New and Emerging Treatments for Alzheimer's Disease

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TENNESSEE MEMORY DISORDERS FOUNDATION AND CLINIC

Disclosures

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- Biogen, Novonordisk, American College of Radiology and Alzheimer's Association, Roche, Amylx, Eli Lilly, Eisai, Bristol-Myers-Squib
- Community Collaborations: University of Tennessee-Knoxville, Alzheimer's Tennessee, Center for Biomedical Research

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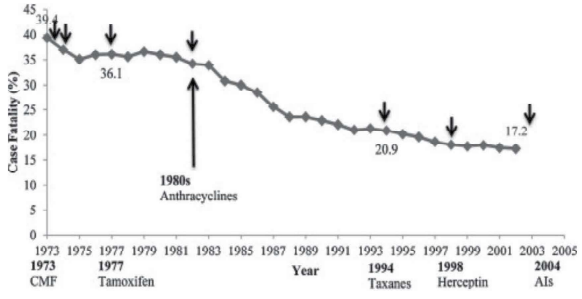
Special Thank you to Lee Watson for his edits as well as his leadership as the Clinical Trial and Infusion Coordinator. **Also thank you to Ed Chacon and the Intern clinical trials team.**

Goals

- History of diagnosis and treatment
- Summarize approved anti-amyloid therapies
- Discuss safety, patient selection and ARIA management
- Explore new biologic directions

1. History of Diagnosis & Treatment

10-Year breast cancer case fatality and historical timeline of breast cancer chemotherapy.



https://www.researchgate.net/profile/Anthony_Miller7/publication/277784730

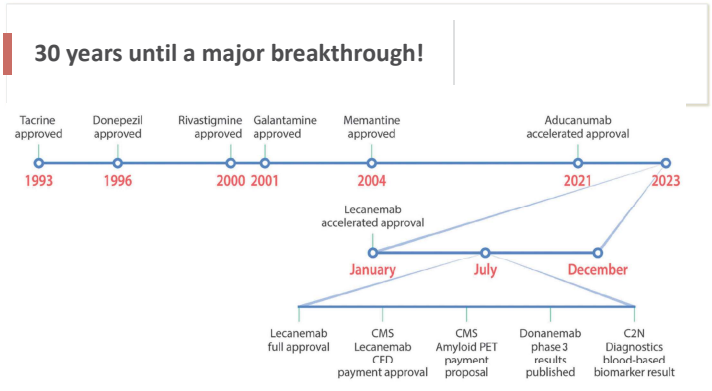
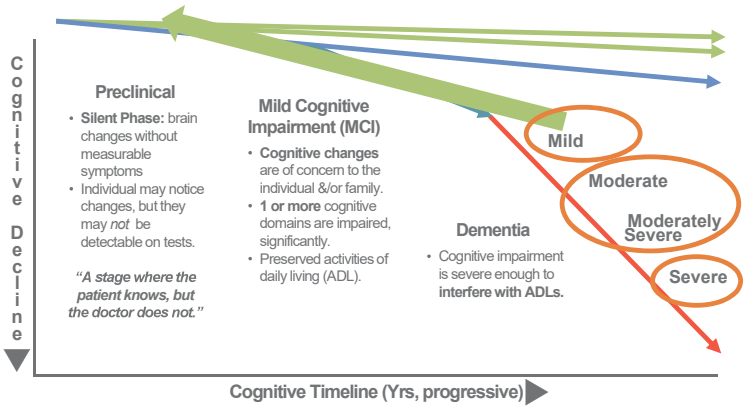


Figure. A timeline of significant milestones in Alzheimer disease diagnosis and treatment.



Old Medications for Cognitive Impairment

- **Tacrine:** no longer available (caused liver damage)
- **Donepezil:** acetylcholinesterase inhibitor
- **Galantamine:** acetylcholinesterase inhibitor + nicotinic modulation
- **Rivastigmine:** butyrylcholinesterase + acetylcholinesterase inhibitor
- **Memantine:** noncompetitive NMDA receptor antagonist (modulates glutamatergic activity)

Amyloid Cascade Hypothesis

Aβ aggregation triggers downstream tau pathology.

- Leads to synaptic dysfunction and neurodegeneration.
- Foundation for anti-amyloid drug development.

