CLINICAL TRIALS IN ALZHEIMER'S DISEASE

Drama or Dramamine?

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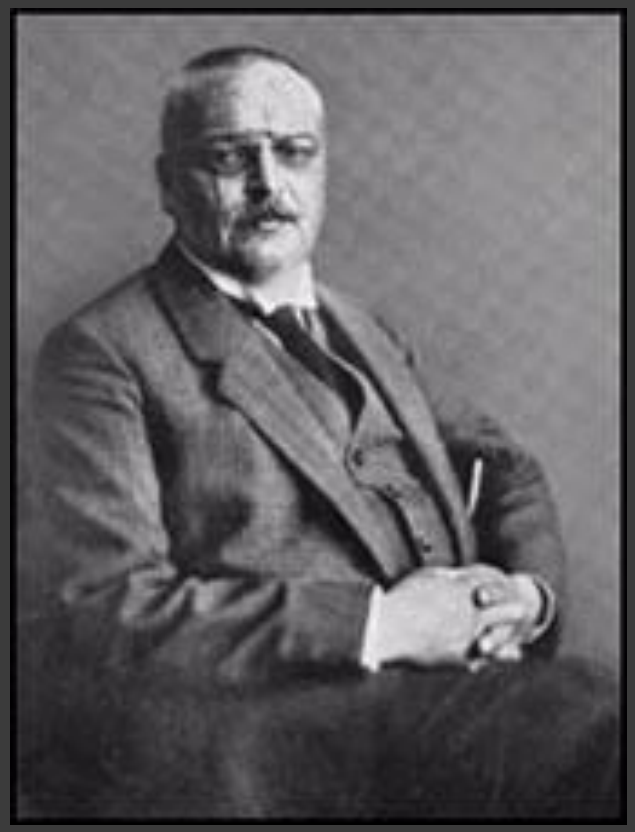
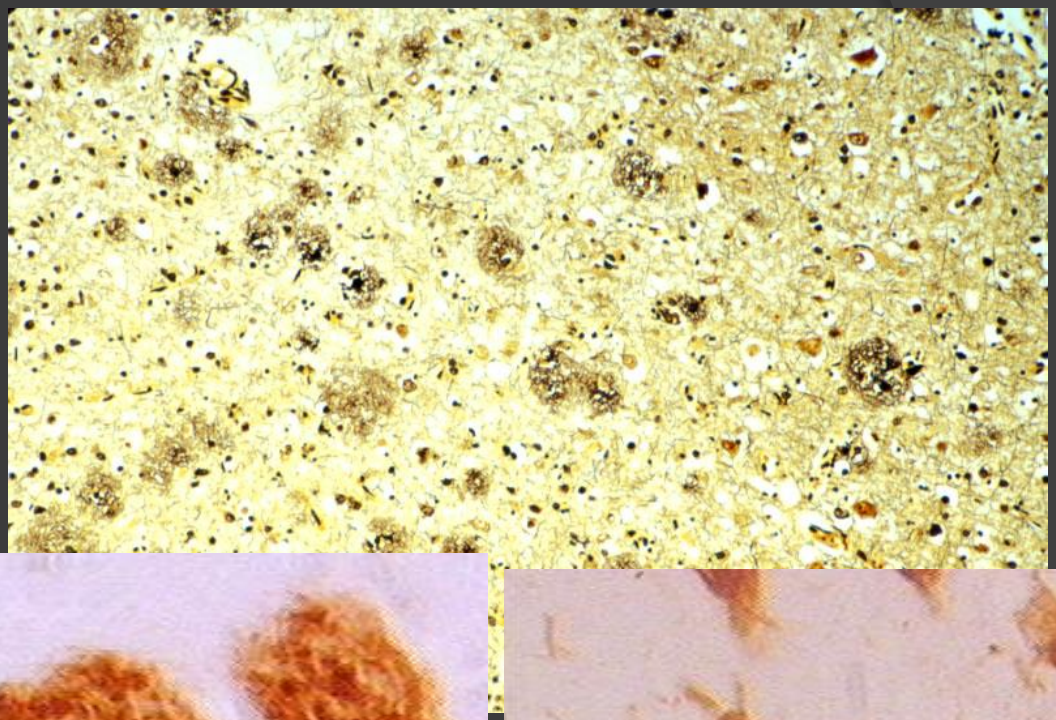
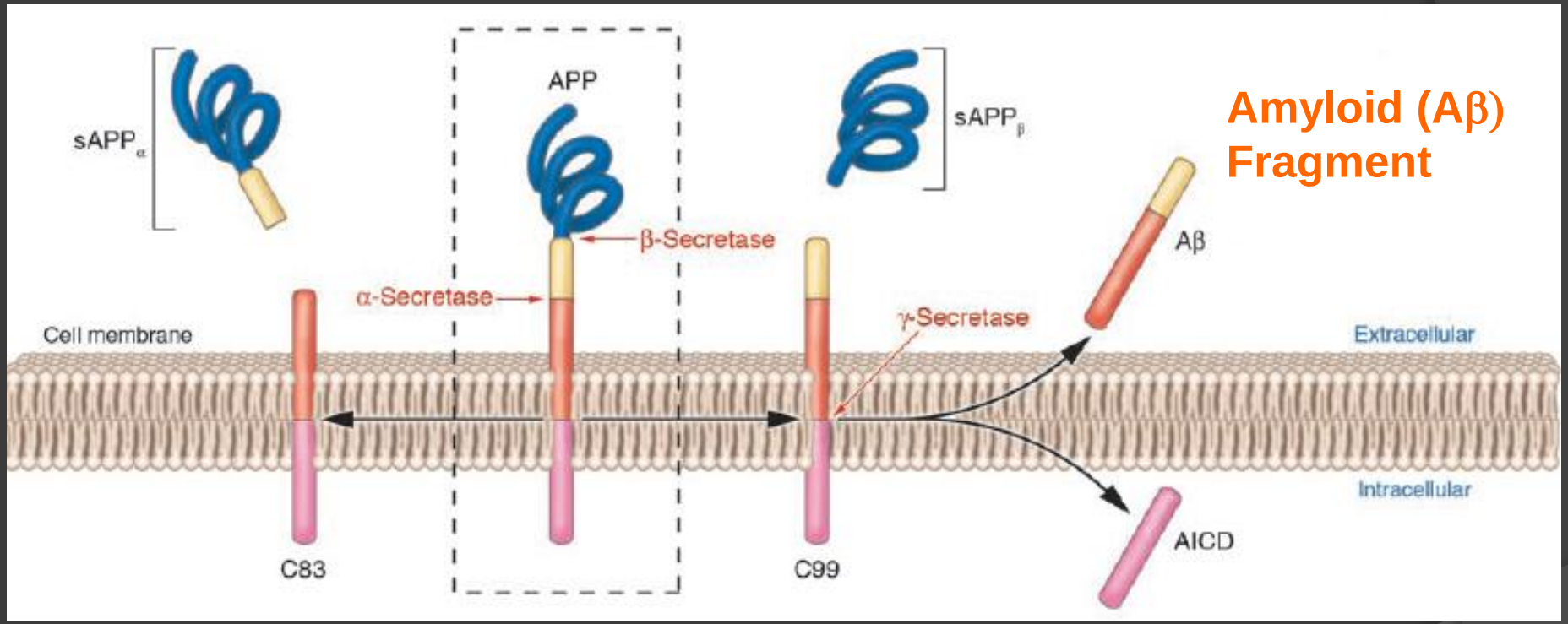
Dr. Alzheimer's disease (AD)



