OVERVIEW OF ELIGIBILITY ASSESSMENT

ANTI-AMYLOID BETA MONOCLONAL ANTIBODIES (ANTI-Aβ mABs)

1 Cognitive Screening

Assessment Scales Sensitive to Mild Impairment: e.g., Montreal Cognitive Assessment (MOCA), St. Louis University Mental Status (SLUMS)

Neuropsychological Testing: Comprehensive evaluation when necessary

Confirm impairment

2 Biomarker Testing

Cerebrospinal Fluid (CSF) Analysis: Invasive but precise for both amyloid and tau analyses

Amyloid Positron Emission Tomography (PET): Non-invasive; often preferred for patient comfort and accuracy

Blood-Based Biomarkers: Emerging option for quick, accessible testing

Confirm Alzheimer's Disease (AD) pathology

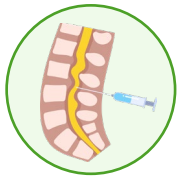
3 Baseline MRI Imaging

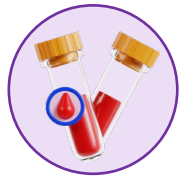
Look for Vascular Risk Factors on Imaging: Include heme-sensitive magnetic resonance imaging (MRI) sequences (e.g., susceptibility weighted imaging [SWI], gradient echo sequence [GRE])

Rule out excessive risk

OVERVIEW OF CURRENT BIOMARKERS IN AD

DIAGNOSIS AND THERAPEUTIC ELIGIBILITY





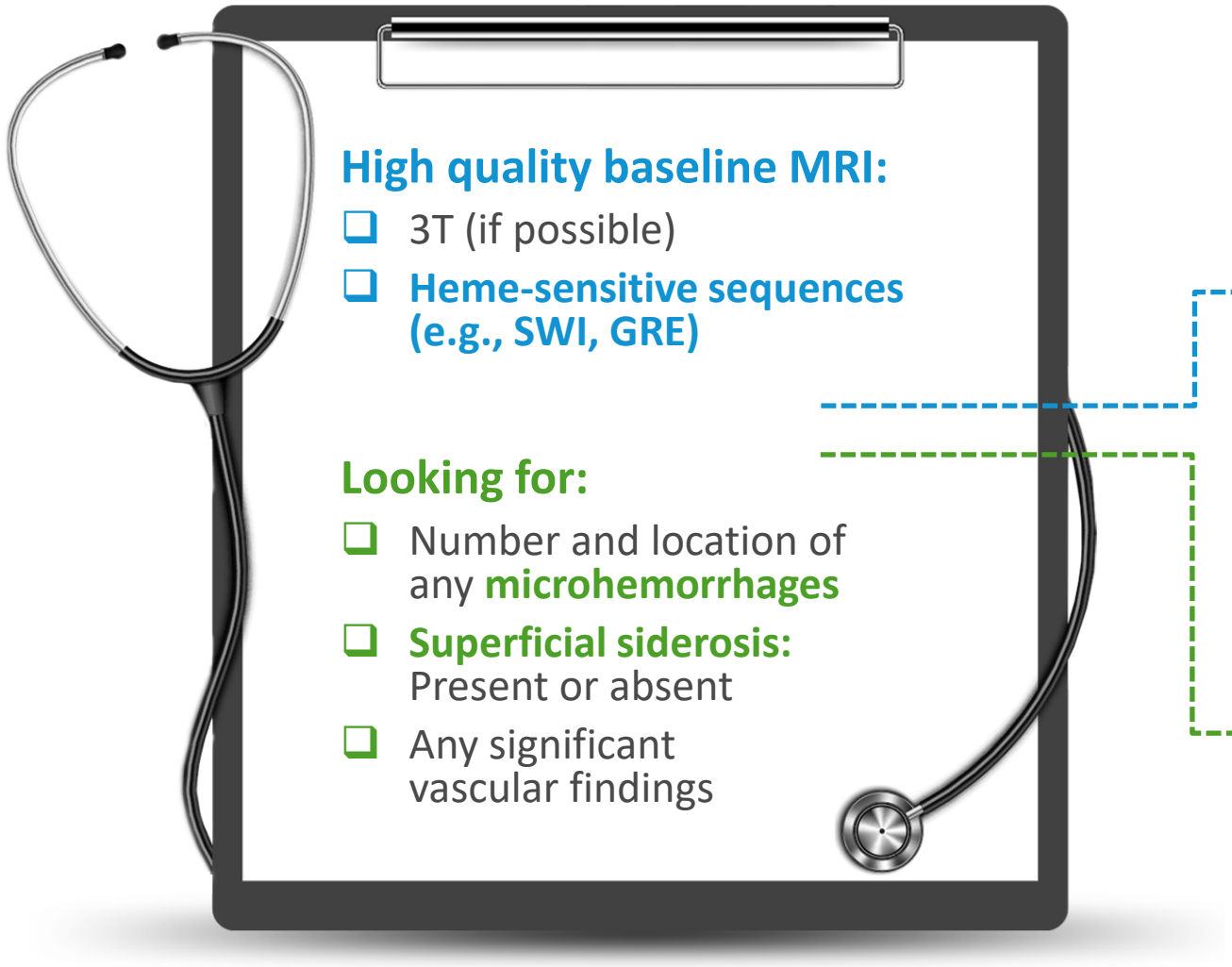
	Imaging	CSF	Blood
Current markers for AD diagnosis	Amyloid PET	p-tau181/Aβ42 t-tau/Aβ42 Aβ42/40	p-tau217
FDA-approved?	**Yes**	**Yes**	**No**
Accepted/ covered by insurance?	**Yes**	**Yes**	***Sometimes***

