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Special Article

Add-on combination therapy with monoclonal antibodies: Implications for drug development

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ABSTRACT

Three anti-amyloid monoclonal antibodies (MABs) including aducanumab, lecanemab, and donanemab have been approved by the FDA and lecanemab and donanemab are available in the US market and a variety of other national markets. The increasing use of anti-amyloid MABs to treat early AD will require that development of novel agents occur as add-on treatment to MABs. There is limited experience with add-on therapy to anti-amyloid agents. In most cases, it is prudent to initiate novel agents after at least six-months exposure to the MAB at the highest dose. Agents with extensive data on pharmacokinetics and pharmacodynamics and well-known safety may employ alternative approaches. Anti-amyloid MABs have different mechanisms of action, titration, and side effect profiles suggesting that add-on trials include only one type of MAB if possible. Demonstration of clinical benefit with add-on therapy will require showing additional slowing beyond that provided by the anti-amyloid MAB. Anti-amyloid therapies have profound effects on biomarkers including amyloid positron emission tomography and plasma p-tau and plasma GFAP measures. Definition of the biomarker profile of a novel agent prior to initiation of add-on therapies, inclusion of target engagement biomarkers specific to the novel intervention, assessment of biomarkers not known to be affected by anti-amyloid MABs, and interrogation of the magnitude, timing, and trajectory of biomarker change in the add-on context compared to monotherapy with MABs will provide insight into the biological impact of the novel therapy on AD. Patient convenience in terms of formulation and timing of add-on therapies will be important to successful clinical implementation. Add-on therapies are an important step in addressing the complexity of AD and optimizing patient outcomes.

1. Introduction

Anti-amyloid monoclonal antibodies (MABs) are the first approved disease-targeted therapies (DTTs) for Alzheimer's disease (AD). They have shown efficacy in early AD (mild cognitive impairment [MCI] and mild dementia due to AD). Aducanumab (Aduhelm®), lecanemab (Leqembi®), and donanemab (Kisunla®) have been approved, and lecanemab and donanemab are currently available on the market in the United States and are approved or being considered for approval in additional world regions [1,2]. MABs markedly reduce amyloid beta protein (Aβ) plaques and slow progression of clinical symptoms of early AD by approximately 30 %. Participants in clinical trials of novel agents may be receiving treatment with anti-amyloid MABs, and the novel agent being assessed in the trial will be an add-on therapy [3]. How existing anti-amyloid MAB therapy may affect clinical outcomes, biomarkers, and adverse events in clinical trials of novel agents is a new area of clinical trial and drug development planning. Here we describe options for the design and conduct of clinical trials of add-on therapies to MABs for treatment of AD.

2. Definitions of combination therapies

We address a specific type of combination therapy in which one or more novel agents is added on to an existing DTT, specifically an anti-amyloid MAB. Participants in these trials have begun therapy with an anti-amyloid MAB and then enter a clinical trial for a novel agent or may be treatment naïve and are begun on a MAB prior to initiating treating with the novel add-on therapy. Other types of combination therapies include development of two or more novel agents that are administered simultaneously or the development of combination products involving

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combinations of drug, device, and biological agent. Subcutaneous administration of an anti-amyloid MAB with an autoinjector is an example of a combination product as defined by the Food and Drug Administration (FDA).

There are substantial challenges in conducting and analyzing clinical trials of novel agents that include participants on anti-amyloid MABs. When to start the novel treatment in relation to the MAB therapy, whether to specify which MAB(s) is(are) allowable, whether to require a specific level of treatment-related amyloid clearance (TRAC) among trial participants, how to accurately attribute adverse events to the MAB or to the add-on therapy, how to interpret the effects of novel therapies on biomarkers in patients on anti- amyloid MABs and exhibiting substantial biomarker changes at baseline, how to choose novel agents to add-on to MAB therapies, and how to analyze outcomes of add-on trials represent important challenges that must be resolved in planning comprehensive drug development programs allowing participants on MABs. We address the main issues below.

3. Anti-amyloid monoclonal antibodies

3.1. Lecanemab and donanemab

Appropriate use recommendations (AURs) are available for lecanemab and donanemab [4,5]. Appropriate candidates for anti-amyloid MAB therapy are those with early AD manifesting Mini-Mental State Examination (MMSE) scores of 20 or higher. Patients must have confirmed Aβ pathology by amyloid positron emission tomography (PET), cerebrospinal fluid (CSF) findings consistent with AD, or highly accurate plasma blood biomarkers such as phosphorylated tau 217 (p-tau 217) in the abnormal range. A baseline magnetic resonance imaging (MRI) scan must show no more than 4 microhemorrhages and should not demonstrate extensive white matter changes. Patients should have genetic testing for the apolipoprotein E ε4 (*APOE4*) genotype since the risk of amyloid related imaging abnormalities (ARIA) is higher in *APOE4* gene carriers, and there is a gene dose effect with the highest risk among *APOE4* homozygotes (discussed in more detail below). Patients with a history of seizures or autoimmune disorders or who are receiving anticoagulant therapy are not appropriate candidates for treatment. AURs are derived from clinical trials and expert opinion and do not supersede clinician judgement for individual cases.