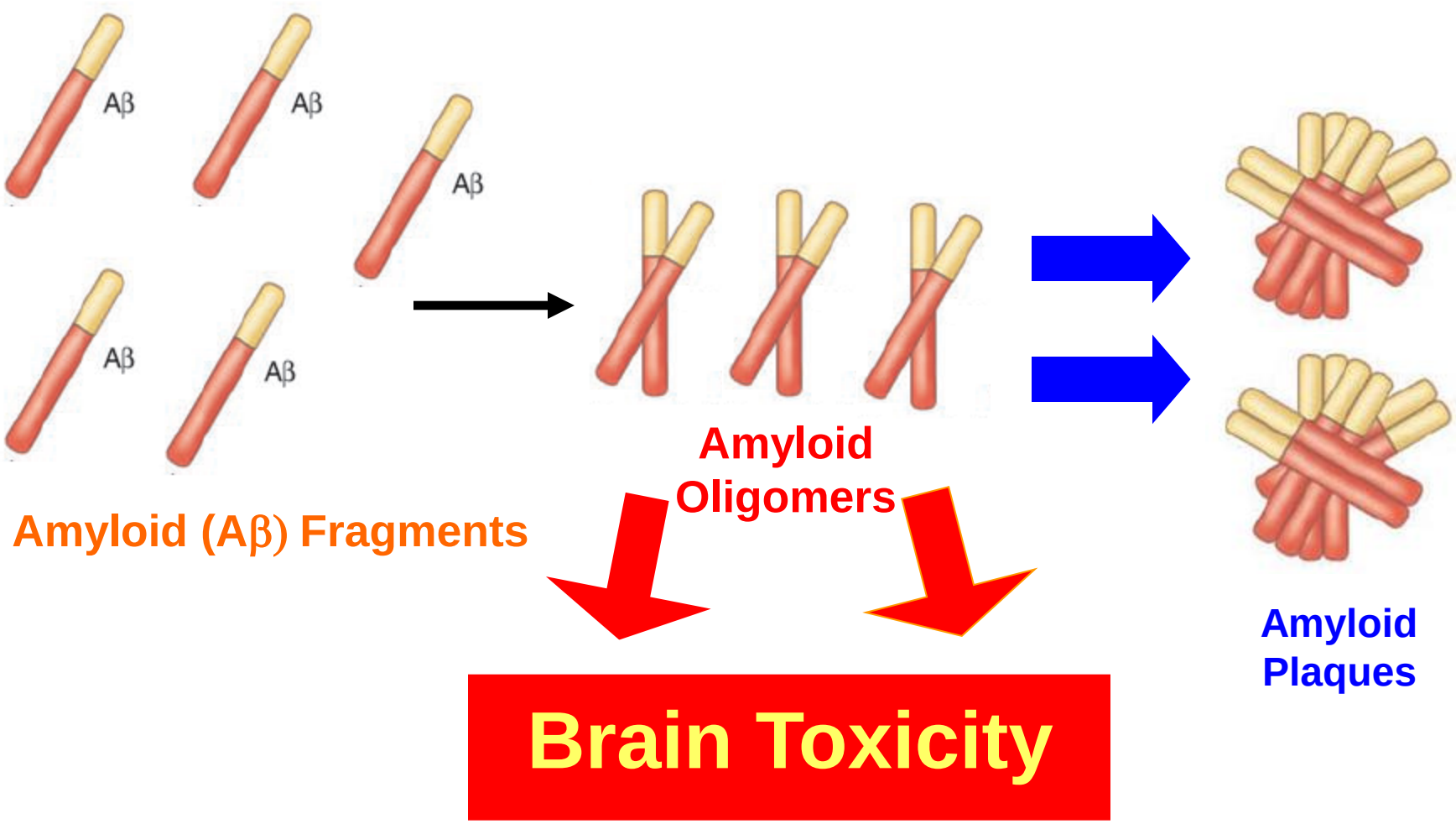
1906

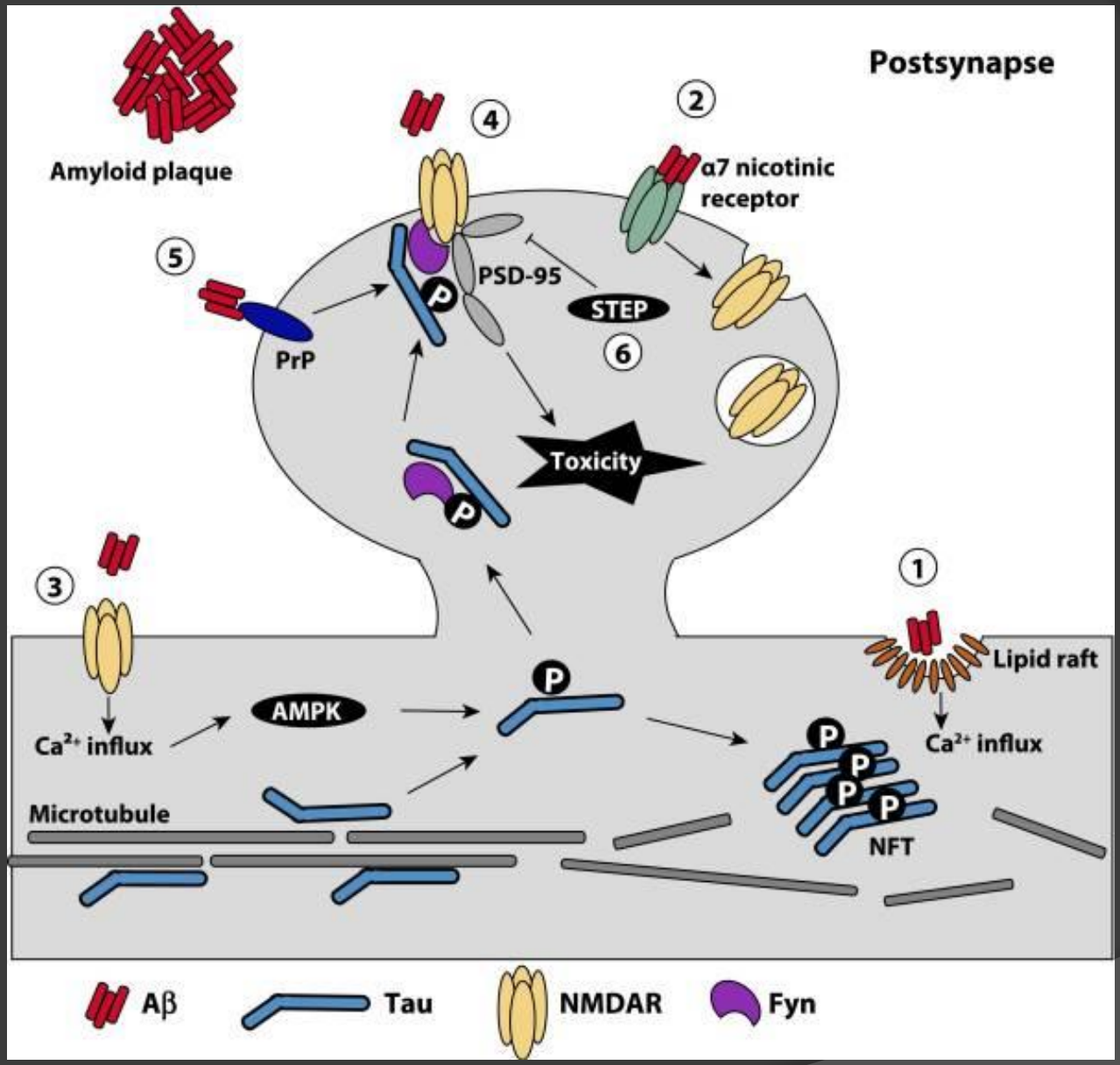


The Creation of Amyloid



The Toxic Effect of Amyloid





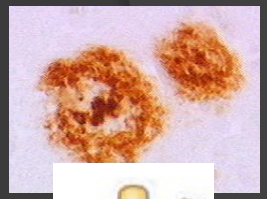
Acta Neuropathol. 2015; 129: 207–220

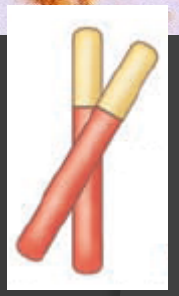
Development of Alzheimer's Disease

Genetic Factors

Environmental Factors

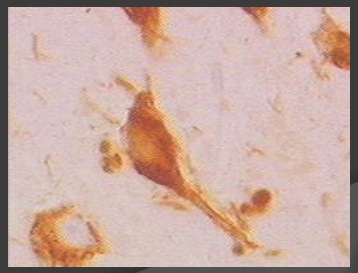
Age





Abnormal Amyloid Deposition

Tau Tangle Formation



Neuron Loss → **Dementia**

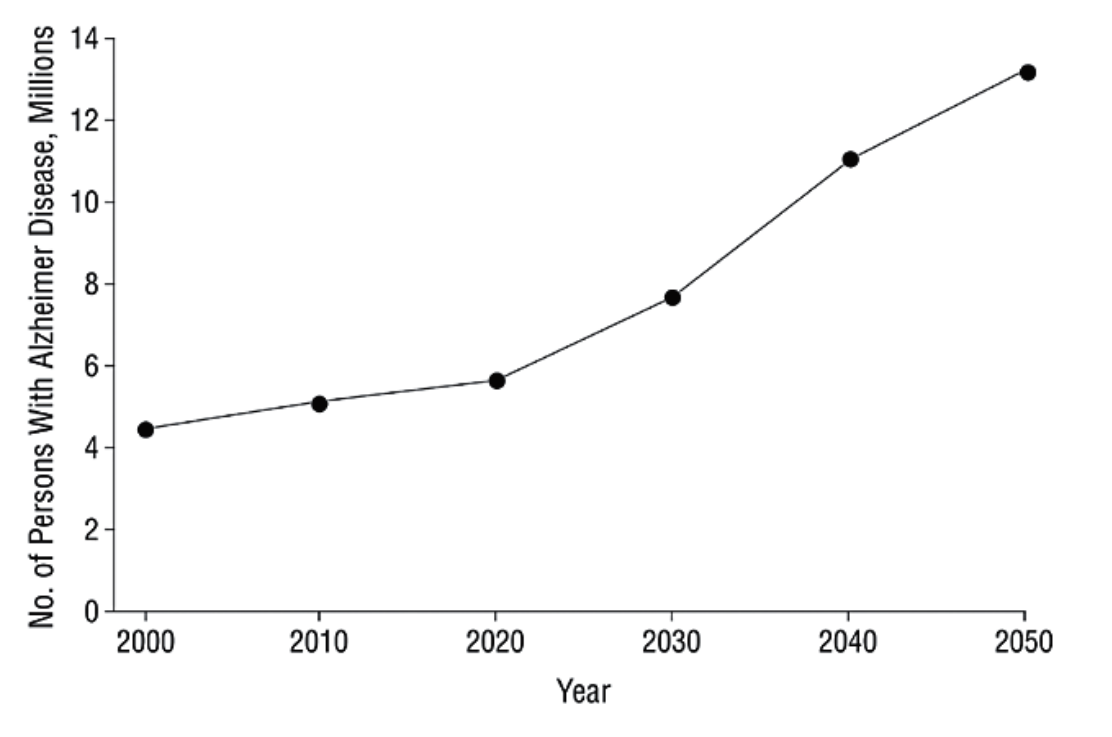
Prevalence of AD

- Aged 65: 2.5%
- Aged 70: 5%
- Aged 75: 10%
- Aged 80: 20%
- Aged 85: 40%

- Doubling of prevalence with every 5 years of age after age 65
- Dementia due to Alzheimer's disease (AD) is a clear threat to an aging population

The Threat of Alzheimer's

- US prevalence



4.5 million (2000) → 13.2 million (2050)

Hebert et al. Arch Neurol. 2003 Aug;60(8):1119-22.

The Threat of Alzheimer's

- In Canada
  - 2012: Estimated 747,000 Canadians have Alzheimer's or a related dementia
  - 2038: Estimated 1,125,000 Canadians will have Alzheimer's or a related dementia
    - Economic cost rising from $15 billion in 2008 to $150 billion in 2038

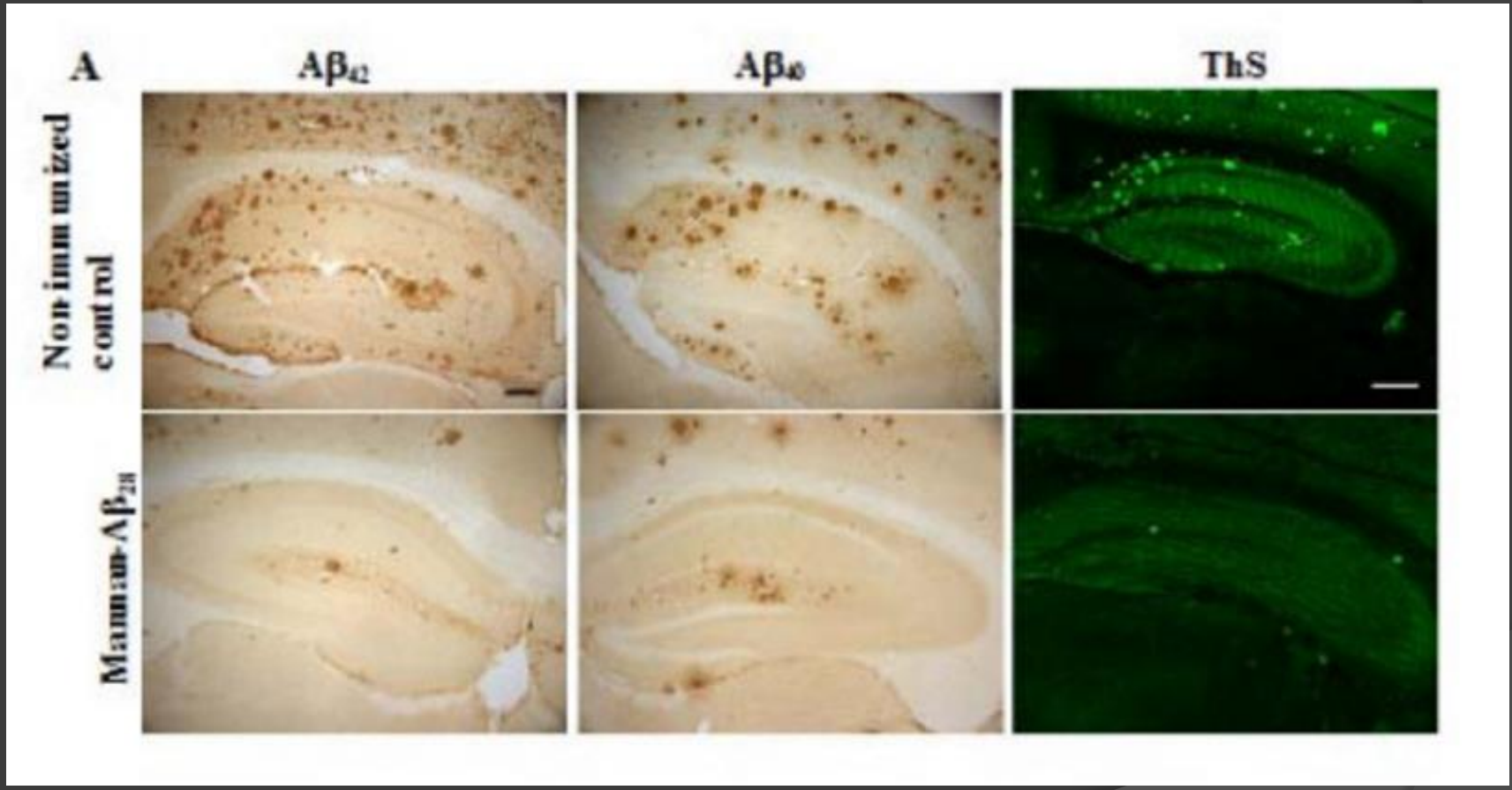
Alzheimer Society of Canada "Rising Tide" Study (January 2010)

Support of the “Amyloid Hypothesis”

- Mutations associated with early-onset plaque/tangle dementia all lead to excessive amyloid production
  - Amyloid-precursor Protein (APP)
  - Presenilin-1 (gamma-secretase)
  - Presenilin-2 (gamma-secretase)
- Down Syndrome (APP located on 21)