FACULTY NOTES

- Some insurers may now accept select blood-based biomarkers in the qualification for anti-Aβ mAbs.
- Some experts use blood markers as a screening tool before pursuing potentially costly or invasive confirmatory testing (particularly if running larger panels).
- Currently, blood markers cannot be used to determine whether or not to continue therapy.

Jack CR Jr et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement*. 2024 Aug;20(8):5143-5169.

BASELINE MRI FOR ANTI-AB MABS



High quality baseline MRI:

- ❑ 3T (if possible)
- ❑ **Heme-sensitive sequences (e.g., SWI, GRE)**

Looking for:

- ❑ Number and location of any **microhemorrhages**
- ❑ **Superficial siderosis:** Present or absent
- ❑ Any significant vascular findings

TREATMENT EXCLUSION CRITERIA

- >4 microhemorrhages
- Prior hemorrhage >1 cm
- Any superficial siderosis
- Vasogenic edema
- Other clinically significant vascular findings (e.g., aneurysm, infarct, severe small vessel, white matter disease)

NOTE

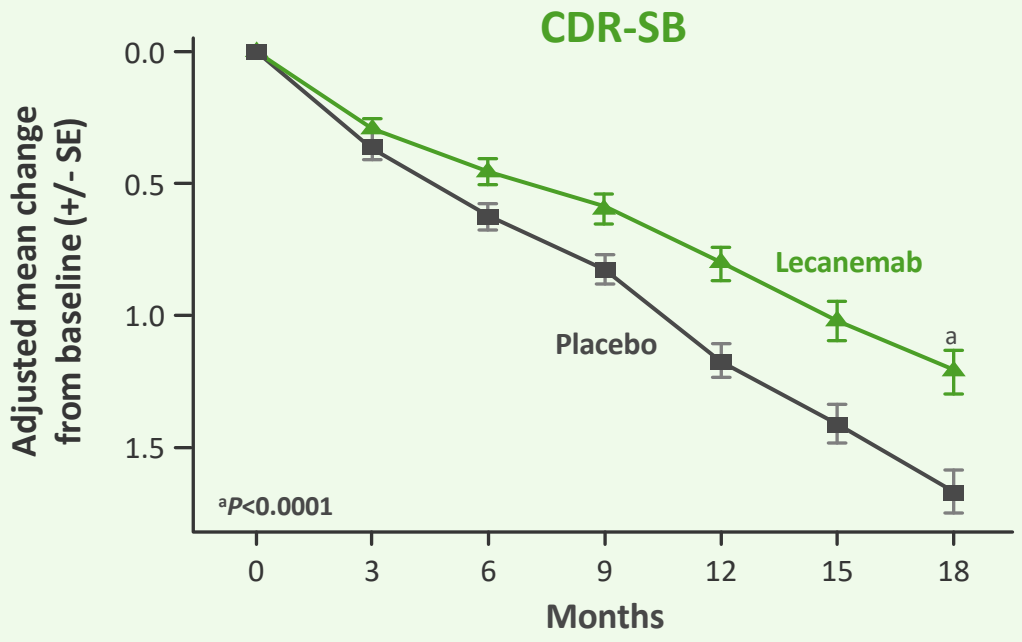
- The number of microhemorrhages must be followed over the course of treatment.

Cummings J et al. Lecanemab: appropriate use recommendations. *J Prev Alzheimers Dis*. 2023;10(3):362-377.

CLINICAL OUTCOMES

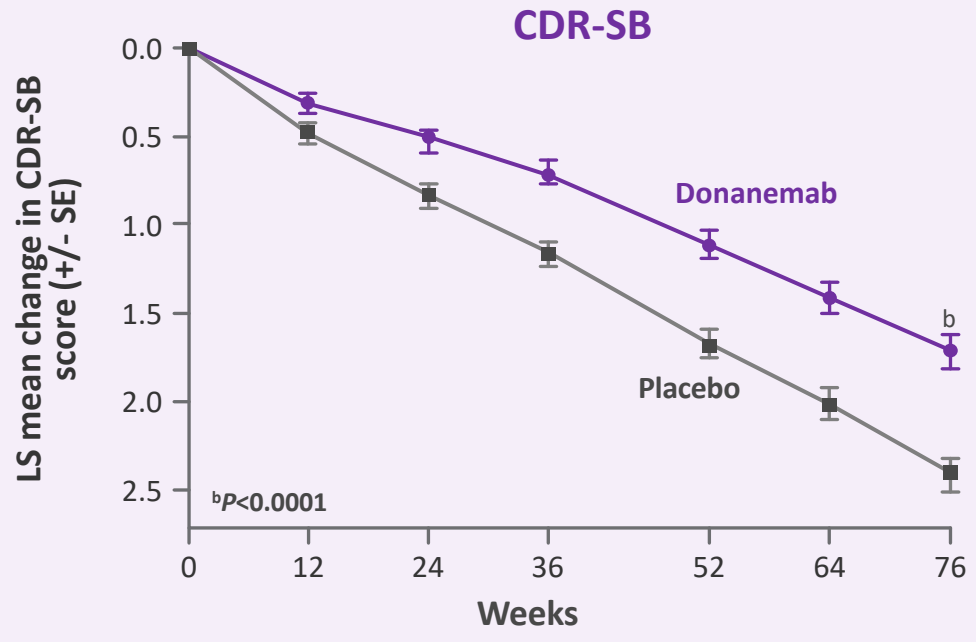
LECANEMAB (CLARITY)[1]