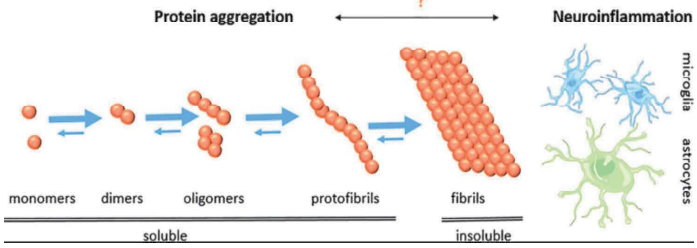
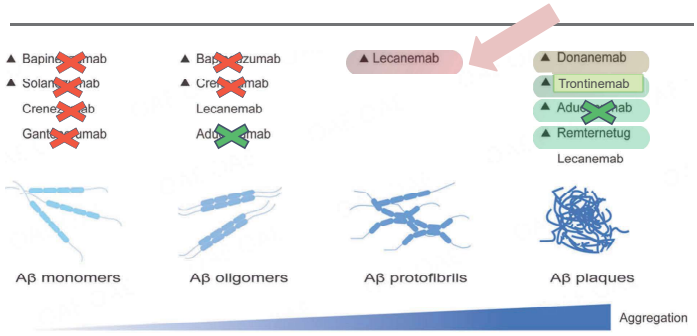


Image source: NIA/NIH Brain Health Library (Public Domain)

Monoclonal anti-amyloid antibodies



Comparison Anti-Amyloid Medications Dosing

Anti-Amyloid Antibody	Formulation	Fixed Dose or Weight-Based Dosing	Administration Schedule	Titration Required	Stopped When Amyloid Plaque Levels are Not
Lecanemab	IV	Weight-based	Q 2 weeks	No	No
Donanemab	IV	Fixed	Q 4 weeks	Yes	Yes
Remternetug	IV/SC	Fixed	Q 4 weeks	Yes	Yes
Trontinemab	IV	Fixed	Q 4 weeks	Yes	No

Content sourced from Maximizing the benefit and managing the risk of anti-amyloid monoclonal antibody therapy for Alzheimer's disease: Strategies and research directions
Cummings, Jeffrey L. Neurotherapeutics, Volume 22, Issue 3, e00570
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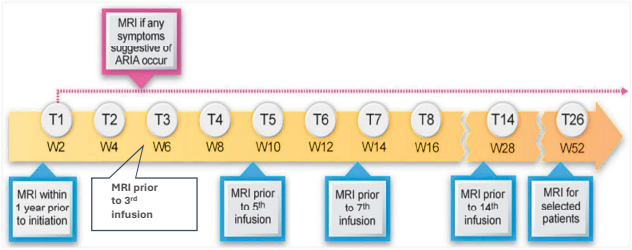
Lecanemab and Phase 3 CLARITY-AD key outcomes

- Approved in 2023 Global early AD population (n ≈ 1,795; MCI + mild dementia)
- Phase 3 CLARITY-AD: Primary endpoint (CDR-SB) slowed by ~27% vs placebo (–0.45 points)
- Amyloid PET reduced by ~59 centiloids at 18 months
- Functional decline (ADCS-MCI-ADL) slowed by ~37%
- Most common serious imaging-related adverse events: ARIA-E (12.6%) & ARIA-H (17.3%)

Adapted from van Dyck C.H. et al., *N Engl J Med.* 2022;387:90-f. DOI:10.1056/NEJMoa2212948.