- Amyloid oligomers induce tau hyperphosphorylation and neurodegeneration in vitro and in vivo

Anti-amyloid vaccination



Journal of Neuroinflammation 2008 5:42

Anti-amyloid vaccination

- AN1792
  - Amyloid fragment+adjuvant SC
  - Induced anti-amyloid antibody titre (in most)
  - Induced meningoencephalitis in 6% of subjects (headache, encephalopathy, ataxia, focal)
  - Study halted in 2002

  - Long-term follow-up of cases
    - Plaque load decreased
    - Small but statistically significant difference in functional decline in antibody responders (1/2200) after 4.6 years

Lancet. 2008 Jul 19;372(9634):216-23. Curr Alzheimer Res. 2009 Apr;6(2):144-51.

Alzhemed/tramiprosate

- Developed in QC
- Binds amyloid in vitro and in vivo (crosses blood-brain barrier)
- Prevents oligomerization

- n=1052; randomized, placebo-controlled, double-blinded
- Oral BID dosing; 18 months
- ADAS-Cog and CDR-SB endpoints

- No safety concerns
- No statistically significant difference found between treated and placebo groups

Arch Med Sci. 2011 Feb;7(1):102-11.

Flurizan/tarenflurbil (flurbiprofen)

- Inspired by epidemiological studies indicating less dementia in patients taking NSAIDs and ibuprofen
- Flurbiprofen found to modulate γ–secretase and lower amyloid levels in vitro

- n=1649; randomized, placebo-controlled, double-blinded
- Oral BID dosing; 18 months
- ADAS-Cog and ADCS-ADL endpoints

- Mild dizziness, anemia, increased infection rate
- No statistically significant difference found between treated and placebo groups

JAMA. 2009 Dec 16;302(23):2557-64.

