)	**70** (12.9)	**87** (15.9)	**67** (12.4)	**64** (11.7)	**66** (11.8)
ARIA-H, superficial siderosis (%)	**14** (2.6)	**50** (9.2)	**73** (13.3)	**10** (1.8)	**48** (8.8)	**86** (15.4)
Fall (%)	**68** (12.4)	**64** (11.8)	**69** (12.6)	**55** (10.2)	**77** (14.1)	**83** (14.9)

This table includes patients who received at least one dose of investigational treatment.

Safety population. Patients randomized to placebo who accidentally received active dose are summarized under active groups (4 in ENGAGE and 1 in EMERGE).
All safety data presented are from the placebo-controlled period.
ARIA-E, amyloid related imaging abnormality-edema/effusion; ARIA-H, amyloid related imaging abnormality-micro-hemorrhages and hemosiderin deposits.

16

ADUHELM (Aducanumab)

- Monitoring for Amyloid Related Imaging Abnormalities (ARIA)
  - MRI brain
    - Within 1 year PRIOR to initiating treatment
    - Before 7th infusion (10 mg/kg dose #1)
    - Before 12th infusion (10 mg/kg dose #6)
  - If 10 or more new incident microhemorrhages or > 2 focal areas of superficial siderosis is observed, treatment may continue with caution only after clinical evaluation and follow up MRI demonstrates radiographic stabilization
- Resuming ADUHELM After Missed Dose
  - If an infusion is missed, resume administration at the same dose ASAP. Infusions are to be administered every 4 weeks and at least 21 days apart

FDA Accelerated Approval Pathway

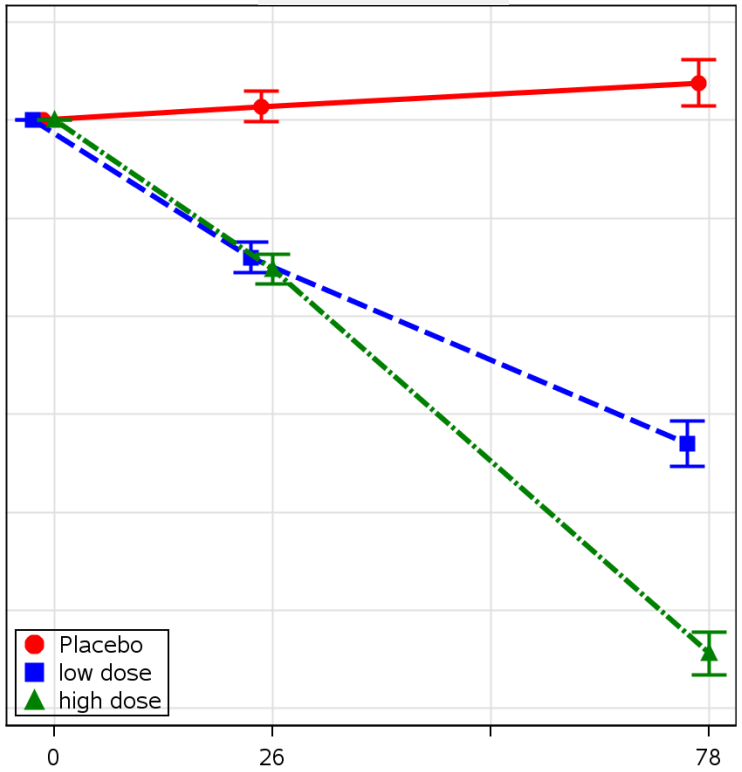
- FDA drug approval typically requires evidence of clinical benefit in 2 positive phase 3 clinical trials
- The Accelerated Approval pathway allows for earlier approval for drugs that treat serious conditions, and that fill an unmet medical need based on a *surrogate endpoint*
- A *surrogate endpoint* is a marker, such as a lab measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit
- Drug companies are still required to conduct phase 4 confirmatory trials to prove clinical benefit
  - If positive, then traditional approval is granted
  - If negative, procedures could remove the drug from market

Accelerated Approval Drugs (Total 269)

- Zalcitabine- 1992
- Betaseron- 1993
- Casodex- 1995
- Docetaxel- 1996
- Midodrine- 1996
- Infliximab- 1998
- Temozolomide-1999
- Kaletra- 2000
- Gleevec- 2002
- Anastrozole- 2002
- Natalizumab- 2004
- Avastin- 2008
- Keytruda- 2013 …
- Opdivo- 2014 …
- Praxbind- 2015
- …
- Aducanumab- 2021