- 1,795 patients aged 50 to 90 years with mild cognitive impairment (MCI) or mild AD dementia
- Randomized 1:1 lecanemab vs placebo for 18 months



DONANEMAB (TRAILBLAZER-ALZ 2)[2]

- 1,736 patients aged 50 to 90 years with MCI or mild AD dementia
- Randomized 1:1 donanemab vs placebo for 18 months



CDR-SB: Clinical Dementia Rating scale Sum of Boxes; LS: least squares; SE: standard error.

1. van Dyck CH, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023 Jan 5;388(1):9-21. 2. Sims JR, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023 Aug 8;330(6):512-527.

NOTABLE DIFFERENCES BETWEEN ANTI-AB MABS

	LECANEMAB[1-3]	DONANEMAB[4]
Target	Soluble amyloid Aβ protofibrils	Plaque-specific epitope *(insoluble, modified, N-terminal truncated form of Aβ)*
Dosing	10 mg/kg	1,400 mg *(following three-dose titration at 700 mg[4])*
Frequency	Biweekly: ~1 hour infusions *(monthly maintenance dosing under FDA review[3])*	Monthly: ~30-min infusions
Duration	Indefinite	Until plaque clearance

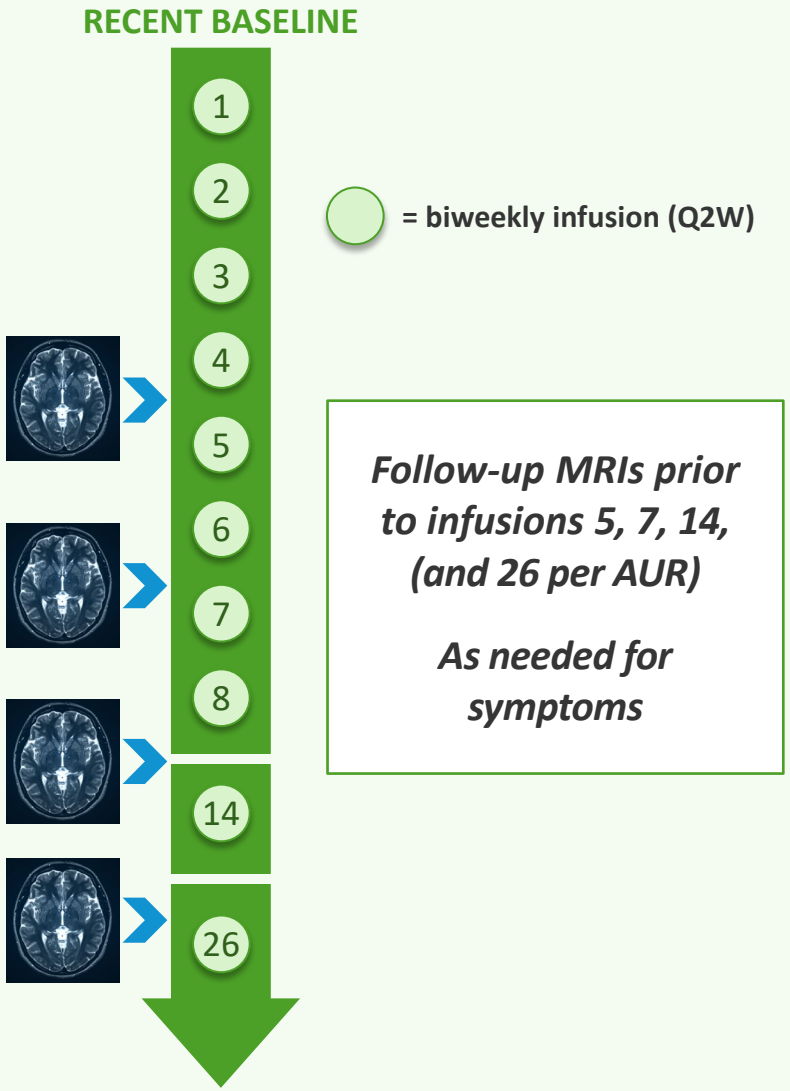
1. LEQEMBI (lecanemab-irmb). Prescribing information. Eisai Inc.; 2023. 2. Cummings J et al. Lecanemab: appropriate use recommendations. J Prev Alzheimers Dis. 2023;10(3):362-377. 3. Eisai Inc. FDA accepts Eisai's filing of lecanemab-irmb supplemental biologics license application for IV maintenance dosing for the treatment of early Alzheimer's disease. Accessed December 18, 2024. https://media-us.eisai.com/2024-06-09-FDA-Accepts-Eisais-Filing-of-LEQEMBI-R-lecanemab-irmb-Supplemental-Biologics-License-Application-for-IV-Maintenance-Dosing-for-the-Treatment-of-Early-Alzheimers-Disease. 4. KISUNLA (donanemab-azbt). Prescribing information. Lilly; 2024.