Anti-amyloid Antibodies

- Passive immunization by way of intravenous infusion qmonthly or q3monthly
- Each targeted against different epitope of amyloid peptide, some binding monomers > fibrils or vice-versa
- Highly effective in reversing cognitive decline in mouse models of AD

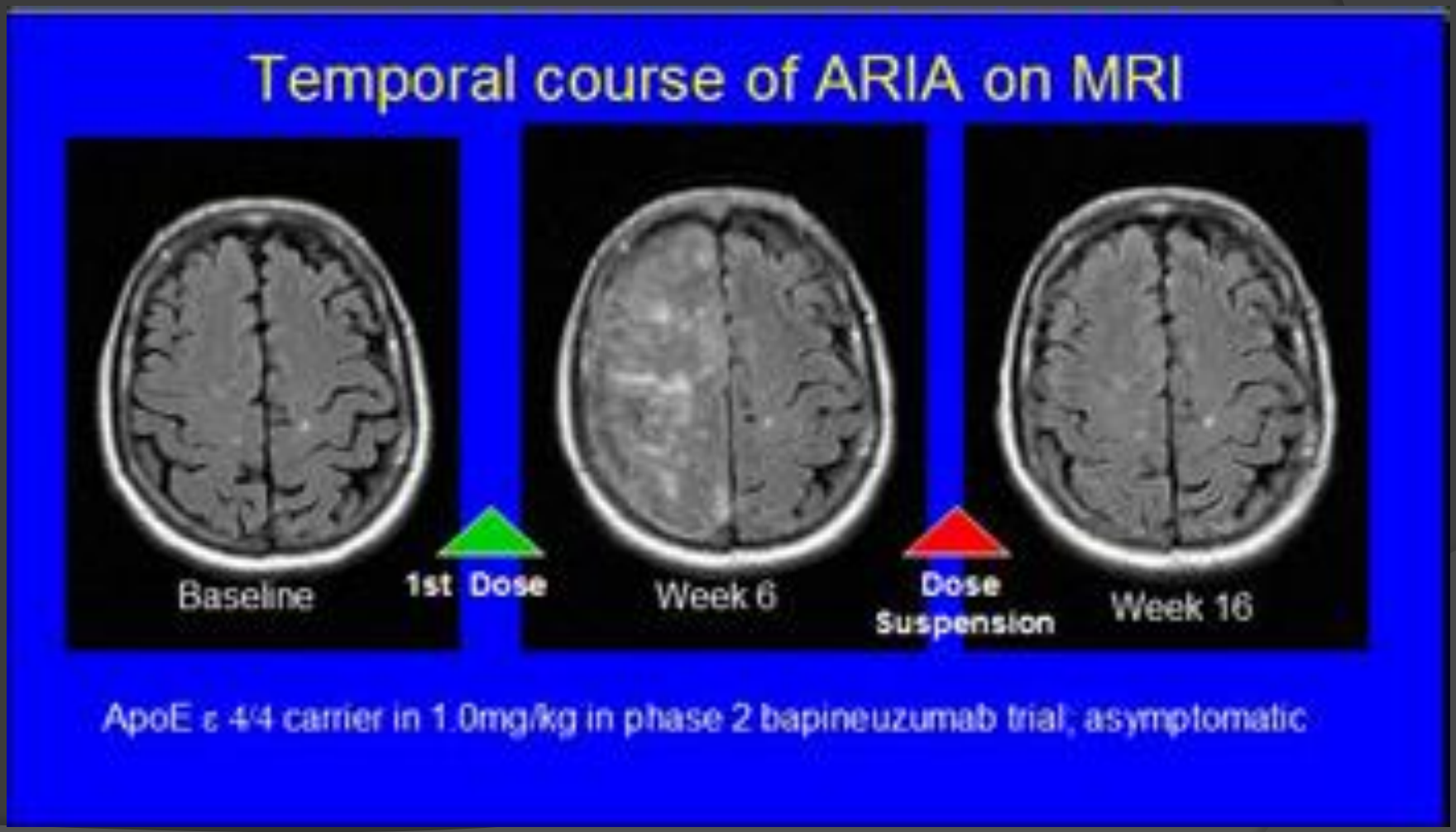
- Bapineuzumab
- Solanezumab
- Crenezumab
- Gantenerumab
- Aducanumab

Bapineuzumab

- Anti-amyloid antibody against fibrillar form of Aβ
- Phase 2 studies showed occurrence of vasogenic edema, especially in ApoE4 carriers
- Renamed ARIA (amyloid-related imaging abnormalities)

- Occurred in ~10%
- Half mildly symptomatic (headache, ataxia)
- Resolves with suspension of treatment

Amyloid-related Imaging Abnormalities (ARIA)



Bapineuzumab

- n=1121 (ApoE4 carriers) + 1331 (ApoE4 non-carriers)
- 1-hour IV infusion q3monthly; 18 months
- ADAS-Cog and DAD endpoints

- ARIA-E occurred more frequently in ApoE4 carriers (~10%)
- No statistically significant difference found between treated and placebo groups

N Engl J Med. 2014 Jan 23;370(4):322-33.

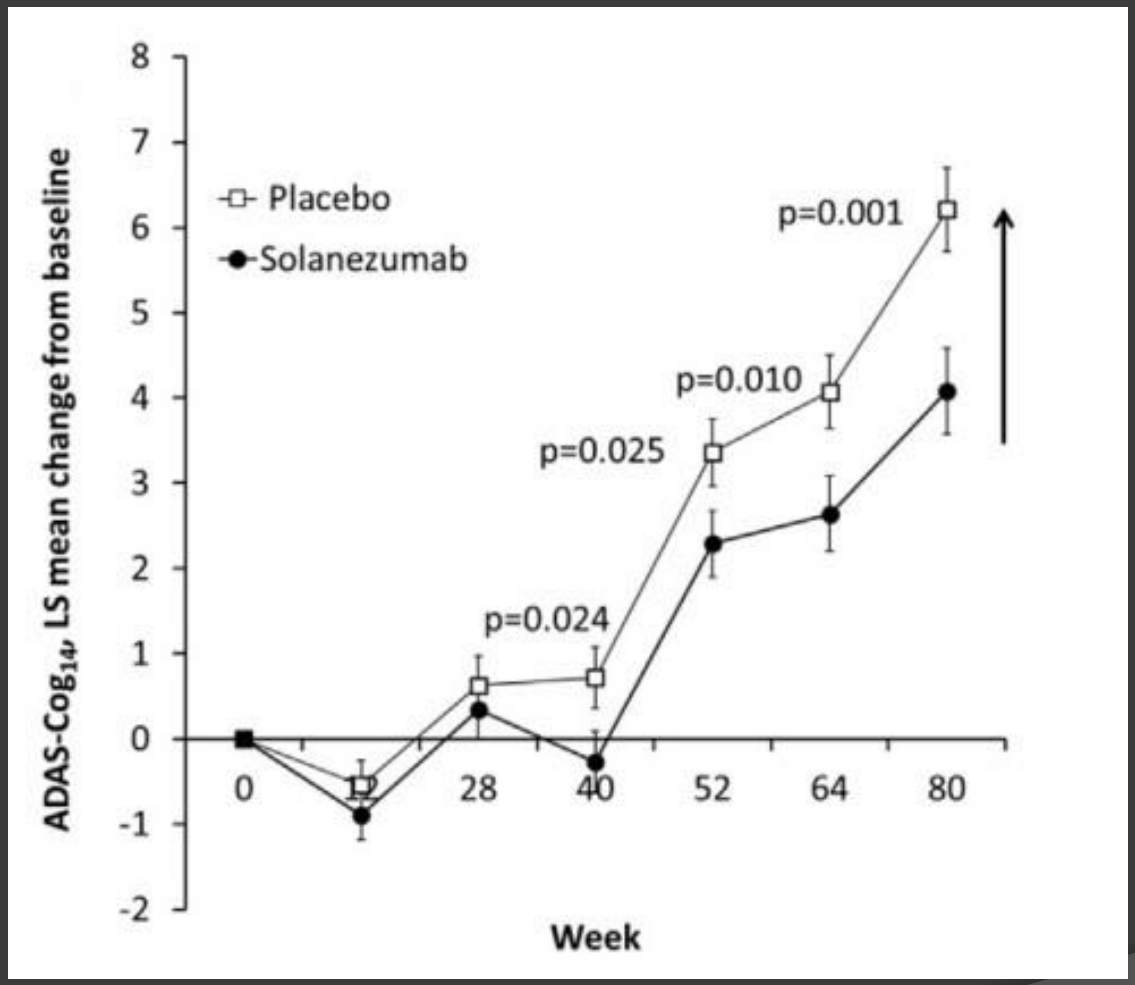
Solanezumab

- n=1012 and n=1040
- 1 hour IV infusion qmonthly; 18 months
- ADAS-Cog and ADCS-ADL endpoints

- ARIA-E occurred infrequently (~1%)
- No statistically significant difference found between treated and placebo groups

N Engl J Med. 2014 Jan 23;370(4):311-21.