Amyloid PET SUVR: 64.2% and 53.5% Reduction

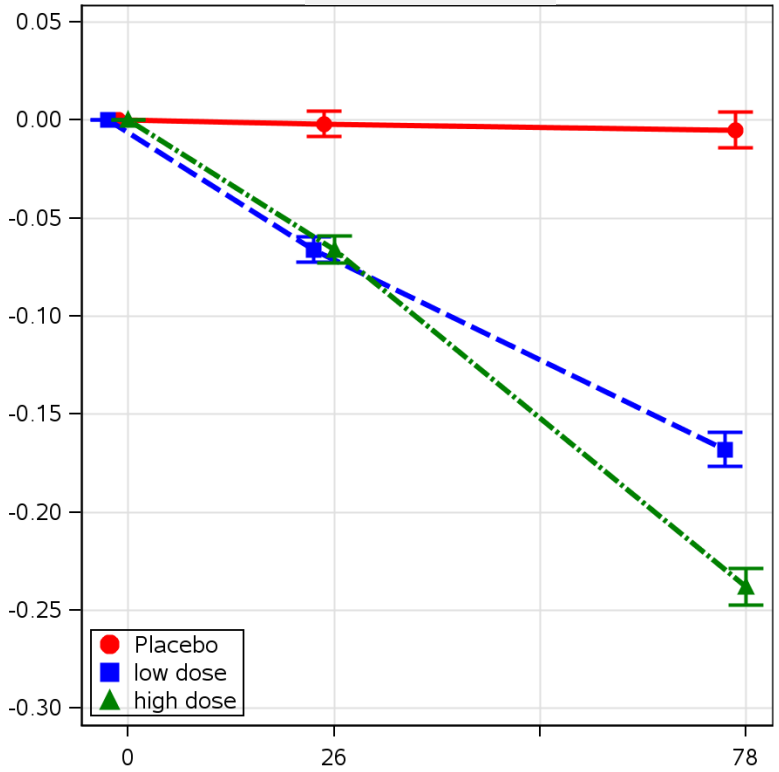
EMERGE



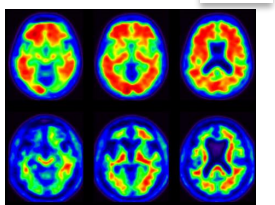
157	128	74
157	125	79
171	136	87

Placebo
Low Dose
High Dose

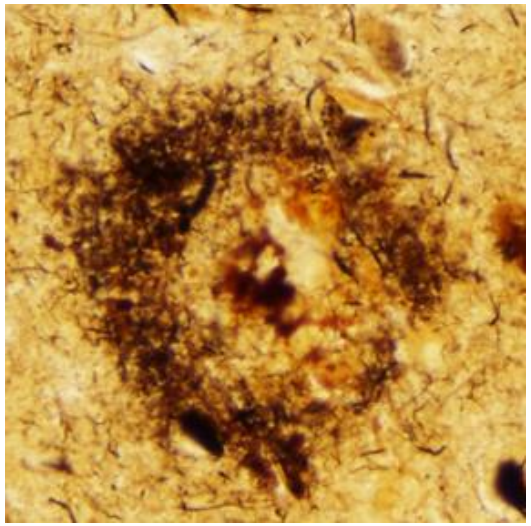
ENGAGE



203	164	104
198	166	116
181	149	97



The Amyloid Hypothesis of Alzheimer Disease



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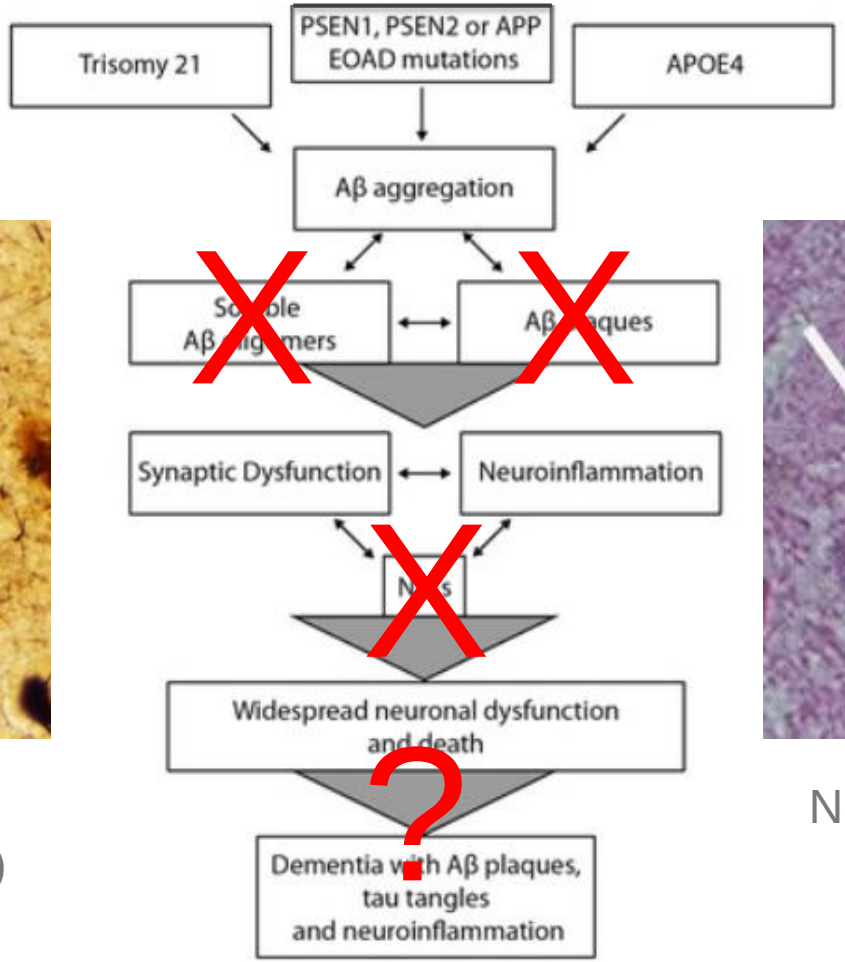