The AURs for anti-amyloid MABs apply to all add-on trials with these agents. Trials of drugs being developed for early AD, for example, may include a substantial number of patients on anti-amyloid MABs since these agents are approved only for patients with early AD at the time of treatment initiation. Novel agents being developed for treatment of mild to moderate AD would be expected to have fewer participants eligible for add-on therapy since initiating MAB therapies in patients with moderate AD would be an inappropriate use of these agents. All patients receiving anti-amyloid MAB therapy will have had a biologically confirmed diagnosis of AD at the time the MAB treatment was initiated. After treatment they may no longer meet amyloid-related criteria for the diagnosis of AD. Repeat of diagnostic studies would not be required unless the novel agent is expected to affect Aβ plaques or CSF or plasma Aβ-related measures and changes from baseline are possible outcomes of therapy. Trials of novel agents in trials allowing participants on MAB therapies will be studying patients who at the time of beginning MAB treatment initiation had 4 or fewer microhemorrhages in the brain, a low burden of white matter pathology, no history of seizures or immune system disturbances, and were not on anticoagulants. Candidates for anti-amyloid MAB treatments must be MRI-eligible since MRI is required to define the baseline the presence of microhemorrhages and to monitor for ARIA. Patients with MRI incompatible pacemakers, claustrophobia, or other reasons for not being able to have an MRI will be excluded from these add-on trials since they would have been ineligible for MAB therapy. These treatment population restrictions will limit the generalizability of conclusions that can be drawn from the trial regarding the effect of the novel agent.

The therapeutic targets, administration frequency, and titration requirements differ for lecanemab and donanemab (Table 1). Lecanemab targets Aβ protofibrils and plaques. The agent is administered intravenously every two weeks; infusion frequency may be decreased to monthly after 18 months of treatment. Lecanemab does not require titration. Therapy is continued until the patient, family, and clinician conclude that continuing therapy is of no benefit. A subcutaneous version of lecanemab is being studied.

Donanemab targets pyroglutamate Aβ found only in fibrillar Aβ plaques. It is administered intravenously monthly for 18 months or until an amyloid PET demonstrates the absence of plaques in the brain. Donanemab is titrated in 2 or 4 dosing steps; the 4-step titration schedule may be associated with a lower frequency of ARIA.

Not all patients receiving anti-amyloid MABs have complete TRAC. Patients included in add-on trials will include a combination of full TRAC and partial TRAC individuals unless the trial requires dmonstration of an absence of detectable Aβ plaques.

ARIA of the effusion type (ARIA-E) or of the hemorrhagic type (ARIA-H) represent the principal side effects associated with anti-amyloid MABs. ARIA is usually asymptomatic but may produce symptoms such as confusion or gait disturbance and can be severe enough to produce status epilepticus or death; treatment candidates must understand the risks associated with MAB treatment. Serial MRIs are collected in the

Table 1
Key features in the active treatment arms of the lecanemab an donanemab observed in Phase 3 trials. The agents have not been directly compared in clinical trials and comparative observations are preliminary.

Drug or Trial Feature	Lecanemab	Donanemab
Target	Protofibrils and plaques	Pyroglutamate amyloid in Aβ plagues
Infusion schedule	Twice monthly for 18 months; monthly thereafter	Monthly
Stop treatment with demonstrated plaque removal	No	Can be considered; treatment was stopped following plaque removal in clinical trials
Titration	None required	2 step titration: 700 mg x3 then 1400 mg on infusion 4 and thereafter 4 step titration: 350 mg x1; 700 mg x1; 1050 mg x1; 1400 mg on infusion 4 and thereafter
Primary outcome: percent reduction in rate of decline	2CDR-SB: 7 % slowing	iADRS: 35.1 % slowing (low/medium tau group)
Secondary outcome/ ADAS-cog: percent reduction in rate of decline	26 % slowing	32.4 % in the low/medium tau group
Secondary outcome/ ADCS-ADL percent reduction in rate of decline	36 % slowing	39.9 % in the low/medium tau group
ARIA - E	12.6 %	24 %
Symptomatic ARIA-E	2.8 %	6.1 %
ARIA-E: noncarriers	1.4 %	15.7 %
ARIA-E: APOE4 heterozygotes	1.7 %	22.8 %
ARIA-E: APOE4 homozygotes	9.2 %	40.6 %
ARIA-H	17.3 %	19.7 %
Percent with infusion reactions	26.4 %	8.7 %