A Ray of Hope?



Pooled Phase 3 Solanezumab trials, mild AD (MMSE 20-26) patients only (n=1322)

Alzheimers Dement. 2016 Feb;12(2):110-20.

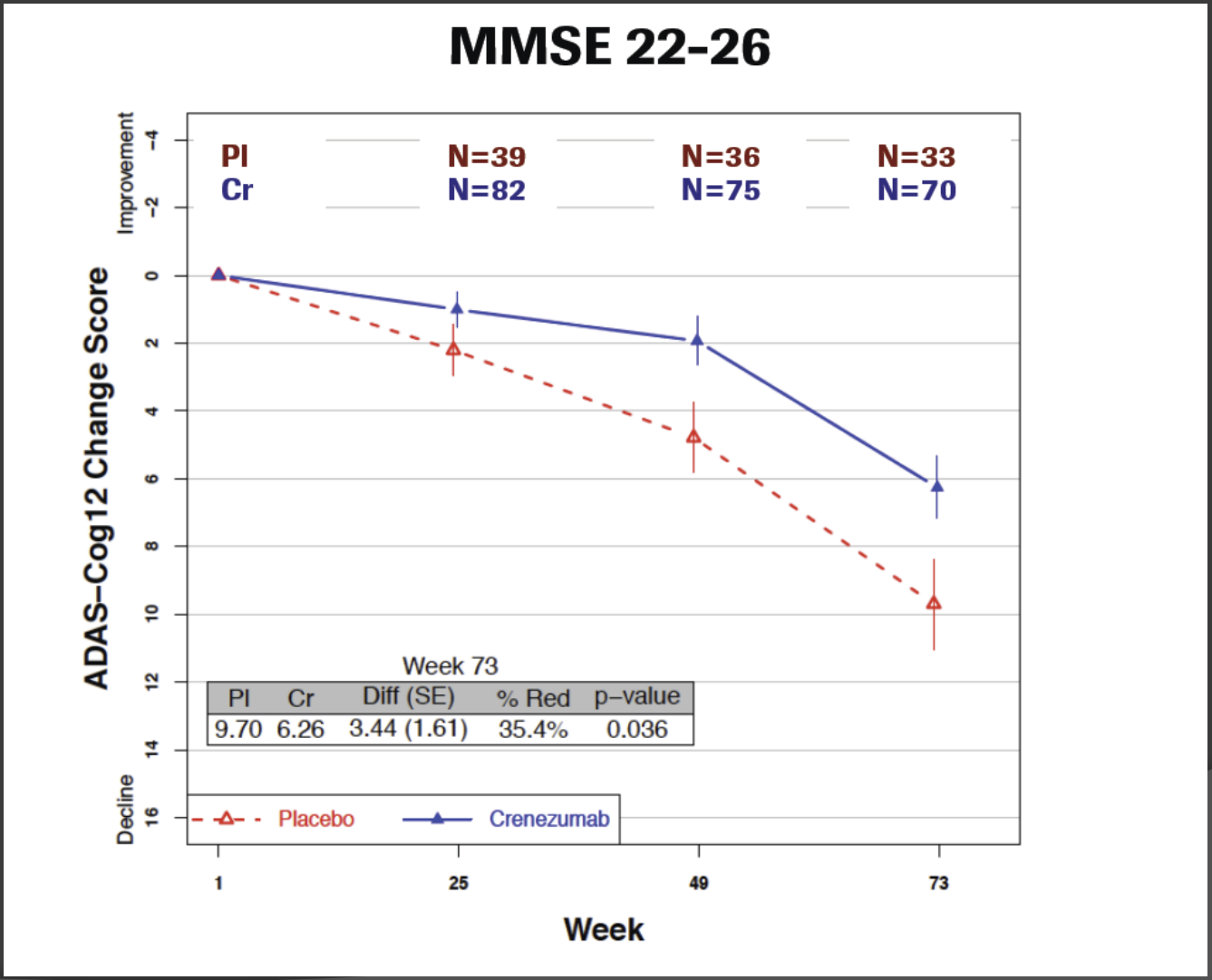
Crenezumab

- n=247
- IV infusion qmonthly; 68 weeks
- ADAS-Cog and CDR endpoints

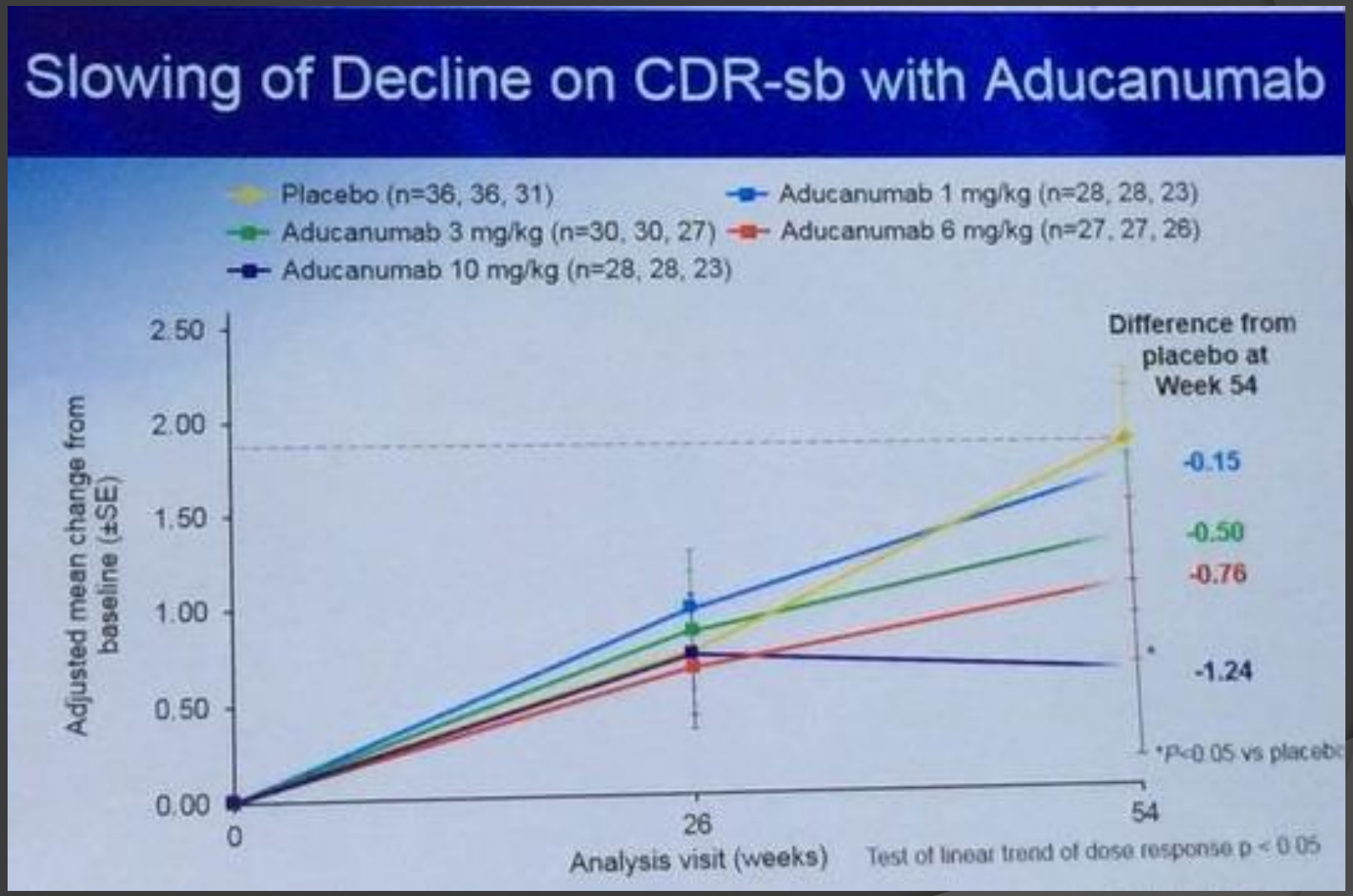
- ARIA occurred in only one case
- No statistically significant difference found between treated and placebo groups

Alzheimer's Association International Conference 2014

Crenezumab


MMSE 22-26
Pl
Cr
N=39
N=82
N=36
N=75
N=33
N=70
ADAS–Cog12 Change Score
Improvement
Decline
-4
-2
0
2
4
6
8
10
12
14
16
Week 73
Pl Cr Diff (SE) % Red p–value
9.70 6.26 3.44 (1.61) 35.4% 0.036
Placebo
Crenezumab
1
25
49
73
Week