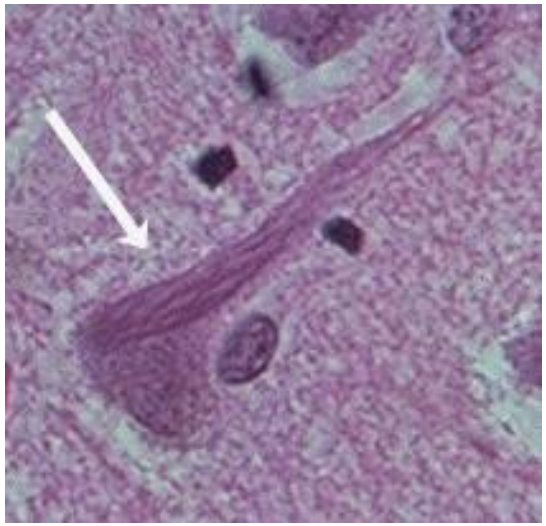

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(H&E Stain)

Morris, G.P., Clark, I.A. & Vissel, B. Inconsistencies and Controversies Surrounding the Amyloid Hypothesis of Alzheimer's Disease. acta neuropathol commun 2, 135 (2014)

Cost Analysis

- Annual Cost = $41,000 (year 1) to **$56,000**
- Additional costs are necessary for the recommended 3+ MRI scans in year 1 and Amyloid imaging or CSF analysis
- CMS has not yet commented with a “National Coverage Determination”
- HMSA has shared that they are likely NOT to cover this drug for its beneficiaries

Institute for Clinical and Economic Review

- ICER has calculated a **fair annual price to be $2500 - $8300** based on the current evidence of effectiveness. If only the positive trial is considered, they estimate a fair price of $11,100 - $23,100 per year

- ICER "believes that the FDA, in approving aducanumab for the treatment of Alzheimer's disease, has failed in its responsibility to protect patients and families from unproven treatments with known harms. Our review of the evidence was concordant with that of many independent experts: current evidence is insufficient to demonstrate that aducanumab benefits patients. The avenue forward has seemed clear: another study would be needed to reduce the substantial uncertainty about the drug's effectiveness, a requirement of even greater priority because of the drug's common and potentially serious side effects."

Summary

- FDA has approved Aducanumab (ADUHELM) for treatment of patients with Alzheimer Disease
- There is encouraging but inconclusive evidence that Aducanumab slows clinical progression of the AD
- There is strong evidence that Aducanumab removes Beta Amyloid from the brains of patients with AD
- Aducanumab is VERY expensive ($41-56K / year) and CMS has not yet made a “National Coverage Determination”
- Recent analysis by ICER suggests that Aducanumab is not cost-effective at the current price point and level of evidence

Aduhelm Approval Sparks Controversy

- The American Geriatrics Society argued that the FDA approval was premature given the state of the science on aducanumab
- Cleveland Clinic and Mt. Sinai Health Systems have decided not to administer this drug
- FDA Commissioner has asked for an independent Federal investigation of the approval process
- 3 of 11 members of the FDA Advisory Committee have resigned in protest

Recommendations For Aduhelm Use

- Expected demand for Aduhelm is very low
- We recommend PCPs to refer interested patients to Neurology for shared decision making
- Plan to develop a detailed, shared decision-making protocol including discussion of questionable benefits, high costs, and significant risks of therapy
- Limit Aducanumab prescriptions to Neurology

Appropriate Use Guidelines (Cummings 2021)

Features	Expert Panel Recs	Dr. Shu Recs
Diagnosis	MCI or Mild AD Dementia	MCI or Mild AD Dementia
MMSE	21-30	**27-30**
Amyloid Testing	PET or CSF analysis	PET or CSF Analysis
Medical History	Stable medically, stable psychiatrically, no organ failure, no active cancer	Stable medically, stable psychiatrically, no organ failure, no active cancer
Bleeding Risk	No anticoagulants, no coagulopathy	No anticoagulants, **no high potency antiplatelets**, no coagulopathy
Neuro Exam	No signs of other neurologic disorders	No signs of other neurologic disorders
MRI Findings	No recent or prior large hemorrhage, < 4 microhemorrhage, no major old infarcts, no diffuse white matter disease	No recent or prior large hemorrhage, < 4 microhemorrhage, no major old infarcts, no diffuse white matter disease

Discussion

Next Webinar:

HHP/HPH Community Webinar:

TBD

Thank you!

- A recording of the meeting will be available afterwards.
- Unanswered question?
  - Contact us at info@hawaiihealthpartners.org

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