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Donanemab for Early-Stage Alzheimer's Disease: Recommendations for Clinical Practice

Slowing Alzheimer's disease (AD) progression in its early stages — mild cognitive impairment (MCI) or mild dementia — can allow patients more time to participate in daily life and potentially live independently. While AD is a complex condition with diverse medical needs, amyloid-β targeting monoclonal antibodies offer a new opportunity to slow its progression in some patients.

Following the U.S. Food and Drug Administration (FDA) approval of donanemab (Kisunla™) for the treatment of early symptomatic AD with confirmed amyloid pathology, the AD and Related Disorders Therapeutic Workgroup developed appropriate use recommendations (AUR) to guide its safe and effective implementation in clinical practice. This summary highlights key recommendations for clinicians, emphasizing patient safety and shared decision-making. The **full AUR** with comprehensive recommendations was published in the *Journal of Prevention of Alzheimer's Disease*.

1. Identify Potential Candidates for Donanemab

Conduct a comprehensive clinical evaluation (including history, neurological examination, cognitive testing and initial labs/imaging) to identify patients presenting with cognitive concerns who may be candidates for donanemab therapy. Consider evaluating patients for treatment who:

- **Present with MCI or mild dementia** consistent with AD Clinical Stages 3 or 4.
- **Have symptoms reflecting gradual and progressive cognitive decline**, verified through clinical history.
- **Exhibit cognitive impairment generally aligning with an MMSE score of 20-30** (or other cognitive screening instrument with a score compatible with early AD) — apply clinical judgement if factors like education, deafness, language proficiency or a language variant may affect scores.
- **Have AD as the suspected primary cause of cognitive impairment**, presenting with either typical amnestic (memory-predominant) syndrome or an established non-amnestic AD phenotype (e.g., logopenic PPA, posterior cortical atrophy, dysexecutive AD).

Donanemab Therapy is Not Appropriate For:

- **Patients with moderate to severe dementia** (Clinical Stage 5 or higher).
- **Patients in the early stages of AD** (Clinical Stages 1 or 2) with no symptoms, regardless of biomarker testing.
- **Patients with more than four cerebral microbleeds**, cortical superficial siderosis or major vascular contribution to cognitive impairment.

About Donanemab

Donanemab (Kisunla™) is an IV-administered monoclonal antibody targeting specific forms of amyloid-β plaque, approved for early symptomatic AD.

2. Perform Required and Recommended Pre-Treatment Evaluations

For potential candidates identified in Step 1, conduct additional evaluations to confirm eligibility, identify contraindications, assess risk and establish necessary baselines before initiating treatment. Treatment should only be considered if all required criteria are met, and no exclusionary criteria are identified.

REQUIRED

Confirm Amyloid Pathology

Treatment may be appropriate if positive amyloid status is confirmed by amyloid PET scan or CSF analysis.

Note: *The FDA cleared the use of pTau217/β-Amyloid 1-42 plasma ratio to detect AD in patients exhibiting cognitive symptoms; however, the field has not generally adopted blood-based biomarkers as having enough confirmatory evidence. Recommendations differ between using them as a step before CSF or PET confirmation, or as acceptable confirmation if the performance is equivalent to CSF tests (sensitivity and specificity of ~90%) and appropriate expertise and clinical context. Some groups have adopted the latter recommendation in practice, and in select cases, are using only high-accuracy blood tests.*

Conduct Baseline Brain MRI

Within 12 months (ideally less than six) of treatment initiation, MRI should ensure the absence of:

- Evidence indicating high ARIA risk, specifically >4 cerebral microbleeds or any cortical superficial siderosis (cSS).
- Significant cerebrovascular disease burden (e.g., multiple or large infarcts, severe white matter disease).
- Findings suggestive of cerebral amyloid angiopathy-related inflammation (CAA-ri).
- Other significant structural abnormalities (e.g., tumors, prior large hemorrhage) or MRI contraindications.

Review Concomitant Medications and Medical History

- **Treatment should not be considered for patients using anticoagulants** (except aspirin and other antiplatelet agents at standard doses when used alone), other anti-amyloid monoclonal antibodies and those who have suffered stroke or TIA within the previous 12 months. In emergencies, thrombolytics for MI or stroke should be avoided.
- **Treatment may not be appropriate for patients with a history of seizures**, some immunologic disorders requiring certain therapies, unstable serious medical conditions and inadequately controlled bleeding disorders, or Alzheimer's Disease mixed with Lewy body dementia (Mx AD/DLB).