Lecanemab INCLUSION	Lecanemab EXCLUSION
Diagnosis of MCI or mild AD dementia MMSE 22-30, CDR 0.5-1, FAST score 2-4, FAQ (if PPA)	Any medical, neurologic, or psychiatric condition that may be contributing to the cognitive impairment or any non-AD MCI or dementia
Must be able to have multiple MRIs (no contraindications)	> 4 microhemorrhages (≤10 mm); any macrohemorrhage >10 mm; any superficial siderosis; evidence of vasogenic edema; >2 lacunar infarcts or stroke involving a major vascular territory; severe subcortical disease with a Fazekas score of 3; evidence of cerebral amyloid angiopathy
Positive amyloid PET or CSF studies indicative of AD	Evidence of other clinically significant lesions on brain MRI that indicate another cause of dementia or would exclude treatment or other major intracranial pathology
50-90 yrs old with physician judgement outside range	Recent history (within 12 months) of stroke or TIAs or seizures
MMSE 22-30 or other cognitive screening instrument with a score compatible with early AD	Mental illness or major depression or suicidal ideation that interferes with comprehension of the requirements, potential benefit, and potential harms of treatment and are considered by the physician to render the patient unable to comply with management requirements *
BMI >17 and <35 with physician judgement outside range	Patients with a bleeding disorder that is not under adequate control (including a platelet count 1.5 for participants who are not on an anticoagulant
Patients may be on cognitive enhancing agents (but not another anti-amyloid therapy)	***Active substance abuse* We also request smoking cessation.***
Have a care partner or family member(s) who can ensure that the patient has the support needed to be treated	Any immunologic disease (eg, lupus erythematosus, rheumatoid arthritis, Crohn's disease) or systemic treatment with immunosuppressants, immunoglobulins, or monoclonal antibodie *****We make an exception for chronic stable disease and biologics***
Patients, care partners, and family should understand the requirements, and the potential benefit and harm	Unstable medical conditions that may affect or be affected by lecanemab therapy
Patients may be on standard of care for other medical illnesses – including aspirin.	Patients on anticoagulants (coumadin, dabigatran, edoxaban, rivaroxaban, apixaban, betrixaban, or heparin) should not receive treatment; tPA should not be administered to individuals on treatment ****We do no not allow for any anticoagulants or any other antiplatelet therapy.**
APOE testing recommended **(we require)**	APOE E4/E4 with caution



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Lecanemab adverse events

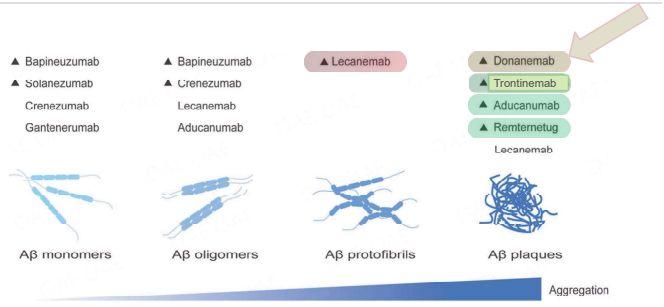
INFUSION-RELATED REACTIONS: 26.4% (VS 7.4% PLACEBO) EISAI.COM+1

AMYLOID-RELATED IMAGING ABNORMALITIES WITH EDEMA/EFFUSION (ARIA-E): 12.6% (VS 1.7% PLACEBO) EISAI.COM+1

AMYLOID-RELATED IMAGING ABNORMALITIES WITH HEMORRHAGE (ARIA-H) / MICROHEMORRHAGES: 17.3% (VS 9.0% PLACEBO) EISAI.COM+1

LONG-TERM EXTENSION (36 MONTHS): ARIA RATE *DECREASED* AFTER FIRST SIX MONTHS.

Donanemab



Anti-Amyloid Medications Dosing

Anti-Amyloid Antibody	Formulation	Fixed Dose or Weight-Based Dosing	Administration Schedule	Titration Required	Stopped When Amyloid Plaque Levels are Not
Lecanemab	IV	Weight-based	Q 2 weeks	No	No
Donanemab	IV	Fixed taper	Q 4 weeks	Yes	Yes
Remternetug	IV/SC	Fixed	Q 4 weeks	Yes	Yes
Trontinemab	IV	Fixed	Q 4 weeks	Yes	No

Content sourced from Maximizing the benefit and managing the risk of anti-amyloid monoclonal antibody therapy for Alzheimer's disease: Strategies and research directions Cummings, Jeffrey L. Neurotherapeutics, Volume 22, Issue 3, e00570

Donanemab TRAILBLAZER results

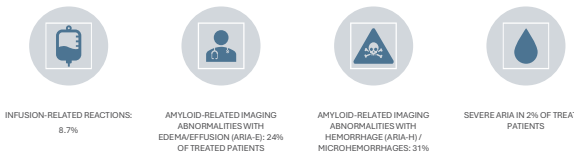
- 1,736 patients; early symptomatic AD.
- 35% slowing in iADRS decline.
- High rate of PET amyloid clearance.
- ARIA-E 24%.
- FDA approved 2024.
- Targets N-terminal pyroglutamate Aβ.
- TRAILBLAZER-ALZ 2: 29% slowing of iADRS decline.
- High ARIA rate (~30%), managed with MRI monitoring. **Unique Feature:** Stop dosing upon amyloid clearance.