Aducanumab



Alzheimer's Association International Conference 2015
Nature 537, 50–56 (01 September 2016)

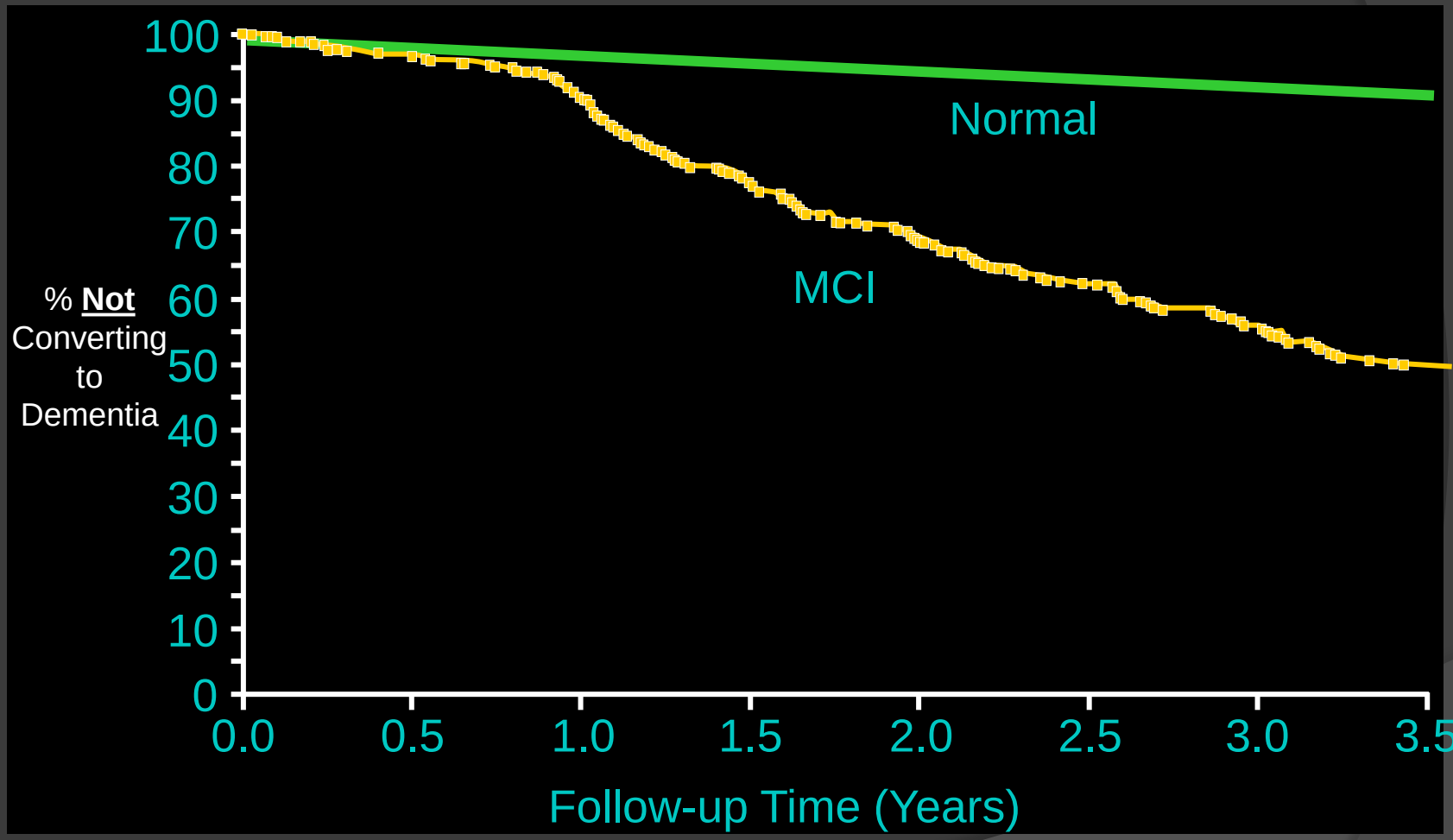
Reasons for Overall Failure

- Patients too advanced
  - Too much neurodegeneration has already occurred
- Patients too heterogeneous
  - Alzheimer's disease vs. "mixed vascular dementia"
- Dosing Inadequate (due to side effects)
- Cognitive Measures Inadequate
- "Amyloid Hypothesis" is incorrect

Mild Cognitive Impairment (MCI)

	Normality	MCI	Dementia
Cognitive Symptoms	Yes or No	Yes	Yes
Cognitive Testing	Normal	Abnormal	Abnormal
Functional (ADL) Independence	Intact	Intact	Impaired

Natural History of MCI



DeKosky ST. *J Am Geriatr Soc*, 2003; Grundman M et al. *Neurology,* 1996.

Purpose of MCI Diagnosis

- MCI diagnosis provides “warning state” for increased risk of future worsening of cognitive symptoms
- **Rate of decline to dementia is ~10-15% per year in MCI, while only ~1-2% in general population (aged 65 or older)**

  Petersen RC, Smith GE, Waring SC, et al. Arch Neurol 1999;56:303–8.

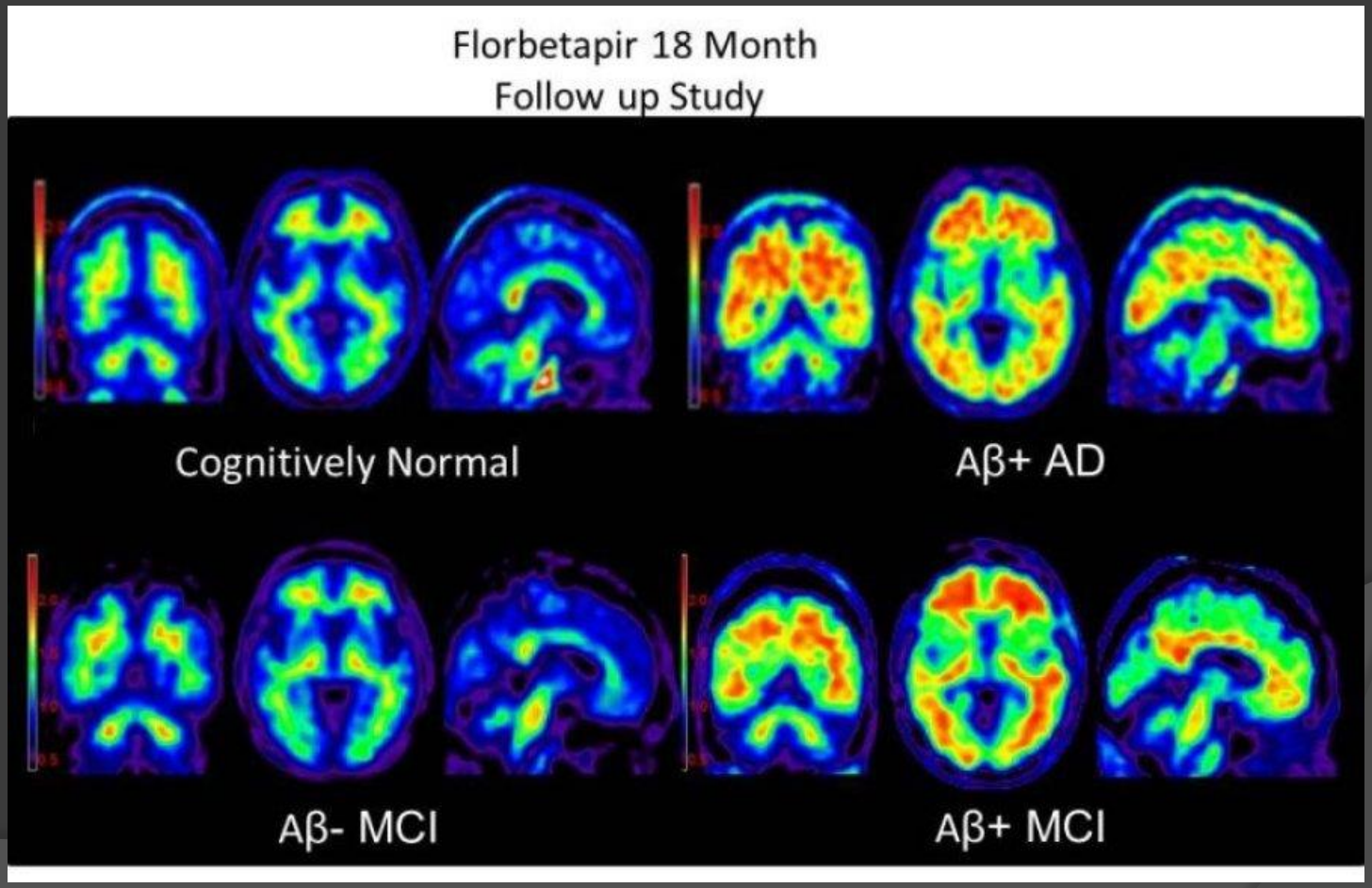
  Bennett DA, Wilson RS, Schneider JA, et al.Neurology 2002;59:198–205.
- Most, but not all cases progress
- Patient’s mild cognitive concerns are not dismissed, and increased follow-up can be provided