Aβ - amyloid-beta protein; ADAS-cog - Alzheimer's Disease Assessment Scale - cognitive subscale; ADCS-MCI-ADL - Alzheimer's Disease Cooperative Study Mild Cognitive Impairment Activities of Daily Living scale; ARIA-E - amyloid related imaging abnormalities - edema type; ARIA-H - amyloid related imaging abnormalities - hemorrhagic type; CDR-SB - Clinical Dementia Rating Sum of Boxes; iADRS - integrated Alzheimer's Disease Rating Scale

initial phases of anti-amyloid MAB therapy to detect asymptomatic ARIA and guide management. Treatment with MABs is discontinued if patients have symptomatic ARIA, more than 2 episode of ARIA, or have severe ARIA as revealed by MRI. Treatment is paused if ARIA is moderate and may be resumed if ARIA-E resolves or ARIA-H stabilizes. Treatment may continue in patients with mild ARIA (observed on MRI) who are asymptomatic [4,5]. The initiation phase of the MAB should be completed before therapy with a novel agent is begun.

In the Phase 3 trial, lecanemab was associated with ARIA-E in 12.6 % of participants receiving active therapy [2]. Symptoms of ARIA-E were apparent in 2.8 % of participants. ARIA- E was more frequent in *APOE4* homozygotes (9.2 %) compared to heterozygotes (1.7 %) or noncarriers (1.4 %). ARIA-H occurred in 17.3 % of participants and was symptomatic in 0.7 %. Approximately half of the cases of ARIA-H occurred in participants with ARIA-E. Seventy-one percent of ARIA events occurred within the first three months of therapy, and 81 % resolved within four months after detection. Infusion reactions occurred in 26.4 % of participants treated with lecanemab.

In the Phase 3 trial of donanemab, ARIA-E occurred in 24 % of participants receiving active therapy and ARIA-H occurred in 19.7 % [1]. ARIA-E was symptomatic in 6.1 % of participants. ARIA-E occurred in 15.7 % of *APOE4* noncarriers, 22.8 % of *APOE4* heterozygotes, and 40.6 %of *APOE4* homozygotes. Most ARIA (57.9 %) occurred within the first three months of treatment. Infusion reactions occurred in 8.7 % of individuals receiving donanemab.

3.2. Anti-amyloid monoclonal antibodies in development

Lecanemab and donanemab or currently available in the US and several other countries. Other anti-amyloid MABs are in clinical trials and could progress to approval include MABs in Phase 3 (remternetug and tertomidine) and MABs in Phase 2 (ABBV-916, sabirnetug, SHR-1707, and trontinemab). Add-on trials including patients on any of these agents can be anticipated.

4. Add-on clinical trials with anti-amyloid antibodies

4.1. Add-on treatment with existing approved treatments

Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) are approved for mild and moderate AD dementia, and donepezil and rivastigmine are approved for severe AD dementia. Memantine is approved for moderate to severe AD dementia [6]. Patients on these drugs have been allowed in clinical trials of anti-amyloid MABs as the standard of care for patients with AD. In the Phase 3 lecanemab clinical trial, 52 % of patients on active therapy were receiving treatment with standard of care (some combination of cholinesterase inhibitors and memantine) [2], and in the Phase 3 trial of donanemab, 56.5 % of patients in the low/medium tau group and 60.6 % of patients on the combined tau group (low/medium tau and high tau) were on standard of care with approved agents [1]. These observations indicate that approximately 50 % of the participants in the anti-amyloid MAB trials were receiving add-on therapy of the MAB to standard of care. Pre-specified sub-analyses are typically conducted to determine if the existence of standard of care influences the clinical outcomes. Development of novel agents as add-on therapies to anti-amyloid MABs are anticipated to include participants on standard of care therapies including cholinesterase inhibitors or memantine.

4.2. Rationale for development of new add-on therapies

There are several reasons to pursue add-on trials with anti-amyloid MABs. AD is a complex disorder with Aβ abnormalities, tau protein aggregation, neurodegeneration, inflammation, oxidative and metabolic abnormalities, synaptic dysfunction, and transmitter deficits, as well as co-pathologies in some patients such as alpha-synuclein and TAR DNA binding protein 43 (TDP-43)(7). Anti-amyloid MABs address one aspect of this complex pathobiology, and achieving a therapeutic response of greater magnitude may involve add-on therapies that have additive or synergistic effects beyond those of the anti-amyloid therapy alone.

Anti-amyloid MABs produce an approximately 30 % slowing of disease progression. The goal of caring for patients with AD is to further slow, stop, or reverse progression; add-on therapies are required to achieve these goals [8,9].