Plasma p-tau 217 was significantly reduced with donanemab treatment compared with placebo in both the low/medium tau and combined populations.

Donanemab INCLUSION	Donanemab EXCLUSION
Diagnosis of MCI or mild AD dementia **MMSE 20-30, CDR 0.5-1, FAST score 3-4 (We allow for FAST 2-4)**	Any medical, neurologic, or psychiatric condition that may be contributing to the cognitive impairment or any non-AD MCI or dementia
Must be able to have multiple MRIs (no contraindications including claustrophobia)	**5+ microhemorrhages** (≤10 mm); any macrohemorrhage >10 mm; **>1 superficial siderosis**; evidence of vasogenic edema; >2 lacunar infarcts or stroke involving a major vascular territory; severe subcortical disease with a Fazekas score of 3; evidence of cerebral amyloid angiopathy
Positive amyloid PET or CSF studies indicative of AD	Evidence of other clinically significant lesions on brain MRI that indicate another cause of dementia or would exclude treatment or other major intracranial pathology
60-85 yrs old with physician judgement outside range	Recent history (within 12 months) of stroke or TIAs or seizures
MMSE 20-30 or other cognitive screening instrument with a score compatible with early AD	Mental illness or major depression or suicidal ideation that interferes with comprehension of the requirements, potential benefit, and potential harms of treatment; any substance abuse
Patients may be on cognitive enhancing agents	Patients with a bleeding disorder that is not under adequate control (including a platelet count 1.5 for participants who are not on an anticoagulant
If previously treated with an Aβ-targeting therapy, must allow washout period of >5 half-lives; must demonstrate current biomarker evidence of Aβ plaques	Active cancer that interferes with the ability to comply with donanemab treatment.
Have a care partner or family member(s) who can ensure that the patient has the support needed to be treated	Any immunologic disease (eg, lupus erythematosus, rheumatoid arthritis, Crohn's disease) or systemic treatment with immunosuppressants, immunoglobulins, or monoclonal antibodies ***We make an exception for chronic stable disease and biologics***
Patients, care partners, and family should understand the requirements, not have severe hearing or vision loss and the potential benefit and harm	Unstable medical conditions that may affect or be affected by therapy, no AD due to Downs
Patients may be on standard of care for other medical illnesses – including aspirin.	Patients on anticoagulants (coumadin, dabigatran, edoxaban, rivaroxaban, apixaban, betrixaban, or heparin) should not receive treatment; tPA should not be administered to individuals on treatment **We do no not allow for any anticoagulants or any other antiplatelet therapy.**
APOE testing required	APOE E4/E4 with caution

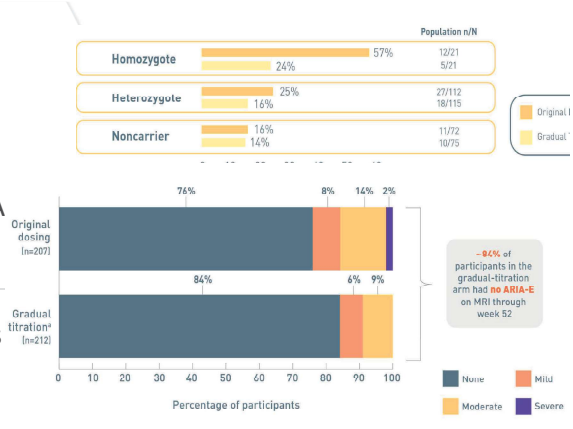
Donanemab MRI schedule

Donanemab adverse events

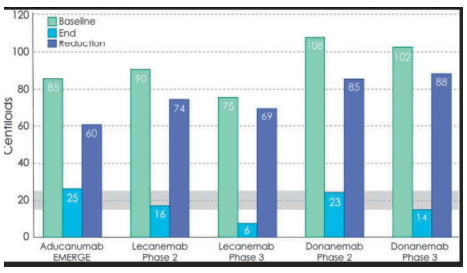


New Donanemab Dosing Schedule

Updated Donanemab titration reduced ARIA rates & severity for APOE E4 homozygotes



Amyloid Burden across mAb clinical trial phases



3. Management of ARIA-H (Amyloid-related imaging abnormalities with hemorrhage/ microhemorrhage) ARIA-E (Amyloid-related imaging abnormalities with edema) and Patient Selection

ARIA-E and ARIA-H

- Class effects of amyloid antibodies
- ARIA-E: vasogenic edema; ARIA-H: microhemorrhages, hemorrhage or superficial siderosis
- Usually asymptomatic, detected on MRI
- Requires dose adjustments or temporary suspension

Rates of ARIA observed in Phase 3 trials of anti-amyloid monoclonal antibodies.

