The Brave New World of Alzheimer's: Disease Modifying Therapies and Biomarkers

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Anti-Amyloid Monoclonal Antibodies Initiate a New Era in Alzheimer Therapeutics

- Marked amyloid plaque lowering on PET
- Reproducible relationship between plaque lowering (to 15-25 centiloids) and slowing of clinical decline
- 30% slowing of disease progression over 18 months
- First disease-modifying therapy (DMT) for Alzheimer’s
- A first step; not a solution

Appropriate Patient

- Early AD: MCI or mild Alzheimer dementia (MMSE score of 22-30 or equivalent)
- Baseline MRI shows no more that 4 microhemorrhages
- Confirmed amyloid pathology by amyloid PET or CSF studies
- No history of immunologic disorders, bleeding disorders, or seizures
- Does not have any condition that would compromise understanding of treatment goals or adherence to treatment requirements
- Is not receiving treatment with aducanumab
- Is not receiving anticoagulants

Cummings J, et al. JPAD 2023; 10: 362-377

Anti-Amyloid Antibodies: Approved and in the Pipeline

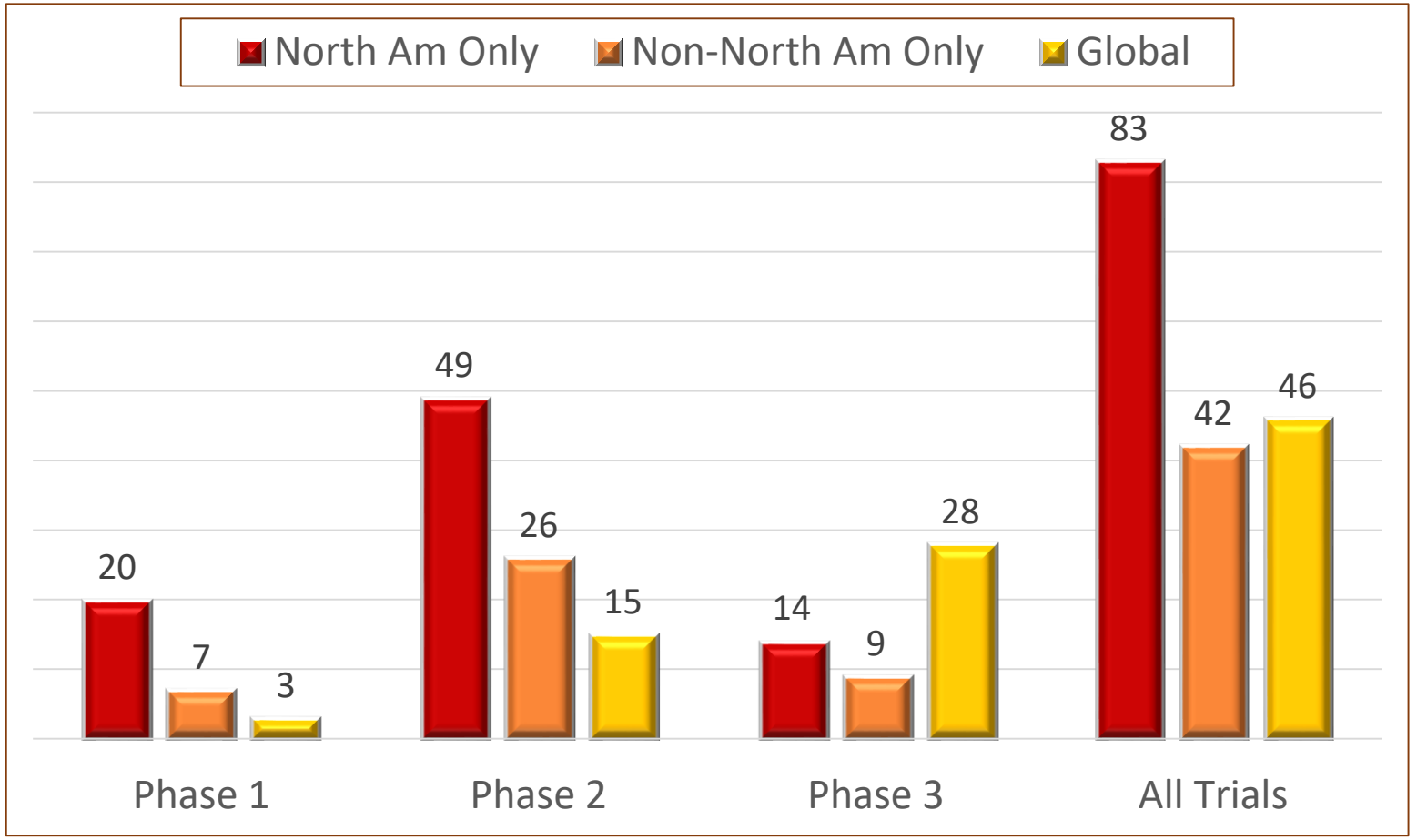
- Approved
  - Lecanemab – accelerated and standard approval
  - Aducanumab – accelerated approval
- Phase 3 readouts: 2023
  - Donanemab – standard outcomes under FDA review
- Phase 3 readout: 2025
  - Remternetug (LY3372993)
- Phase 2
  - Trontinemab (gantenerumab shuttle)
- Phase 1
  - ACU193; SHR-170; PRX012; PMN310