Combination therapies might address safety issues of MABs. ARIA-E and ARIA-H follow interruption of the blood brain barrier, and the likelihood of ARIA may be enhanced by the presence of vascular inflammation [10]. Add-on therapies that reduce peripheral inflammation or enhance blood brain barrier integrity may reduce ARIA and improve the safety of anti-amyloid MAB therapy.

Since many early AD patients may be on anti-amyloid MABs, establishing the safety and efficacy of add-on therapy is important to assure clinicians that, if the test agent is approved, it can be employed in their patients receiving MAB treatment.

4.3. Rationale for specific combinations of treatment in add-on trials

A variety of types of add-on therapies might be considered for patients receiving anti-amyloid MABs. For example, tau abnormalities are another core AD pathology and could be targeted in an add-on trial [7]. Tau therapies could complement the effects of the Aβ-directed therapies, and this hypothesis is currently being tested with the anti-tau agent, E2814, combined with lecanemab in participants with dominantly inherited Alzheimer's disease (DIAD) in the Dominantly Inherited Alzheimer Network Trial Unit (DIAN-TU).

Addressing pathophysiological changes that occur in AD including inflammation and neurodegeneration comprise potential therapeutic targets. Co-pathologies such as vascular changes, alpha-synuclein aggregates, and TDP-43 aggregation when shown to be present by emerging biomarkers could be targeted in patients who harbor these complex multi-protein combinations.

How to choose the best agent or combination of agents to add to anti-amyloid MAB therapy is a vexing challenge. Predictive efficacy tools are lacking. Computational strategies are a promising means of identifying drugs whose effects engage the AD pathological network and would complement the known effects of anti-amyloid MABs [11,12].

4.4. Timing of add-on therapy in clinical trials of novel agents

An important concern when considering add-on therapy to an anti-amyloid MAB is the occurrence of ARIA and its possible misattribution to the experimental agent. To avoid this, initiation of the test agent should occur after the period when most ARIA occurs with MAB treatment. ARIA events are observed relatively soon after initiation of anti-amyloid MAB treatment. Approximately 70 % of observed ARIA occurred within the first three months of treatment with lecanemab, and 60 % of documented ARIA occurred within the first three months of treatment with donanemab using the 2-step titration schedule.

No specific guidelines or studies have emerged regarding when to initiate treatment with a novel agent in the add-on setting. A prudent approach is to wait six months after initiation of the highest dose of the anti-amyloid MAB before introducing the novel agent. There is no dose titration with lecanemab, and initiation of the test agent could begin six months after initiation of lecanemab treatment. In the case of donanemab, a six-month observation period would suggest initiating treatment six months after initiation of treatment with the highest dose. Donanemab infusions occur at baseline and monthly thereafter, with the highest dose beginning with the 4th (highest) dose at the end of month 3.

In most cases, initiation of treatment with an anti-amyloid MAB after introduction of the novel agent in a trial should be avoided since the occurrence of ARIA in such patients could not automatically be attributed to the anti-amyloid MAB. Triggering Receptor Expressed on

Myeloid cells 2 (TREM)2 agents, for example, produce ARIA, indicating that ARIA is not unique to anti-amyloid MABs [13].

In unique instances when the scientific rationale and hypothesis for the pharmacologic effect and safety of the combination supports doing so, the novel therapy might be initiated prior to the start of the MAB (e.g., a study in an asymptomatic population where starting the novel therapy prior to start of MAB allows capture of data on the novel agent prior to co-administration with a MAB as is done in the DIAN-TU trial design). Another exception to delaying add-on of a novel agent for six months beyond the initiation of maximal therapy of the MAB are trial designs in which agents designed to reduce ARIA may be administered simultaneously with or prior to the anti-amyloid MAB with the intent of reducing this important side effect encountered with anti-amyloid MAB therapy. Anti-inflammatory agents may be candidates for this combination approach given the apparent relationships among vascular amyloidosis, inflammation, and ARIA risk [10].

4.5. Prespecification of the type of allowable MAB therapy in clinical trials

Sponsors will determine if they allow participants on any of the available anti-amyloid MABs or if a specific MAB will be required. The available MABs have different biological targets, different titration schedules, and different ARIA and infusion reaction liabilities (Table 1). Consideration of these aspects will influence whether sponsors allow participation of individuals on any MAB or will pre-specify the specific MAB population to be allowed. When randomizing treatment naive patients, sponsors could specify and provide a MAB and then add a novel therapy. Patients entering trials on MABs would continue MAB therapy if the agent is lecanemab and could have treatment stopped when amyloid plaque levels are sufficiently reduced if the agent is donanemab

