Sixth Annual Participant Appreciation Day Conference on Healthy Brain Aging

Victor W. Henderson, MD

Departments of Epidemiology & Population Health and of Neurology & Neurological Sciences
Director, Farrukh–Jamal Stanford Alzheimer’s Disease Research Center

Healthy Brain Aging Study
Farrukh–Jamal Stanford Alzheimer’s Disease Research Center (ADRC)
Lewy Body Scientific Partnership for Advancing Research and Knowledge (LB-SPARK)
Stanford Clinical Trials Programs
Stanford Aging and Memory Study (SAMS)
Longitudinal Early-onset Alzheimer’s Disease Study
Asian Cohort for Alzheimer’s Disease (ACAD)
CAB (Community Advisory Board)

- Stella De La Pena: Alzheimer’s Association
- Leslie DuBridge: Senior advocate
- Denise Coley: Parkinson’s disease advocate
- Sandra Green: Alzheimer’s Association
- Sara Langer: Stanford ADRC participant volunteer
- Kirk Leu: Caregiver
- Ting Pun: Vi Senior Housing Community
- Scott Roney: Veteran
- Elissa Wellikson: Veteran
- Sandra Winters: Senior Coastsiders
- Benjamin Yen: Caregiver
- Amy Yotopolous: Avenidas

579 scientific publications in the National Library of Medicine (PubMed Central) cite the Stanford ADRC NIH grant, July 2015 to October 2023
New FDA-approved treatments for mild cognitive impairment and mild dementia due to Alzheimer’s disease

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Director, Farrukh–Jamal Stanford Alzheimer’s Disease Research Center
New FDA-approved treatments for mild cognitive impairment and mild dementia due to Alzheimer’s disease.

Before 2021, there were several approved therapies for Alzheimer-dementia but no approved therapies for the treatment of MCI.

- Aducanumab: Accelerated approval by the FDA, June 2021
- Lecanemab: Regular approval by the FDA, July 2023
- Donanemab: Under FDA review

These are IgG1 monoclonal antibodies that target β-amyloid and reduce brain amyloid.
Amyloid Plaque

Plaques and tangles

- Plaque cores: β-amyloid protein
- Neurofibrillary tangles: Tau protein (hyperphosphorylated)
Amyloid hypothesis of Alzheimer’s disease (early 1990s)

By age 70, over a third of cognitively normal adults are amyloid (+).
Jansen et al., JAMA Neurol. 2022

Amyloidosis

Hyperphosphorylated tau

Synaptic loss, neuronal injury

Cognitive impairment

Worse

Better

Time

Aducanumab: Impressive amyloid reductions in a Phase-1b trial and two Phase-3 trials

Phase 1b trial

Placebo

Low dose (3 mg/kg)

Medium dose (6 mg/kg)

High dose (10 mg/kg)