MRI MONITORING SCHEDULES

Serial MRIs are needed to monitor for amyloid-related imaging abnormalities (ARIA)

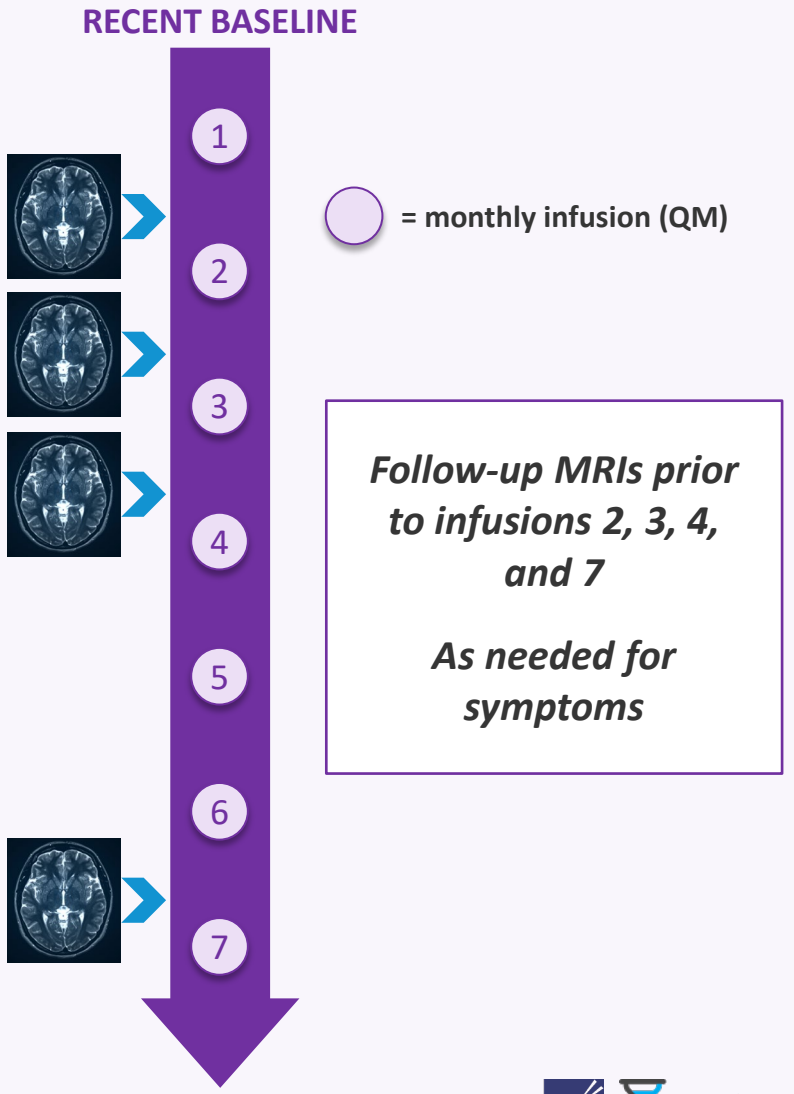
LECANEMAB[1,2]

Biweekly *~1-hour IV infusions (10 mg/kg)*



DONANEMAB[3]

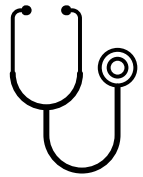
Monthly *~30-min infusions (1,400 mg following the three-dose titration at 700 mg)*



AUR: appropriate use recommendations; IV: intravenous; Q2W: every 2 weeks; QM: every month.

1. LEQEMBI (lecanemab-irmb). Prescribing information. Eisai Inc.; 2023. 2. Cummings J et al. Lecanemab: appropriate use recommendations. *J Prev Alzheimers Dis*. 2023;10(3):362-377. 3. KISUNLA (donanemab-azbt). Prescribing information. Lilly; 2024.