Recruitment will be facilitated by allowing participants on any available MAB, however, trial operations and interpretation may be complicated by including patients on a variety of MABs. If the mechanism of action of the test agent interacts with the target of one of the MABs (e.g., protofibrils for lecanemab or pyroglutamate Aβ for donanemab) limitation of trial participants to one of the MABs may be desirable to facilitate understanding the biological impact of the novel agent. Glutaminyl cyclase inhibitors, for example, target pyroglutamate Aβ production and could interact with the mechanism of action of donanemab [14]. In allowing any available MAB, consideration should be given to management of patients who may clear amyloid during the study and would otherwise be candidates for discontinuation of the MAB (i.e., if receiving donanemab). Until additional data are available regarding the course of decline following discontinuation are available, an approach to minimizing variability in response over time favors standardizing the MAB and continuinh dosing during the double blind period of treatment with the novel agent. This may be particularly important for Phase 2 studies with small sample sizes.

4.6. Expanding the use of MABs in add-on trials

MAB add-on trials might provide the opportunity to extend the populations for which anti-amyloid MABs are indicated. Antibody therapies are currently indicated for patients with MCI due to AD or mild AD dementia. Expanded indications for use of MABS are currently being explored in trials of cognitively normal preclinical AD populations. Combination therapies in these studies could extend the period of normal cognitive function. Anti-amyloid MAB treatments in combination with other drugs could be explored in amyloid bearing conditions such as dementia with Lewy bodies, Down syndrome, Parkinson's disease dementia with concomitant amyloid plaques, and vascular dementia with concomitant AD pathology. These trials would represent new or expanded indication for MABs, and combination strategies may differ from those developed for early AD.

4.7. Clinical development plans for add-on therapies

Given the presence of anti-amyloid MABs in the market, the likely increase in the number of anti- amyloid MABs available, and the increasing treatment of early AD patients with anti-amyloid MAB therapy, clinical development plans of new therapies for AD should consider planning for add-on therapy as one aspect of the development program. Consideration should be given to the potential for safety issues following administration of novel treatments to participants on an anti-amyloid MAB. Non-clinical safety studies may be required to study these questions. In the absence of such concern, non-clinical studies may not be warranted.

4.8. Design of add-on trials

Several types of add-on trial designs for Phase 2 and 3 studies

Table 2
Clinical trial designs involving add-on strategies.

Clinical Trial Design	Information to be Derived
All participants are treated with an anti-amyloid MAB at a stable dose for a specific period and continue dosing for the duration of the trial, participants are randomized to: Arm 1: novel agent with MAB as background Arm 2: placebo with MAB as background	Sequential add-on design; novel therapy is introduced after ARIA risk has declined; allows safety and efficacy comparison of the add-on therapy (MAB + novel agent to the anti-amyloid MAB treatment (MAB + placebo)
Arm 1: novel agent allowing participants to be on anti-amyloid MABs Arm 2: placebo	Safety of the add-on therapy combination
Arm 1: novel agent allowing participants to be on anti-amyloid MABs Arm 2: novel agent alone (i.e., excluding participants on anti-amyloid MABs)	Safety of novel agent with and without add-on of anti-amyloid MAB
Arm 1: Combination treatment with novel agent requiring participants to be on anti-amyloid MABs Arm 2: Monotherapy of novel agent excluding participants on anti-amyloid MABs	Safety and efficacy of novel agent with and without add-on of anti-amyloid MAB
Arm 1: Combination treatment with novel agent requiring participants to be on anti-amyloid MABs Arm 2: novel agent alone (i.e., excluding participants on anti-amyloid MABs) Arm 3: Placebo	Frequentist design: Safety and efficacy of novel agent with and without add on anti-amyloid MABs; arms 1 and 2 can be compared to placebo (arm 3)
Arm 1: Combination treatment with novel agent requiring participants to be on anti-amyloid MABs Arm 2: Monotherapy of novel agent excluding participants on anti-amyloid MABs Arm 3: Placebo	Bayesian adaptive design: response-adaptive randomization allows adjustment of randomization probabilities to favor treatment arms demonstrating better efficacy or more favorable risk benefit profiles
Arm 1: Combination treatment with novel agent requiring participants to be on anti-amyloid MABs Arm 2: Monotherapy of novel agent excluding participants on anti-amyloid MABs Arm 3: Monotherapy of anti-amyloid MAB	Each agent (arms 1 and 2) is compared to combination (arm 3); if arm 3 exceeds arm 1, arm 2 must be contributing to efficacy; if arm 3 exceeds arm 2, arm 1 must be contributing to efficacy
Arm 1: Combination treatment with novel agent and anti-amyloid MABs Arm 2: novel agent along Arm 3: anti-amyloid MAB alone Arm 4: Placebo (control)	2 × 2 factorial design; each agent and the add-on combination are compared to placebo

MABs – monoclonal antibody; note: in all scenarios it is anticipated that trial design will require stable background therapy symptomatic medications (i.e., acetylcholinesterase inhibitors, memantine, unless contraindicated or not tolerated),

involving anti-amyloid MABs can be envisioned (Table 2). The specific design chosen will depend on the phase of development, objective of the study, data required to advance the treatment to the next phase or milestone, and logistical, operational, and financial considerations.