Universe of Drugs in the 2023 Alzheimer's Drug Development Pipeline

- 141 unique drugs
- 78% disease modifying treatments
- 35% biologics
  - Notable Phase 1
- 44% DMT small molecules
- 11% cognitive enhancers
- 11% drugs for behavioral symptoms
  - Notable Phase 3 activity
- 28% repurposed agents

Cummings J, et al. Alz&Dem: TRCI 2023 9(2):e12385. doi: 10.1002/trc2.12385.

Late-Stage Trials Require Global Participation



Global Trial Distribution

- 44% of all registered trials are conducted in the US
- In Phase 3, 55% of trials are global

Consider This:

- On index date 1/1/2023
- 6 trials in Russian federation
- 4 Trials in Ukraine
- Trials suspended
- Patients must be followed
- Data must be collected
- Need policy for extreme circumstances: pandemics, war, earthquakes, mass displacement, severe weather

Biomarkers Used in Clinical Trials have a Defined Context of Use (CoU)

Context of Use	Biomarker
Risk	APOE genotyping; tau PET
Diagnosis	Amyloid PET; CSF A$\mathcal{B}$ 42/40; ADAD mutation
Prognosis	Tau PET; p-tau 181, 217; GFAP
Pharmacodynamic; target engagement	SILK; CSF A$\mathcal{B}$; drug mechanism-related
Pharmacodynamic; disease modification	ATX(N)
Monitoring	p-tau 181, 217; GFAP
Predictive	Amyloid reduction on PET (accelerated approval); APOE4 predicts ARIA risk
Safety	MRI for ARIA

A$\mathcal{B}$ - amyloid beta protein; ADAD – autosomal dominant Alzheimer's disease; APOE – apolipoprotein E; ARIA – amyloid related imaging abnormalities; ATX(N) – amyloid, tau, "other", neurodegeneration; CSF – cerebrospinal fluid; GFAP – glial fibrillary acidic protein; PET – positron emission tomography; p-tau – phosphorylated tau; SILK – stable isotope labeled kinetics

FDA-NIH Biomarkers Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource, 2021

The Brave New World of Alzheimer's: Disease Modifying Therapies and Biomarkers

- Approval of first disease modifying therapies for Alzheimer's disease!
- New treatments are the beginning of the long process toward halting AD
- Most drugs in the pipeline address disease modification
- The pipeline has a diverse repertoire of targets and agents
- 60,000 participants are needed for current trials
- Biomarkers are rationalizing clinical trials and drug development
- Biomarkers have specific contexts of use in clinical trials