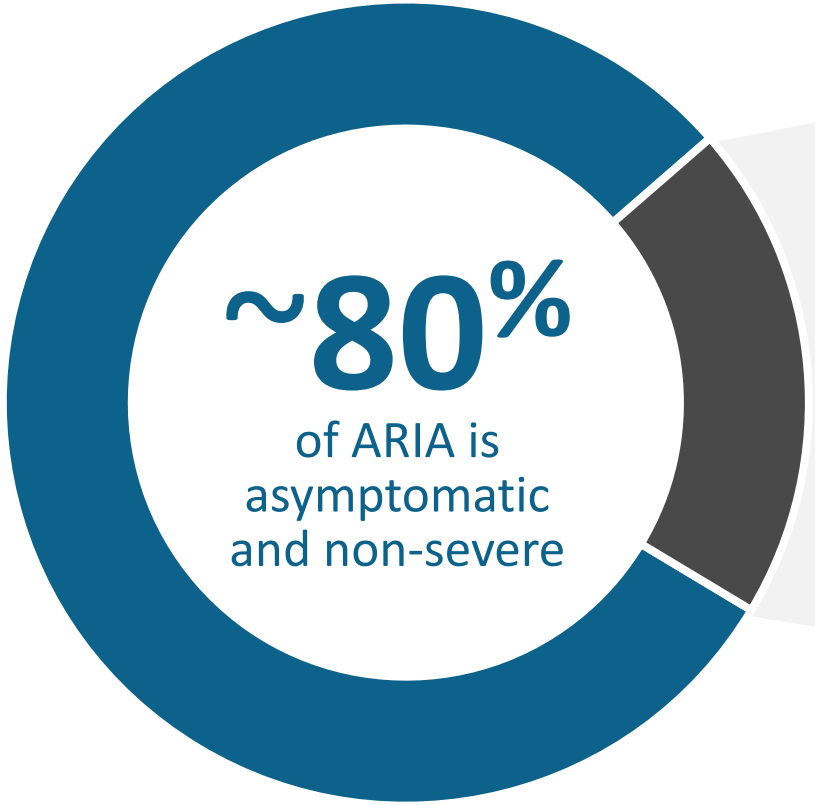
RISK FACTORS FOR ARIA



	APOE E4 Status	Time On Treatment	Baseline Vascular Findings on Imaging
	One of the most robust known risk factors for ARIA Risk increases with number of alleles (homozygotes vs. heterozygotes) In trials, carriers had a ~30% to 40% risk of ARIA compared to ~7% to 10% of noncarriers.	ARIA risk is highest at the beginning of treatment and decreases over time of exposure.	Cerebral amyloid angiopathy (CAA) increases vascular permeability and can cause spontaneous ARIA-like events in patients with AD regardless of anti-mAb treatment.
CLINICAL IMPLICATIONS	***Patient counseling*** ***More frequent MRI monitoring***	***Multiple required MRIs in the first year of treatment***	***Patients with significant vascular risk factors excluded from treatment***

Cummings J et al. Lecanemab: appropriate use recommendations. *J Prev Alzheimers Dis*. 2023;10(3):362-377.

ARIA PRESENTATION AND SYMPTOMS



RATES OF SYMPTOMATIC/SEVERE ARIA*

	LECANEMAB[1]	DONANEMAB[2]
Symptomatic **ARIA**	3%	6%
Severe **ARIA**	<1%	<2%

*Note: Trials are not directly comparable.
Caution is needed when making cross-trial observations.

KEY SYMPTOMS (IF SYMPTOMATIC): HEADACHE, CONFUSION, DIZZINESS, NAUSEA/VOMITING, AND VISION DISTURBANCE

1. LEQEMBI (lecanemab-irmb). Prescribing information. Eisai Inc.; 2023. 2. KISUNLA (donanemab-azbt). Prescribing information. Lilly; 2024.

MODIFIED DONANEMAB TITRATION

TRAILBLAZER-ALZ 6[a]

OBJECTIVE

Assess effects of different donanemab dosing regimens on ARIA and amyloid reduction in early symptomatic AD

PRELIMINARY FINDINGS

MODIFIED (n=212) VS. STANDARD (n=208) DOSING

Lower rates of:

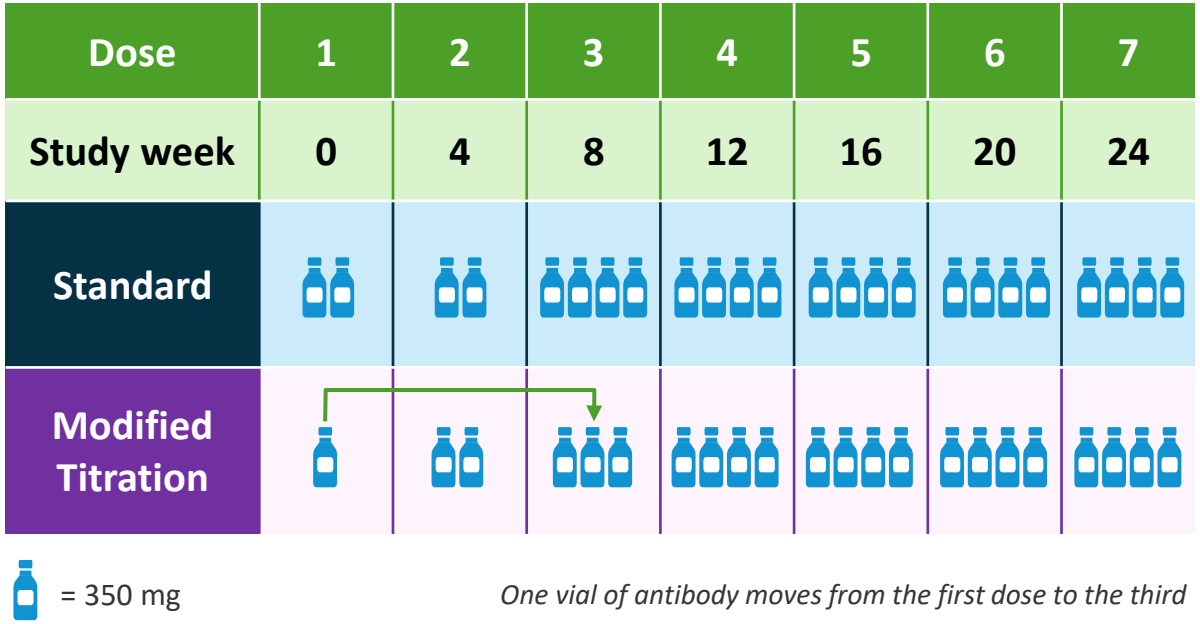
- Total ARIA-edema/effusion (ARIA-E): **14% vs 24%**
- ARIA-E in APOE ε4/4 carriers: **19% vs 57%**
- Symptomatic ARIA-E: **2.8% vs 4.8%**