There are few precedents in AD drug development for establishing efficacy of add-on therapies. In the memantine development program, the efficacy of monotherapy was established in one trial and the efficacy of memantine in participants receiving donepezil was established in another [15]. In the add-on trial, all patients received donepezil and were then randomized to receive memantine or placebo; no placebo only arm was included [16]. Demonstration of efficacy in patients receiving donepezil suggested that combination therapy of the two agents was superior to monotherapy with donepezil alone. This strategy was also used in trials of aducanumab, lecanemab, and donanemab where standard of care was allowed and participants were randomized to the anti-amyloid MAB or placebo on top of stable symptom targeted therapies. A similar strategy might be followed for demonstrating the efficacy of a novel agent in patients receiving therapy with an anti-amyloid MAB. For registration trials, proposed study designs should be reviewed with regulatory authorities for feedback on appropriateness to support a proposed indication and product labeling.

Phase 1 trials will focus on establishing the safety and pharmacokinetic profile of the novel agent. At this stage of development, it is unlikely that add-on therapy designs will be employed given the importance of understanding the safety and pharmacokinetics of the novel agent before advancing into add-on trials. Biomarker data can be collected in the absence of anti-amyloid MAB effects; these data are critical to the interpretation of later add-on trials. If there are concerns regarding the potential for pharmacokinetic or pharmacodynamic interactions, with possible safety concerns, a Phase 1b add-on study in the target population may be required.

Combining novel therapies with MABs may offer the best opportunity for additive or synergistic disease slowing. The most efficient design at this stage may be the requirement that all subjects enrolled have been on stable treatment (for a least 6 months of the highest dose) with an anti-amyloid MAB followed by randomization to the novel agent (1 or more doses) or placebo. At this stage, trial emphasis is on safety and tolerability, evaluation of target engagement, and pharmacodynamic effect / biomarker changes for the combination vs MAB alone, while assessing qualitative evidence for directional change on cognitive measures. In these circumstances, the number of participants on anti-amyloid MABs would be small and analyses would be insufficiently powered to allow conclusions regarding enhanced clinical efficacy as an add-on therapy to the anti-amyloid MAB. Study of the directional outcomes of patients with add-on treatment versus monotherapy, the consistency of add-on versus monotherapy differences across outcome measures, the trajectory of monotherapy versus add-on treatment groups, and the effects on biomarkers of the two groups might provide preliminary information on possible additional efficacy of the add-on approach. Data generated from such trials inform the design of larger Phase 2b/3 trials required to establish the added benefit of combination therapy. Acknowledging the potential operational complexity, size and cost of such studies, Table 2 present several clinical trial designs that could be considered for Phase 2. Sponsors should consider the potential benefits of alternate trials designs including Bayesian adaptive approaches such as those used for dose finding in the Phase 2 study of lecanemab in early AD [17].

For development candidates that progress to Phase 3, the safety of add-on therapy to an anti-amyloid MAB should be established by allowing participation of a sufficient number of individuals receiving these therapies or conducting a separate trial involving patients required to be on anti-amyloid treatment. It is anticipated that emerging therapies will be used together in clinical practice and the safety of combinations must be established prior to the end of the Phase 3 program.

To establish superior efficacy of add-on therapy over anti-amyloid MAB treatment alone, a sufficiently well powered trial with participants on anti-amyloid MAB therapy alone compared to an anti-amyloid MAB plus the novel add-on agents would be required. Superiority trials of this type may require prohibitively large numbers of participants. Alternative clinical trial designs relevant to Phase 3 are summarized in Table 2.

As anti-amyloid MABs continue to establish a role in the care of patients with early AD it may be more difficult to conduct monotherapy trials. In global regions where approval has not yet been granted regulatory authorization, Phase 1b/2a monotherapy studies can establish safety, target engagement, pharmacodynamic measures, and initial indications of clinical efficacy to support proof of mechanism/proof of concept [18]. In all global regions, there will be many patients who are not candidates for MABs who may be enrolled in monotherapy trials.