Treatment of MCI

- Multiple treatment trials have been negative
  - Aricept/donepezil
  - Exelon/rivastigmine
  - Reminyl/galantamine
  - Rofecoxib
  - Piracetam
  - Ampakine CX516
- No treatment currently approved for MCI

Amyloid Imaging

- Pittsburgh compound-B (PiB) or florbetapir, IV injection (10 mL) followed by PET acquisition 50 minutes later lasting 10 minutes



Solanezumab Second Phase 3

- Mild dementia only (MMSE=20-26)
- Amyloid presence confirmed via amyloid-PET or CSF measures

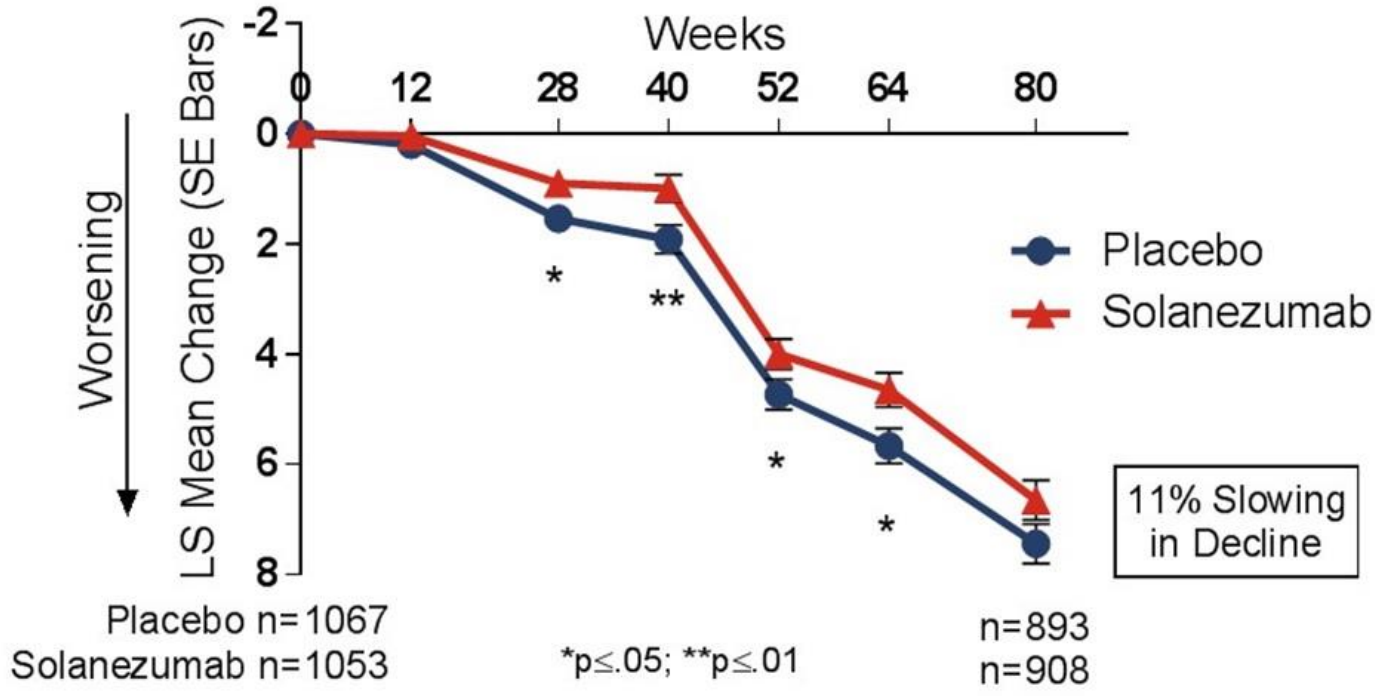
- n=1822
- IV infusion qmonthly; 76 weeks
- ADAS-Cog primary endpoint

- Results released November 2016

Solanezumab Second Phase 3

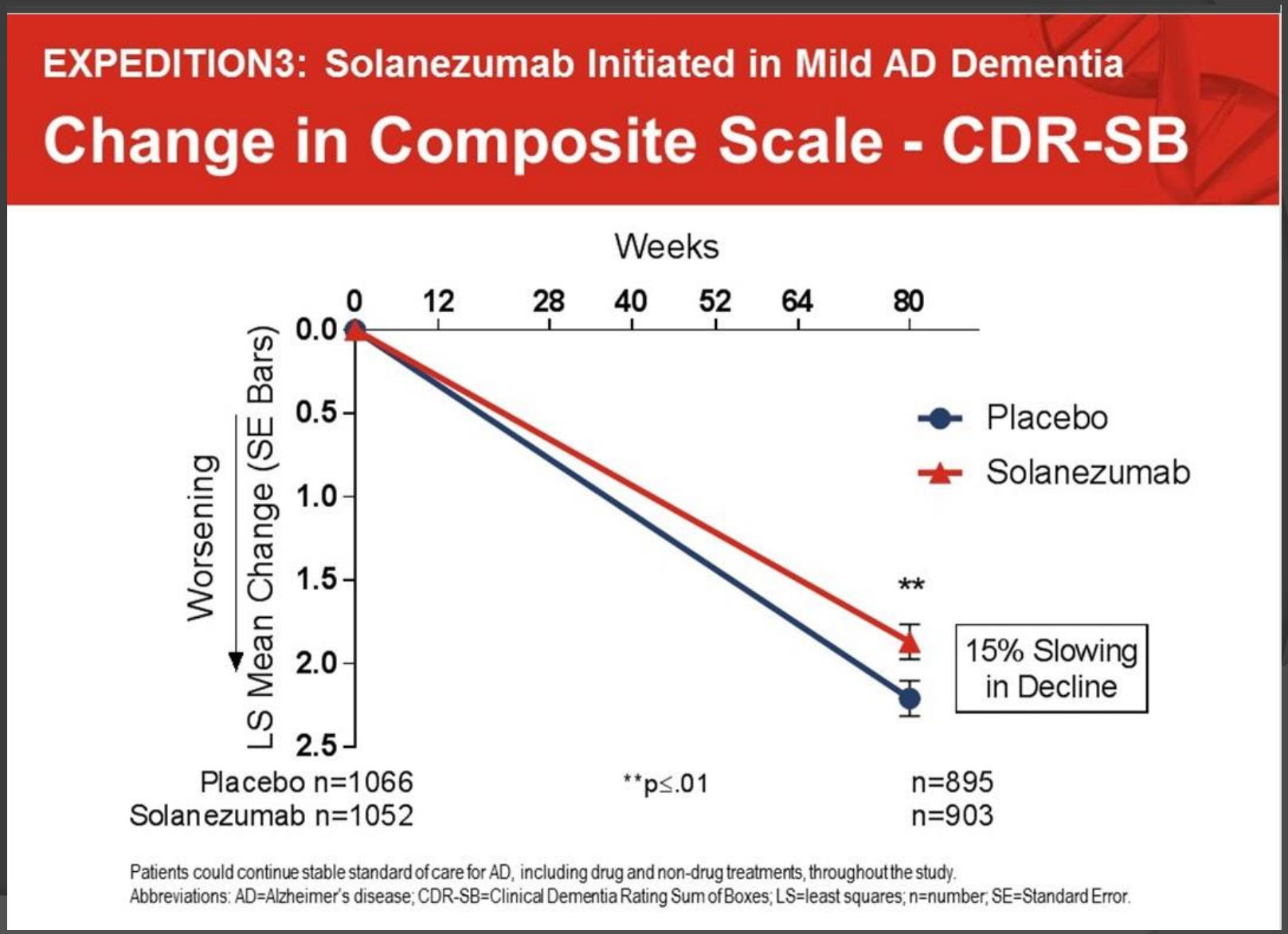
EXPEDITION3: Solanezumab Initiated in Mild AD Dementia

Change in Cognition - ADAS-Cog$_{14}$ (Primary)



Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study.
Abbreviations: AD=Alzheimer's disease; ADAS-Cog$_{14}$=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=Standard Error.