Lower radiographic severity across ARIA-E

Comparable reduction in amyloid and p-tau217

Comparable adverse event (AE) rates

Modified titration differs from standard dosing by timing change of a single vial

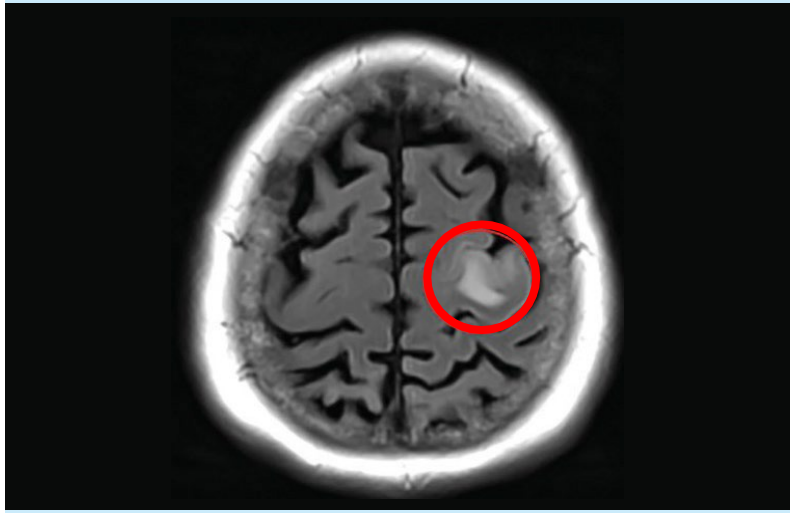


[a]The results of this study have not yet been incorporated into published prescribing guidelines.

1. Wang H, et al. The effect of different donanemab dosing regimens on ARIA-E and amyloid lowering in adults with early symptomatic Alzheimer's disease: primary outcome results from TRAILBLAZER-ALZ 6. Presented at CTAD 17th Annual Conference. Madrid, Spain. October 29-November 1, 2024. #0C1

ARIA-E APPEARANCE BY SEVERITY

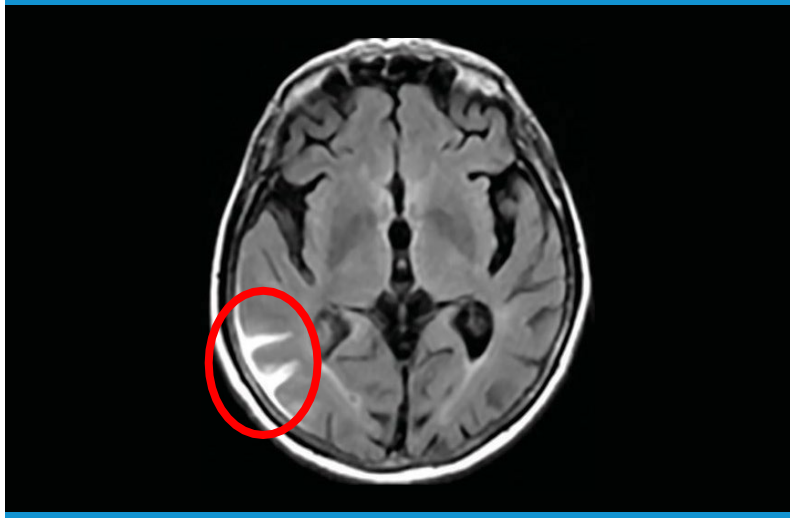
MILD
One location; <5 cm



Mild ARIA-E (edema)