4.9. Clinical outcome measures for add-on therapy trials

Clinical outcomes used in add-on therapy trials are the same as those employed in monotherapy trials. Lecanemab and donanemab used the Clinical Dementia Rating Sum of Boxes (CDR-sb) and the integrated Alzheimer's Disease Rating Scale (iADRS), respectively, as primary outcome measures in Phase 3 trials [1,2]. The Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog), Alzheimer's Disease Composite Score (ADCOMS), and Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for mild cognitive impairment (ADCS-MCI-ADL) comprised the secondary outcomes for the Phase 3 trial of lecanemab. Secondary outcomes in the Phase 3 donanemab trial included the ADAS-cog and ADCS instrumental ADL (ADCS-iADL) scale. Alternatives to these conventionally used outcome measures such as the Neuropsychological Test Battery [19] for cognition or the Amsterdam ADL scale [20] for function can be considered. Presentation of the psychometric properties of novel assessments to regulatory agencies is required before integration into clinical trials.

Noncognitive clinical measures that enhance understanding of the therapeutic benefit of combination therapy are available. Aducanumab trials included the Neuropsychiatric Inventory and showed a drug-placebo difference in favor the active therapy [21]. Measures of quality of life and caregiver burden provide insight into treatment ramifications on caregiver and patient lives as shown in the lecanemab Phase 3 trial [2,22]. Funding and reimbursement decisions may be informed by including resource utilization and health outcome measures in trials [23].

Demonstration of superior cognitive benefit of add-on therapy will require demonstration of slowing beyond that observed in anti-amyloid MAB monotherapy trials (Table 1). Establishing superiority will require large, long Phase 3 trials or agents that have large effect sizes.

4.10. Biomarker outcome measures for add-on therapy trials

Biomarkers, particularly for target engagement, are critical for derisking clinical development programs. AD biomarkers are markedly changed by anti-amyloid MABs making their use difficult for assessment of novel add-on therapies. Establishing the biomarker profile of a novel agent in Phase 2 in the absence of an add-on therapy is a key goal of the development program. This is the principal opportunity to understand the biological impact of the novel therapy as reflected in biomarkers in the absence of simultaneous administration of the anti-amyloid MAB. Informed consent to store samples for later studies will allow interrogation of blood or CSF when new questions arise.

Production of a measurable clinical benefit in clinical trials of anti-amyloid MABs requires reduction of amyloid plaque levels on amyloid PET imaging below 15 to 25 Centiloids. All successful agents produce reductions of this magnitude in plaque burden [9]. In addition to the plaque reduction observed on amyloid PET, the Phase 3 trial of lecanemab demonstrated CSF biomarker changes including an increase in Aβ 1-42, decreased Aβ 1-40, decreased total tau, decreased p-tau 181, and decreased neurogranin. There was no drug-placebo difference in

neurofilament light (NfL). In the same study, the plasma Aβ42/40 ratio decreased and tau 181 and glial fibrillary acidic protein (GFAP) decreased, with no consistent change in NfL [2]. In the donanemab Phase 3 study reductions in plasma p-tau 217 and GFAP were observed. There were no changes in the plasma Aβ42/40 ratio or NfL [24]. Reductions in p-tau 217 and GFAP were significantly correlated with the Centiloid changes in plaque amyloid burden observed on PET.

Target engagement biomarkers for the novel agent provide insight into the pharmacologic or biologic activity of the intervention even in the presence of an anti-amyloid MAB. In addition, reductions in p-tau 181, p-tau 217, or GFAP of greater magnitude or with a different time trajectory than the changes observed following treatment with anti-amyloid MABs monotherapy might provide information about the impact of the novel therapy on the underlying biology of AD [8]. When several biomarkers are collected, review of the profile of biomarker effects may reveal differences between changes produced by the novel agent as add-on and those produced by anti-amyloid MAB monotherapy.

Agents that have effects on biomarkers not known to be affected by anti-amyloid MABs such as markers of synaptic dysfunction in CSF may provide information on the mechanisms of novel agents [25]. Fluorodeoxyglucose (FDG) PET or MRI connectivity studies conducted in concert with the initiation of the add-on therapy might provide useful data [26,27].

4.11. Formulation considerations with add-on therapies

Consideration of patient and care partner burden and convenience is critical to successful introduction of new therapies for AD. Patients receiving treatment with an anti-amyloid MAB will receive their treatment by intravenous infusion or possibly via subcutaneous administration. Frequency of dosing may vary between weekly for some subcutaneous formulations to monthly or twice monthly for intravenous therapies. Intrathecal administration of the anti-tau agent BIIB080 is required every three to six-months. Add-on therapies that do not increase patient and care partner burden include oral treatments or antibody or other therapies that could be administered simultaneously with the anti-amyloid MAB. Intranasal therapies might be considered if consistent dosing can be achieved. Early review of formulation alternatives may facilitate market entry of novel treatments introduced as add-on therapies.