STRONGLY RECOMMENDED

Assess *APOE-e4* Genotype Status

For Consideration
Due to increased risks associated with ARIA, exercise caution when considering treatment for *APOE-e4* carriers, especially homozygotes (e4/e4). All patients require diligent ARIA monitoring during donanemab therapy.

While *APOE-e4* status does not determine eligibility, carriers have higher risk of recurrent, symptomatic and severe amyloid-related imaging abnormalities (ARIA), which may inform discussions of risk, monitoring and treatment decisions*.

*See alternative dosing schedule below.

Determine Care Partner Availability

A reliable care partner who is available and willing to participate in the patient's care and monitoring during treatment is an important factor in treatment decisions.

OPTIONAL

Perform Tau PET Scan

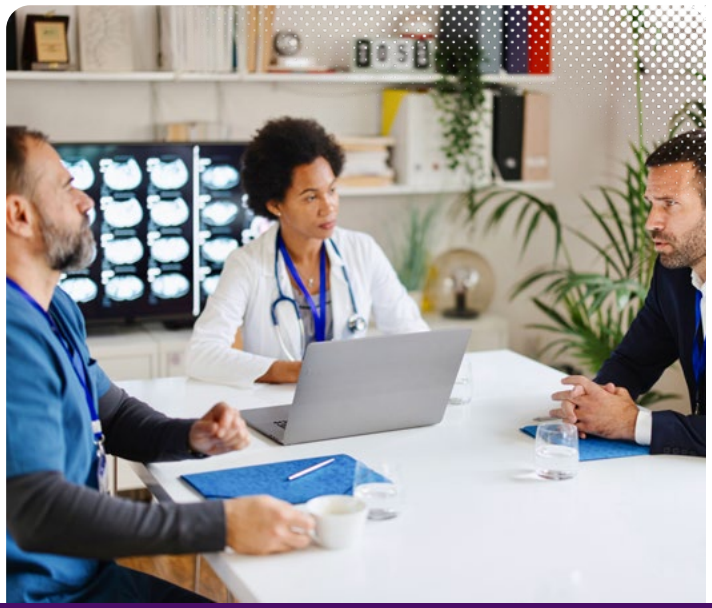
While results from a tau PET scan do not determine eligibility, they may help inform discussions about the potential magnitude of clinical benefit.

Note: *These recommendations may be updated as clinical trial results for donanemab treatment at earlier clinical stages become available.*

3. Finalize Treatment Decision Through Shared Decision Making

For confirmed eligible candidates, engage the patient and their care partner in a comprehensive discussion before making a final treatment decision. This should include:

- **Review evaluation findings** and clearly communicate results from clinical evaluation and tests, including amyloid status, key MRI findings and *APOE* genotype with associated ARIA risk implications.
- **Discuss potential benefits, risks and considerations** to ensure a thorough understanding of the potential for treatment to slow clinical decline (not cure or reverse symptoms), individual risk factors for ARIA and potential for infusion reactions and other serious adverse events and treatment requirements (e.g., monthly infusions, required monitoring, surveillance MRIs, office visits, medication restrictions and prompt symptom reporting).
- **Explore alternatives** and discuss other available AD management strategies.
- **Align with patient values** and discuss how treatment may or may not align with their individual goals, values and preferences.
- **Consider obtaining informed consent/assent** and document the patient's and care partner's confirmed understanding and agreement to undertake treatment.
- **Confirm patient commitment to adherence** and ensure the patient and their care partner understand and feel able to adhere to the treatment and monitoring plan.
- **Plan for treatment duration** and discuss potential discontinuation before starting treatment. If follow-up PET imaging to assess changes in amyloid is not feasible, consider agreeing on a limited treatment.



4. Administer Donanemab and Monitor Treatment

For eligible patients who have collaboratively decided to move forward with treatment, initiate and manage donanemab therapy according to AUR protocols:

- **Route and frequency:** Administered intravenously (IV) monthly.
- **Standard dose titration:** 700 mg monthly for three doses, then 1400 mg monthly.
- **Procedure**: Infuse over approximately 30 minutes, observe post-infusion (one hour after the first four infusions and may reduce to 30 minutes beginning with the 5th infusion, depending on tolerance).
- **Manage infusion reactions (see section 6 of the AUR for Grade definitions)**:
  - Grade 1-2: Stop infusion, manage symptoms and consider premedication for future infusions.
  - Grade 3+: Permanently discontinue donanemab.
- **Alternative dose titration schedule:** Discuss potential use of modified schedule (from 350→700→1050→1400 mg) for possible ARIA risk mitigation in high-risk groups. *This differs from the FDA-approved label.*
- **Required monitoring:**
  - **Obtain safety MRIs** (FLAIR and T2*/heme sequences) prior to the 2nd, 3rd, 4th and 7th infusions.
  - **Consider an additional MRI** prior to the 12th infusion for higher-risk patients.
  - **Maintain vigilance for any clinical signs or symptoms** potentially related to ARIA or infusion reactions throughout treatment.
- **Treatment duration:** Obtain follow-up amyloid PET at ~12-18 months and consider discontinuing treatment if negative. If follow-up PET is not feasible, consider limiting treatment to ~18 months, though no discontinuation protocol has been firmly established.