This image: Hyperintensity <5 cm involving the left superior frontal lobe

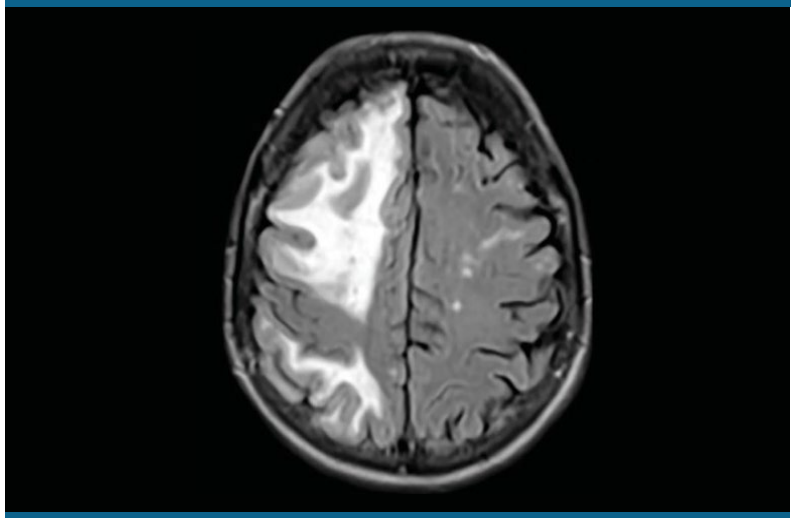
MODERATE
One location; 5-10 cm **OR** more than one location; <10 cm



Moderate ARIA-E (effusion)

This image: Hyperintensity in one location (5-10 cm) involving the right temporal-occipital sulci

SEVERE
One or more locations; >10 cm



Severe ARIA-E (edema)

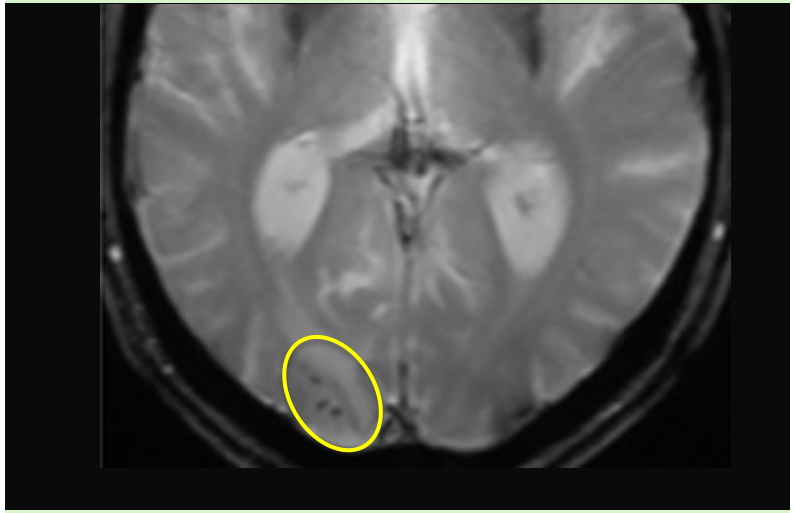
This image: Hyperintensity in two locations (>10 cm) involving the right frontal and parietal lobes

Cogswell PM et al. Amyloid-related imaging abnormalities with emerging Alzheimer disease therapeutics: detection and reporting recommendations for clinical practice. AJNR Am J Neuroradiol. 2022;43(9):E19-E35.

ARIA-HEMORRHAGE (ARIA-H) APPEARANCE BY SEVERITY

MILD[1]

One focal area of superficial siderosis **AND/OR** ≤ four microhemorrhages

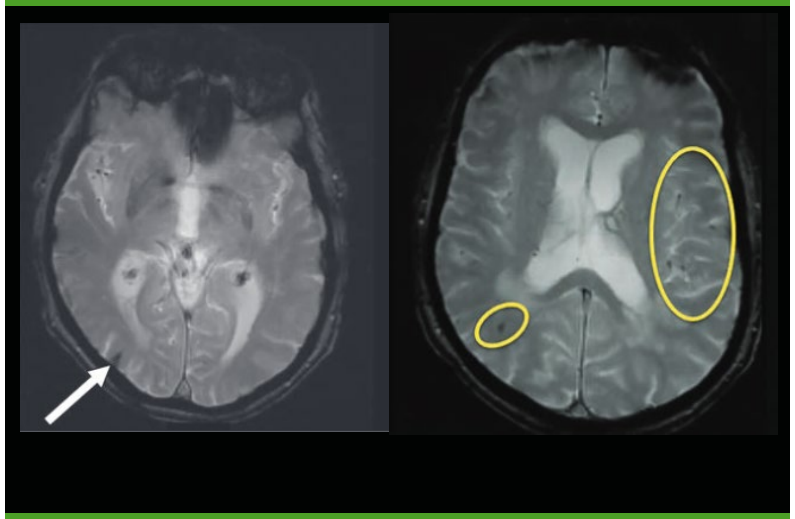


Mild ARIA-H

This image:
Three microhemorrhages (oval)[2]

MODERATE[1]

Two focal areas of superficial siderosis **AND/OR** five to nine microhemorrhages