One year later

Phase 3 trial ENgage

Low dose aducanumab

High dose aducanumab

Placebo

Phase 3 trial EMerge

Low dose aducanumab

High dose aducanumab

SUVr = Standardized uptake value ratio

Haeberlein et al., J Prev Alz Dis 2022;2:197

4% increase from baseline

71% decrease from baseline

1% decrease from baseline

59% decrease from baseline
### Clinical Dementia Rating (CDR) Sum of Boxes score

<table>
<thead>
<tr>
<th>NONE</th>
<th>QUESTIONABLE 0.5</th>
<th>MILD</th>
<th>MODERATE 2</th>
<th>SEVERE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>No memory loss or slight inconstant forgetfulness</td>
<td>Consistent, slight forgetfulness; partial recollection of events; &quot;wrong&quot; forgetfulness</td>
<td>Moderate memory loss; more marked for recent events; deficit interferes with everyday activities</td>
<td>Severe memory loss; only highly learned material retained; new material rapidly lost</td>
</tr>
<tr>
<td>Orientation</td>
<td>Fully oriented</td>
<td>Fully oriented except for slight difficulty with time relationships</td>
<td>Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere</td>
<td>Severe difficulty with time relationships; usually disoriented to time, often to place</td>
</tr>
<tr>
<td>Judgment &amp; Problem Solving</td>
<td>Solves everyday problems &amp; handles business &amp; financial affairs well; judgment: good in relation to past performance</td>
<td>Slight impairment in solving problems, similarities, and otherness</td>
<td>Moderate difficulty in handling problems, similarities, and otherness; social judgment usually maintained</td>
<td>Severely impaired in handling problems, similarities, and otherness; social judgment usually impaired</td>
</tr>
<tr>
<td>Community Affairs</td>
<td>Independent function at usual level in job, shopping, volunteer and social groups</td>
<td>Slight impairment in these activities</td>
<td>Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection</td>
<td>No pretense of independent function outside home</td>
</tr>
<tr>
<td>Home and Hobbies</td>
<td>Life at home, hobbies, and intellectual interests well maintained</td>
<td>Life at home, hobbies, and intellectual interests slightly impaired</td>
<td>Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned</td>
<td>Only simple chores preserved; very restricted interests, poorly maintained</td>
</tr>
<tr>
<td>Personal Care</td>
<td>Fully capable of self-care</td>
<td>Needs prompting</td>
<td>Requires assistance in dressing, hygiene, keeping of personal effects</td>
<td>Requires much help with personal care, frequent incontinence</td>
</tr>
</tbody>
</table>

CDR sum of boxes ranges from 0 (best) to 18 (worst). Minimal clinically important difference estimated at 1-2 points.

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**Clinical Dementia Rating (CDR): based on cognition and function**

Hughes et al, Brit J Psychiatry, 1982; Morris, Neurology, 1993

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**Aducanumab: Unimpressive clinical results**

- **80% MCI, 20% mild AD-dementia**
  - **EMERGE phase 3 trial**
    - 18 months, monthly infusions, n = 1638
    - Very small benefit
  - **ENGAGE phase 3 trial**
    - 18 months, monthly infusions, n = 1647
    - No benefit

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**Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer’s Disease**

**Figure 3.1. Meta-Analysis of Difference in CDR-SB versus Placebo**

<table>
<thead>
<tr>
<th>CDR-SB Diff. from Placebo</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Dose</td>
<td></td>
</tr>
<tr>
<td>EMERGE</td>
<td>-0.40</td>
</tr>
<tr>
<td>ENGAGE</td>
<td>-0.70</td>
</tr>
<tr>
<td>Overall</td>
<td>-0.10</td>
</tr>
</tbody>
</table>

This difference is 2/5 point

Favors Aducanumab

Favors Placebo

The overall mean difference is less than 1/5 point

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Lecanemab infusions versus placebo every two weeks

MCI (62%) or mild AD-dementia (38%), n = 1795

Primary outcome: Change in CDR-Sum of Boxes at 18 months

Mean difference of -0.45 points (95% CI, -0.23 to -0.67) on an 18 point scale

Donanemab infusions versus placebo every 4 weeks

MCI or mild AD-dementia, n = 1736

Primary outcome: change in iADRS (Integrated Alzheimer’s Disease Rating Scale) at 72 weeks

Mean difference of -3.3 points (95% CI, -4.9 to -1.7) on a 144 point scale

Secondary outcome

Mean difference of -0.68 points (95% CI, -0.94 to -0.42) on an 18 point scale
Amyloid Related Imaging Abnormalities (ARIA): Edema and Hemorrhage

ARIA-E

<table>
<thead>
<tr>
<th>Drug</th>
<th>ARIA-E</th>
<th>ARIA-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aducanumab* (ENGAGE)</td>
<td>33% (36% vs. 3%)</td>
<td>13% (19% vs. 6%)</td>
</tr>
<tr>
<td>Aducanumab* (EMERGE)</td>
<td>32% (35% vs. 2%)</td>
<td>13% (20% vs. 7%)</td>
</tr>
<tr>
<td>Lecanemab (Clarity AD)</td>
<td>11% (13% vs. 2%)</td>
<td>6% (14% vs. 8%)</td>
</tr>
<tr>
<td>Donanemab (Trailblazer-Alz 2)</td>
<td>22% (24% vs. 2%)</td>
<td>14% (27% vs. 13%)</td>
</tr>
</tbody>
</table>