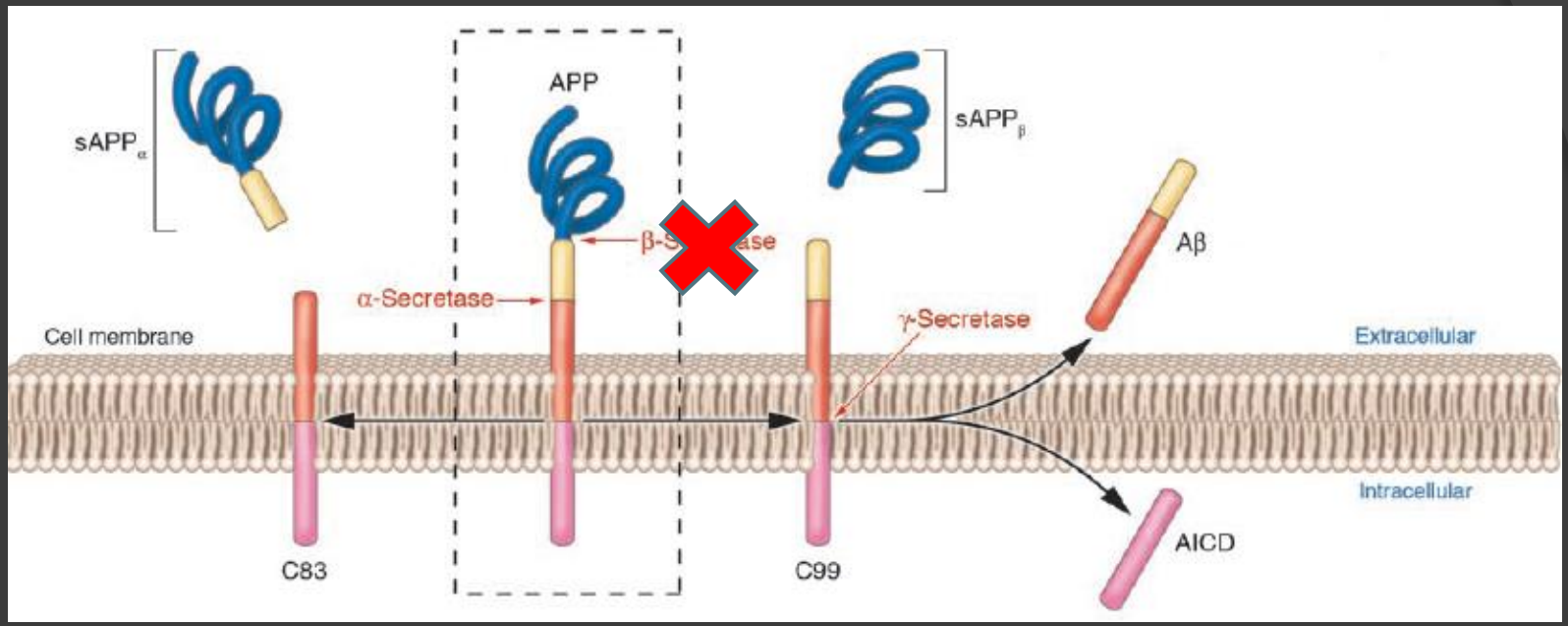
Solanezumab Second Phase 3



Currently in Phase 3

- Crenezumab
  - Phase 3 in MCI and mild dementia/AD (Amyloid+ proven)
  - Begun 2016
  - Additional study underway in “pre-symptomatic” autosomal dominant AD mutation carriers in Colombia, South America
- Aducanumab
  - Phase 3 in MCI and mild dementia/AD (Amyloid+ proven)
  - Begun 2016

β-secretase (BACE) Inhibitors



- Verubecestat
- LY3314814

- Oral once-daily administration
- Currently in Phase 3 studies in MCI and mild dementia/AD

A4 (Anti-Amyloid Asymptomatic Alzheimer's) Study

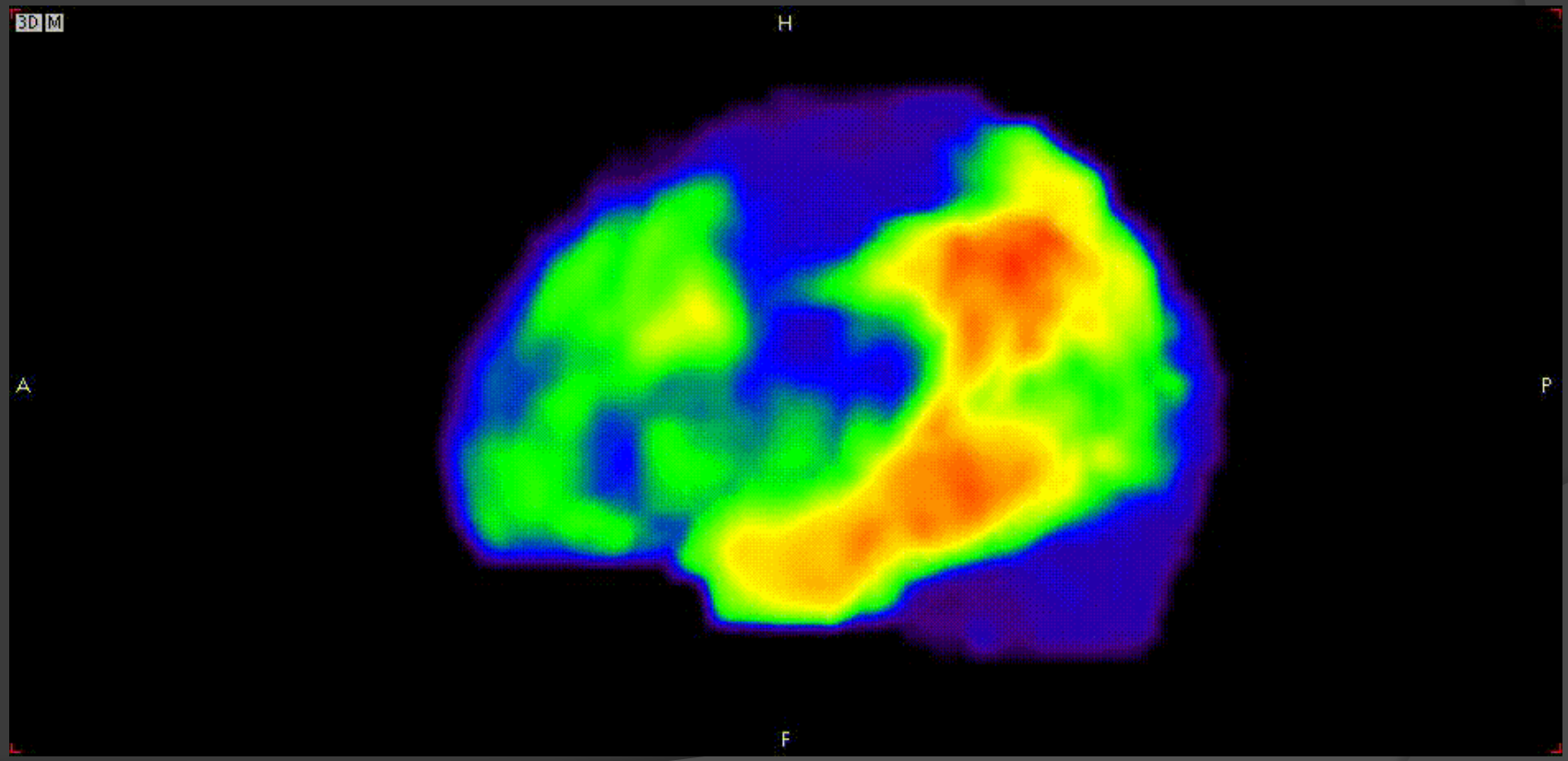
- Asymptomatic patients
- Normal neuropsychological profile
- Evidence of amyloid positivity on amyloid-PET

- Randomized to IV solanezumab vs. placebo

- Followed cognitively over 4+ years

Tau Imaging

- AV-1451 Tau-PET tracer (flortaucipir)



Tau-directed therapy

- Tau-aggregation Inhibitor (TAI)
  - TRx0237
  - Oral BID dosing
  - Phase 3 studies in mild/moderate dementia/AD and bvFTD
  - July 2016: Negative results in AD
  - August 2016: Negative results in bvFTD
- Anti-Tau antibody in Phase 1 studies

Conclusions

- The “amyloid hypothesis” remains under intense investigation by way of numerous Phase 3 studies
  - Intravenous anti-amyloid antibodies
  - Oral β-secretase (BACE) inhibitors
- Studies are selecting for mildly affected or asymptomatic patients, with biomarker-proven amyloidopathy (i.e. amyloid-PET, CSF)
- Anti-tau therapies also in development
- Results continue to be forthcoming