For more information and professional resources on anti-amyloid therapies, including systems-specific recommendations, check out the curated anti-amyloid collection on ALZPro **alz.org/Anti-Amyloid**.

Managing ARIA Risk — CRITICAL SAFETY INFORMATION

Amyloid-related imaging abnormalities (ARIA) require careful monitoring and management. Risk is significantly higher in *APOE-e4* carriers, especially homozygotes (e4/e4).

ARIA symptoms: Can be asymptomatic (MRI finding only). Symptoms can range from mild to moderate (headache, confusion, dizziness, nausea, visual or gait changes) to severe (seizures, encephalopathy, focal deficits, death). **Any new, concerning neurological symptom requires URGENT clinical evaluation and MRI.**

ARIA Management Actions:

- **Asymptomatic mild ARIA:** Continue dosing, increase vigilance and obtain monthly MRIs until resolution or stabilization.
- **Symptomatic or moderate ARIA:** Suspend dosing, monitor clinically and obtain monthly MRIs. Consider resuming treatment only if symptoms resolve AND MRI shows ARIA-E resolution/ARIA-H stabilization AND patient and care partner provide informed agreement.
- **Severe ARIA (radiographic or symptomatic):** Permanently discontinue treatment. Requires close monitoring and potential hospitalization. Consider high-dose glucocorticoids for severe cases.

ARIA vs. stroke: Symptomatic ARIA can mimic stroke. **MRI is essential**.

- **Mechanical thrombectomy:** Consider for confirmed large vessel occlusion stroke in donanemab-treated patients (does not appear to increase CAA-related hemorrhage risk).

PERMANENTLY STOP donanemab for ARIA if:

- radiographically severe ARIA-E or ARIA-H occurs.
- any macrohemorrhage occurs.
- >10 new microhemorrhages develop since treatment initiation.
- >1 area of superficial siderosis develops.
- a third ARIA event occurs.
- a serious ARIA symptom occurs.
- patient requires anticoagulant treatment.
- patient develops grade 3+ infusion reactions.

System Readiness: Ensure rapid access to MRI, expert interpretation, emergency care and neurological consultation for managing potential ARIA complications.

Conclusion

This summary outlines key appropriate use recommendations (AUR) designed to support clinicians in the practical application of donanemab for early symptomatic Alzheimer's disease. The recommendations emphasize a structured approach encompassing patient identification, confirmation of eligibility, risk assessment (especially for ARIA via MRI and *APOE* status), informed shared decision-making and diligent monitoring during treatment. As a novel therapy, ongoing learning is expected; clinicians should use this guidance alongside the comprehensive AUR document and remain updated on evolving clinical data and experience to ensure the continued safe and appropriate use of donanemab.

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For additional information and professional resources, visit **alz.org/ALZPro**.

Reference

Rabinovici GD, Selkoe DJ, Schindler SE, Aisen P, Apostolova LG, Atri A, Greenberg SM, Hendrix SB, Petersen RC, Weiner M, Salloway S, Cummings J. Donanemab: Appropriate use recommendations. *J Prev Alz Dis*. 2025, Apr. 7; 21:18. Online March 27, 2025. **https://doi.org/10.1016/j.tjpad.2025.100150**.

Understanding Appropriate Use Recommendations (AURs)

An appropriate use recommendation (AUR) provides timely, expert-informed guidance on a specific new therapy. Its development is driven by expert consensus and opinion, based on a review of available clinical trial data and regulatory information, but does not follow an extensive evidence-to-decision process. These recommendations are typically developed by independent therapeutic workgroups, and do not represent recommendations from the Alzheimer's Association or its workgroups.

About Alzheimer's Association

The Alzheimer's Association is a worldwide voluntary health organization dedicated to Alzheimer's care, support and research. Our mission is to lead the way to end Alzheimer's and all other dementia — by accelerating global research, driving risk reduction and early detection and maximizing quality care and support. Our vision is a world without Alzheimer's and all other dementia®. Visit **alz.org** or call 800.272.3900.

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