ARIA-H

<table>
<thead>
<tr>
<th>Drug</th>
<th>Microhemorrhage</th>
<th>Superficial siderosis</th>
<th>Macrohemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aducanumab</td>
<td>13% (16% vs. 2%)</td>
<td>14% (16% vs. 2%)</td>
<td>-</td>
</tr>
<tr>
<td>Lecanemab</td>
<td>13% (13% vs. 3%)</td>
<td>10% (13% vs. 3%)</td>
<td>-</td>
</tr>
<tr>
<td>Donanemab</td>
<td>14% (16% vs. 3%)</td>
<td>13% (16% vs. 3%)</td>
<td>-</td>
</tr>
</tbody>
</table>


*Results for high-dose aducanumab subgroup.
†Flu-like symptoms, nausea, vomiting, hyper- or hypotension, oxygen desaturation; transient decreased LC counts (38% vs. 2%) and increased leukocyte counts (22% vs. 1%)
§Percent difference; Alves et al., Neurology 2023;100:e2114
### Adverse events: Drug – placebo differences in phase-3 trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>ARIA-E</th>
<th>ARIA-H</th>
<th>Infusion reaction†</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Aducanumab**
(ENGAGE)               | 33%    | 13%    | 14%                |       |
| (36% vs. 3%)          | (19% vs. 6%) | (16% vs. 2%) | 8 drug / 5 placebo |
| **Aducanumab**
(EMERGE)               | 32%    | 13%    | 10%                |       |
| (35% vs. 2%)          | (20% vs. 7%) | (13% vs. 9%) |                |
| **Lecanemab**
(Clarity AD)            | 11%    | 6%     | 3%                 | 19%   |
| (13% vs. 2%)          | (14% vs. 8%) | (6% vs. 3%) | 5 drug / 1 placebo |
| **Donanemab**
(Tailblazer-Alz 2)  | 22%    | 14%    | 13%                | 8%    |
| (24% vs. 2%)          | (27% vs. 13%) | (16% vs. 3%) | 3 drug / 2 placebo |


*Results for high-dose aducanumab subgroup.
†Flu-like symptoms, nausea, vomiting, hyper- or hypotension, oxygen desaturation; transient decreased LC counts (38% vs. 2%) and increased leukocyte counts (22% vs. 1%)
§Percent difference; Alves et al., Neurology 2023;100:e2114

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**Adverse events: Drug – placebo differences in phase-3 trials**

<table>
<thead>
<tr>
<th>Drug</th>
<th>ARIA-E</th>
<th>Micro-hemorrhage</th>
<th>Brain volume loss$^6$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Aducanumab**
(ENGAGE)               | 33%    | 13% (19% vs. 6%) | 0%                   |
| (36% vs. 3%)          |        | (16% vs. 2%)     |                      |
| **Aducanumab**
(EMERGE)               | 32%    | 13% (20% vs. 7%) | 4%                   |
| (35% vs. 2%)          |        | (13% vs. 9%)     |                      |
| **Lecanemab**
(Clarity AD)            | 11%    | 6% (14% vs. 8%)  | 26%                  |
| (13% vs. 2%)          |        | (6% vs. 3%)      |                      |
| **Donanemab**
(Tailblazer-Alz 2)  | 22%    | 14% (27% vs. 13%)| 23%                  |
| (24% vs. 2%)          |        | (16% vs. 3%)     |                      |


*Results for high-dose aducanumab subgroup.
†Flu-like symptoms, nausea, vomiting, hyper- or hypotension, oxygen desaturation; transient decreased LC counts (38% vs. 2%) and increased leukocyte counts (22% vs. 1%)
§Percent difference; Alves et al., Neurology 2023;100:e2114
What are other considerations?

- Aducanumab, lecanemab, and (presumably) donanemab are expensive.
- Screening, treatment, and monitoring are resource intensive.
- There are equity concerns.
For the first time, there are approved treatments for mild cognitive impairment and mild dementia associated with an Alzheimer biomarker. 😊

Patients worsen despite treatment. 😞

The average difference in decline at 18 months is significant (e.g., 27% for lecanemab). 😊

But the average clinical difference at 18 months is probably not noticeable. 😞

We don’t yet know the long-term clinical outcomes.

- There may be meaningful long-term benefit, or
- There may be long-term harm, or
- There may not be much of a difference.
Alzheimer's Disease Research Centers are congressionally designated NIH Centers of Excellence

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