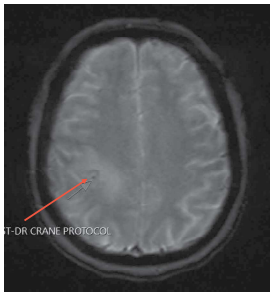
	Aducanumab (EMERGE)	Aducanumab (ENGAGE)	Lecanemab (Clarity)	Donanemab (Trailblazer-ALZ2)
ARIA-E placebo	2	3	1.7	1.9
ARIA-E Tx; symptomatic	20	29	2.8	6.1
ARIA-E Tx; APOE non-carriers	18	23	5.4	15.7
ARIA-E Tx; APOE carriers	43	42	15.8	NA
ARIA-E Tx; APOE heterozygotes	NA	NA	10.9	22.8
ARIA-E Tx; APOE homozygotes	65	65	32.6	40.6
ARIA-H placebo; microhemorrhage	7	6	7.6	12.5
ARIA-H placebo; siderosis	3	2	2.3	3.0
ARIA-H Tx; microhemorrhage	20	19	14.0	26.8
ARIA-H Tx; siderosis	13	16	5.6	15.7

ARIA management guidelines for anti-amyloid therapy

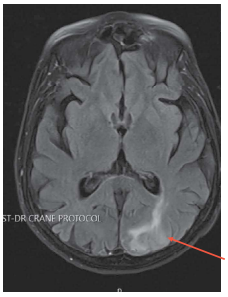
Clinical Symptom Severity	ARIA-H Severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	May continue dosing at current dose and schedule	Suspend dosing[a]	Suspend dosing[b]
Symptomatic	Suspend dosing[a]		

Clinical Symptom Severity[a]	ARIA-E Severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	May continue dosing at current dose and schedule	Suspend dosing[b]	Suspend dosing[b]
Mild	May continue dosing based on clinical judgment	Suspend dosing[b]	
Moderate or Severe	Suspend dosing[b]		

ARIA-H (Amyloid Related Imaging Abnormality-Hemorrhage)



ARIA-E (Amyloid Related Imaging Abnormality-Edema)



Logistical/Clerical Considerations

Dosage tracking
ARIA screening and patient response

MRI Scheduling
Complex with biweekly and monthy infusons
Correct protocols
Close communication with neuroradiology
Prescirbing physician should be comfortable with reviewing images prior to the availability of reports

Navigating Insurance
-Different requirements and timelines
Specific verbiage may greatly increase insurance approval odds reducing denials/appeals.

Navigating Financial Aid
-Practical programs available for patients requires extensive time
--Eg: Some programs require a combination of denials & appeals for the patient to be eligible

Partner Facilities
-Need excellent communication and clerical burden --
Examples:
•---Handling PA's & recerts
•---Holding doses that require MRI clearance
•---Vital monitoring/ symptom screening @ radiology/infusion appointments

Dedicated staff
-Eases family anxiety in having a specific person, team, phone extension they know is dedicated to them
-Focal point within prescribing providers office to reduce errors.

4. New biologic directions

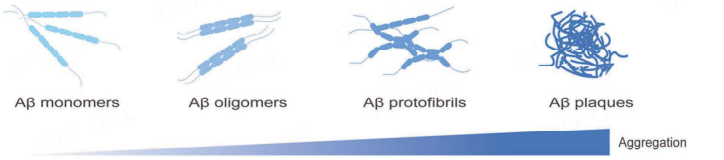
Remternetug

▲ Bapineuzumab
▲ Solanezumab
Crenezumab
Gantenerumab

▲ Bapineuzumab
▲ Crenezumab
Lecanemab
Aducanumab

▲ Lecanemab

▲ Donanemab
▲ Trontinemab
▲ Aducanumab
▲ Remternetug
Lecanemab



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Remternetug	IV/SC	Fixed	Q 4 weeks	Yes	Yes
Trontinemab	IV	Fixed	Q 4 weeks	Yes	No

REMTERNETUG (TRAILRUNNER-ALZ3 LAKI trial)

Next-generation anti-amyloid antibody (Phase 3)
- Randomized, Double-Blind, Placebo-Controlled, Parallel-group study

Evaluating whether Remternetug delays the onset or worsening of memory, thinking, or daily functioning problems in very early biological Alzheimer's

MMSE 27-30 with minimal or no impairment **(Prevention!)**

Similar to donanemab with improved pharmacokinetics
- Targets Pyroglutamate Aβ in plaques.