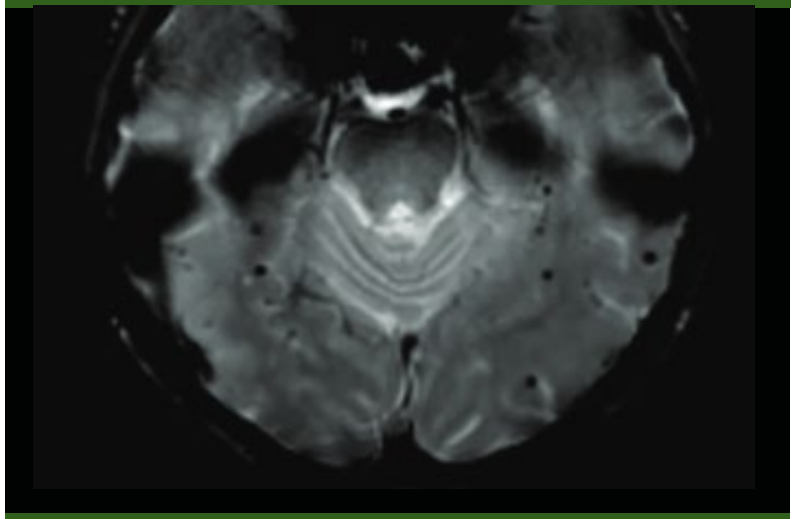


Moderate ARIA-H

This image: Superficial siderosis (arrow) and > five microhemorrhages (ovals)[3]

SEVERE[1]

More than two focal areas of superficial siderosis **AND/OR** ≥10 microhemorrhages

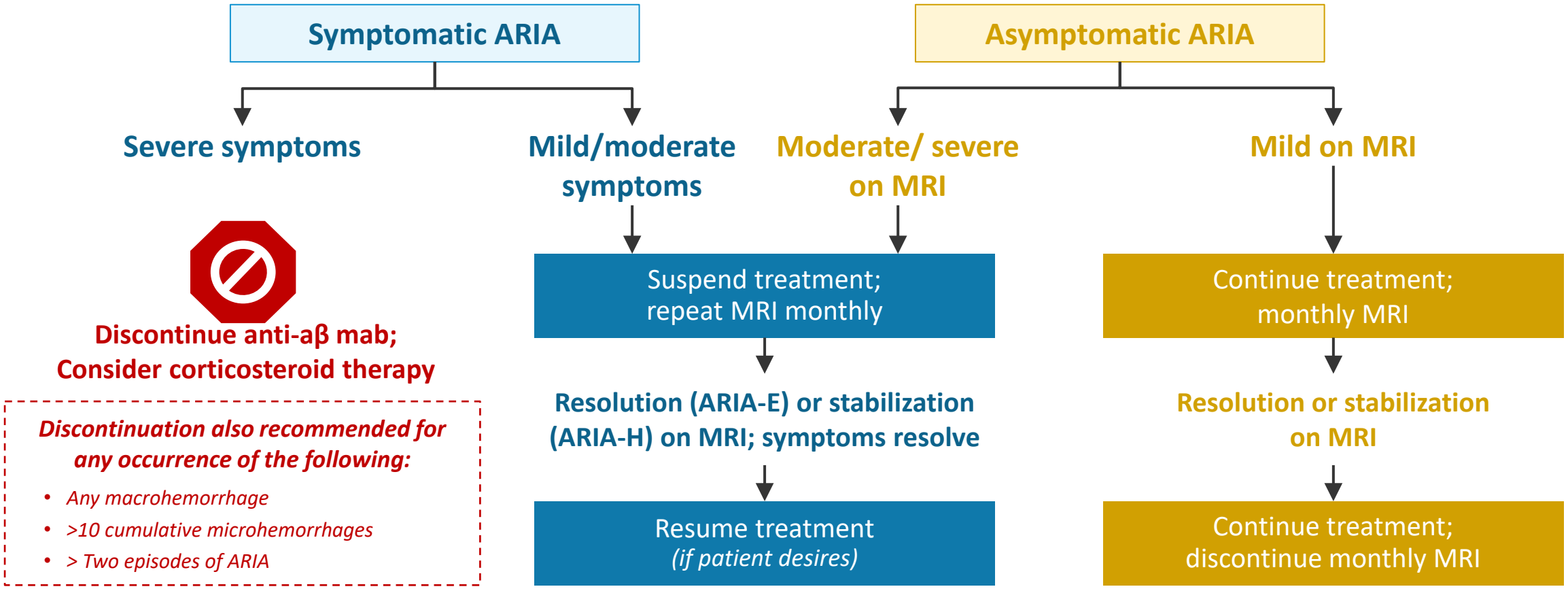


Severe ARIA-H

This image: >10 microhemorrhages[3]

1. Cogswell PM et al. Amyloid-related imaging abnormalities with emerging Alzheimer disease therapeutics: detection and reporting recommendations for clinical practice. *AJNR Am J Neuroradiol*. 2022;43(9):E19-E35. 2. Agarwal A et al. Amyloid-related imaging abnormalities in Alzheimer disease treated with anti-amyloid-β therapy. *Radiographics*. 2023;43(9):e230009. 3. Roytman M et al. Amyloid-related imaging abnormalities: an update. *AJR Am J Roentgenol*. 2023;220(4):562-574.

RECOMMENDED ARIA MANAGEMENT



This chart is a recommendation and not a predetermined algorithm. Clinical judgment and discussion with the patient is critical.

Cummings J et al. Lecanemab: appropriate use recommendations. J Prev Alzheimers Dis. 2023;10(3):362-377.

COMMUNICATION ESSENTIALS