5. Discussion

Anti-amyloid MABs represent a new era in the treatment of AD. As the first DTTs for AD, they represent an important milestone in advancing therapeutics for AD and neurodegenerative disorders. The modest efficacy and narrow population for which these agents are approved set the stage for continuing research to identify more efficacious, safer, more convenient, and more broadly applicable therapies. In some cases, new DTTs may replace current monotherapies and in other cases they will be add-on medications provided to patients receiving anti-amyloid MABs [28]. Clinical trials and drug development programs must anticipate the complexities of including patients on anti-amyloid MABs.

Clinicians have been hesitant in adopting new therapies with unfamiliar monitoring requirements. These circumstances create an opportunity for monotherapy of novel compounds when anti-amyloid MABs are not yet perceived as the required standard of care.

Anti-amyloid MABs require substantial healthcare technology integrated into advanced health care systems for their safe and effective administration. Amyloid confirmation, MRI monitoring, and genotyping are required for use of these agents. Many global health care systems will not meet the resource standards required for integration of these new therapies. In some countries, the necessary resources will be available only in academic or urban environments and available only to selected patients. Unavailability of these agents in some global regions creates a geography for conduct of monotherapy trials for novel agents. Phase 2 trials may be conducted in regions where there is limited availability of anti-amyloid MABs. Add-on therapies to MABs may occur preferentially in Phase 3 programs. Treatments tested and shown to be efficacious in low resource global regions should become available in those countries if approved.

Currently available MABs specifically target amyloid-related targets. Approval of DTTs for non-amyloid therapies relevant to AD will inevitably lead to add-on therapy in clinical practice where clinicians are striving to keep their patients functioning at the highest level for the longest time. For this reason, demonstration of safety of add-on therapy is critical to achieve in development programs prior to marketing. Evidence of efficacy of add-on therapies will require a weight of evidence approach that may include non-clinical studies, early- and late-phase trial observations, and registry and real-world evidence. Superiority of combination therapy over anti-amyloid MAB monotherapy may require large, long trials that may not be feasible. With more robust use of anti-amyloid MABs, electronic medical records and claims data will be a source of real-world observations to help inform effectiveness, safety, adherence, and use in a broader population than those participating in clinical trials [29]. Capture of real-world data in registries such as the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET), the International Registry for Alzheimer's Disease and Other Dementias (InRAD), or other available registries represent a critical information-generating strategy when introducing new DTTs and add-on therapies into clinical practice [30].

6. Summary

Lecanemab and donanemab are increasingly used to treat early AD. Approvals are occurring globally and familiarity with use of these agents is leading to their increased use by clinicians. Management of ARIA in community settings is proving to be feasible and there is increasing confidence in the safety of these agents [31]. Several monoclonal anti-amyloid MABs are in Phase 2 and Phase 3 clinical trials indicating that this therapeutic strategy will continue to be a part of the AD therapeutic landscape. The increasing use of anti-amyloid MABs in clinical practice implies that more patients interested in clinical trials of novel agents will be on treatment with these therapies when they enter trials. Strategies for incorporating patients on MABs into trials must be defined and how best to assess the safety and efficacy of add-on therapy must be understood.

Add-on therapy has unique challenges in terms of the timing of treatment with a novel agent after initiation of the MAB, the impact on measures of clinical and biomarker measures, and the interrogation of safety, tolerability, and convenience of the add-on combination. We suggest that introduction of a novel agent be delayed until the patient has been on the highest dose of the MAB for at least 6 months. This will ensure that most ARIA that may occur with MAB therapy has occurred and will not be misattributed to the novel agent. Clinical measures used in combination trials are the same as those used in monotherapy trials with anti-amyloid MABs or other agents. We suggest that biomarker strategies include a robust collection of biomarkers in Phase 2 monotherapy trials prior to allowing add-on therapy. In add-on trials, use of biomarkers not affected by MABs, identification of target engagement biomarkers unique to the novel agent, and inspection of the response profile of biomarkers may indicate whether the magnitude, timing, or trajectory of response differs from those observed in anti-amyloid MAB monotherapy trials. The biology of AD is complex and optimizing the response to therapy will require add-on therapies to the currently available anti- amyloid MABs. Optimizing patient care requires incorporation of add-on strategies into drug development programs.

CRediT authorship contribution statement

Jeffrey Cummings: Conceptualization, Project administration,

Writing – review & editing, Writing – original draft. **Aaron H Burstein:** Conceptualization, Project administration, Writing – review & editing. **Howard Fillit:** Conceptualization, Project administration, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jeffrey L Cummings reports a relationship with Acadia Pharmaceuticals Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Acumen Pharmaceuticals Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with ALZpath Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Annovis Bio Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Artery Therapeutics Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Axsome Therapeutics Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Biogen Inc that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Biohaven Ltd that includes: consulting or advisory. Jeffrey L Cummings reports a relationship with Bristol-Myers Squibb Company that includes: consulting or advisory. 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