IV/SC at a Fixed dose every 4 weeks.

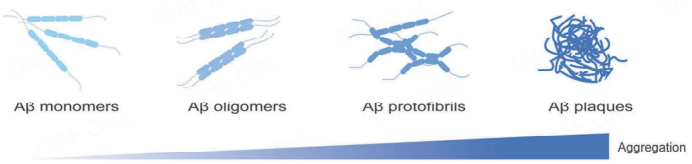
Trontinemab

▲ Bapineuzumab
▲ Solanezumab
Crenezumab
Gantenerumab

▲ Bapineuzumab
▲ Crenezumab
Lecanemab
Aducanumab

▲ Lecanemab

▲ Donanemab
▲ Trontinemab
▲ Aducanumab
▲ Remternetug
Lecanemab



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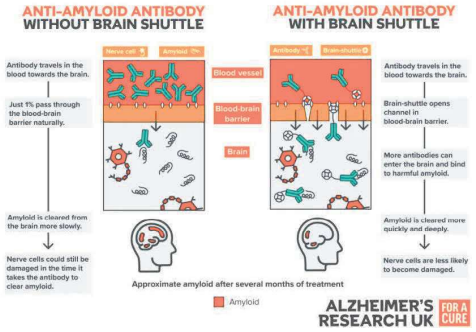
Trontinemab Phase 3 trial

- Blood-brain barrier-penetrant bispecific antibody (originally Gantenerumab).
- Targets Aβ and transferrin receptor for enhanced delivery.
- Early phase clinical data:
  - improved amyloid clearance with lower ARIA



A Double Standard?

Mortality Perspective:
- *Anti-amyloid therapies:* 0.7% mortality rate among treated patients
- *Adjuvant chemotherapy in older breast cancer patients:* 2.9% mortality within one year of diagnosis (study of 21,536 patients)

Cost Comparison:
- We routinely cover $100,000+ treatments for conditions like rheumatoid arthritis
- A non-curative treatment that allows an infant with spinal muscular atrophy more months of life is over 2 million
- Anti-amyloid therapies cost ~$26,000–$30,000 annually

Value Proposition:
- Investing in Alzheimer's treatments can yield ***billions in savings*** through delayed disease progression, preserved independence, and reduced caregiving costs
- Adds years of higher-quality, functional life for patients and relief for caregivers

PATIENT AND CARE PARTNER EXPECTATIONS AND EMOTIONAL EXPERIENCES OF LECANEMAB :
A SOCIAL MEDIA LISTENING STUDYMonica Crane,[1] Lee Watson, [2] Amanda Blackwood, [1] Pippa Brown, [3] Vicky Britton, [3] Alison Buckley, [3] Marc DeCongelio, [3] Craig Plauschinat, [4] Feride Frech, [4] Hideki Toyosaki [4]
1. Tennessee Memory Disorders, Foundation, Genesis Neuroscience Clinic, Knoxville, Tennessee, *USA. 2.* University of Tennessee-Knoxville, USA , *3.* Oracle Life Sciences, USA, *4.* Eisai Inc., Nutley, New Jersey, USA

Social media offers a fast and scalable way to capture real-world experiences associated with treatment use.

- Recent research shows that care partners commonly use platforms like Reddit to seek accessible treatment information and manage emotional stress.
  - The emotional themes of risk, hope, family, fear, and more time are interwoven throughout treatment discussions.
  - Considerable hope for treatment to delay disease progression was expressed on social media platforms, while risk and fear are alluded to as reasons for declining treatment.
  - Providing emotional support and addressing risks, without creating fear, are identified as potential unmet patient needs for treatment decision making.

TENNESSEE MEMORY DISORDERS FOUNDATION AND CLINIC

Thank you Alzheimer's Tennessee

There is HOPE

Contact Information:

For any questions feel free to reach out to our team at clinical.trials@tmdf.org