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Special Article

Alzheimer Combination Therapies: Overview and Scenarios

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ABSTRACT

Progress in understanding the complexity of Alzheimer's disease informs the search for combination therapies that can successfully prevent or substantially slow the progression of the disease. Anti-amyloid monoclonal antibodies are the first approved disease targeted therapies; they slow disease progression by approximately 30 %. Building on these agents in add-on therapies is one avenue to designing combination treatments. Development of combination drugs consisting of two or more novel interventions is an alternate pathway for combination treatment development. Combination therapies can involve small molecule drugs, biological agents, devices, stem cells, gene therapies, lifestyle interventions, or cognitive training. Nonclinical assessment of drug combinations may involve animal models or new approach methodologies such as induced pluripotent stem cells or organoids. Phase 1 trials are required to characterize each member of a novel combination. Phase 2 trials may use a 2-by-2 factorial design comparing each drug to placebo and the drug combination. In Phase 3, comparison of the novel combination to standard of care may be sufficient or more complex designs may be required. Targets for combination therapies beyond amyloid-related processes include tau abnormalities, inflammation, neurodegeneration, and co-pathologies such as alpha-synuclein and TDP-43. The choice of combination therapies will depend on the strength of the information regarding the target, biomarkers to guide clinical trials, and a candidate agent with the appropriate mechanism of action. Computational strategies based on network analysis of disease and drugs, validation in non-clinical models, and use of real-world data may facilitate prioritization of candidates for combination treatments.

Combination therapy is the necessary response to recognition that Alzheimer's disease (AD) is a complex multifaceted disorder with a plethora of contributing processes[1,2]. In addition to the core abnormalities of amyloid plaques and neurofibrillary tangles, pathophysiological abnormalities including Inflammation and neurodegeneration as well as co-pathologies such as alpha-synuclein and TAR DNA protein 43 (TDP-43) represent pathologies that contribute to the progression of AD and are potential targets for therapeutic intervention[3].

The need for combination therapy is further amplified by the observation that therapies addressing a single pathology — amyloid plaques — produce 30 % slowing of cognitive decline, leaving 70 % of cognitive decline unaddressed[4,5]. Progress in disease targeted therapies (DTTs) represented by the anti-amyloid monoclonal antibodies (MABs) indicates that intervention in the biological processes of AD is a viable therapeutic endeavor. Similarly, recent observations of antisense oligonucleotides (ASO) reducing RNA transcription of the Microtubule-Associated Protein Tau (MAPT) gene to reduce tau protein levels suggest that tau pathways are vulnerable to therapeutic manipulation[6]. Success in DTT development encourages the search for novel combination and add-on therapies to create more efficacious interventions.

Drug development of DTTs is guided by diagnostic, pharmacodynamic, and safety biomarkers. Biomarkers are increasingly available to guide drug development and to report on the pathophysiological impact of treatment in clinical trials[7,8]. Biomarkers may play a role in a variety of contexts of use including diagnosis, identification of risk, provision of prognostic information, measurement of pharmacodynamic effects, generation of predictive information forecasting benefit or harm, use for monitoring of treatment effects over time, or following the safety of treatment[9].

Progress in understanding the neurobiology and complexity of AD, the success in developing DTTs, the need to amplify the efficacy of current DTTs, and the availability of biomarkers to guide clinical trials combine to provide the foundation for successful development of

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combination therapies.

Key aspects of advancing combinations treatments that may improve the benefical effects on patient cognition and function involve regulatory considerations, impact of anti-amyloid MABs on trial design, novel designs for combination therapies, statistical analyses relevant to clinical trials of combination therapy, operational issues that emerge when administering at least 2 agents to trial participants (e.g., regimen, formulation, etc.), and strategic considerations when agents of the combination are at different levels of development or are being developed by different companies[1].

Here we provide an overview of types of combination treatments and opportunities and challenges for developing combination therapies for AD. We describe formulation issues associated with combination therapy. We discuss clinical trial designs relevant to assessing combination treatment in different phases of drug development. We discuss the effects of combination therapies on biomarkers and the use of biomarkers in drug development programs for combination treatments. We note the challenges in prioritizing drugs for use in novel or add-on combinations. We emphasize combination DTTs, while noting the wide variety of combination interventions that are feasible.

1. Types of combination therapies

There are a variety of types of combination therapies comprised of the simultaneous administration of two or more interventions with the intent of slowing disease progression or improving symptoms[10]. We describe the principal types of combinations and give examples from AD therapeutics or treatments of other neurodegenerative disorders (NDDs) when they are available (Table 1). We note that each type of combination may require a different development pathway or clinical trial design [11]. Combination therapies seek to increase the pharmacodynamic impact of treatment; in some cases, this is done by adding two or more pharmacodynamically active agents, in others it is accomplished by combining agents that reduce peripheral side effects or peripheral metabolism allowing greater entry of the pharmacodynamically active element into the brain. Combinations could be two or more small molecules, two or more biological agents, or some combination of small molecules and biological therapies. Beyond combinations of drugs, combination therapies may involve devices, stem cells, genes, lifestyle, or cognitive training interventions. In 2025 there were 20 trials involving combinations of drugs. This included trials with two pharmacodynamically active agents, trials with one pharmacodynamically active agent and one to reduce peripheral side effects, and trials with one active agent and one to reduce peripheral metabolism[1].

The US Food and Drug Administration (FDA) Distinguishes between "combination products" and combination therapies. Combination products are entities such as a drug-device combination where the device is required for administration of the drug (discussed below). "Combination therapies" refers to two or more agent administered together[12] .

1.1. Combinations of novel agents

Two or more novel agents may be combined in the drug development process to produce outcomes better than those expected with monotherapy. Efficacy of each element of the combination must be demonstrated during the development process for each of them to be marketed as monotherapy in addition to their use in combination therapy. If one agent is to be introduced first followed by add-on of a second novel agent, the sequence will be determined by pharmacologic, biomarker, safety, and operational factors.

Combination treatment might address amyloid beta protein (Aß) _plus tau, tau plus inflammation, tau plus synaptic plasticity, tau plus neuroprotection or other combinations where each agent is expected to contribute to the pharmacodynamic response[13]. Combinations might also address co-pathologies involving the core pathological changes of

Table 1
Types of combination therapies and examples from Alzheimer's disease or other neurodegenerative disorders or proposed combinations.

Type of Combination	Example
Two or more agents in combination; one or more of the elements may be repurposed	Ciprofloxacin and Celecoxib (NCT06185543) to reduce inflammation; Rotigotine + Rivastigmine (NCT06702124) to augment 2 transmitters (dopamine and acetylcholine)
Add-on of a novel agent to an existing therapy such as a monoclonal antibody	DIAN-TU study in which for patients with symptoms, lecanemab is administered for 6 months and then E2814 or placebo is added on (NCT06602258)
Combination products	Subcutaneous lecanemab administered with an autoinjector (NCT03887455)
Sequential combinations	Proposed combination: anti-amyloid monoclonal antibody to reduce amyloid plaque followed by a gamma-secretase modulator to prevent re-accumulation of amyloid plaques
Single agents that have multiple effects	Rasagiline exhibited neuroprotective, anti-inflammatory, and p-tau effects in a Phase 2 trial (NCT02359552); ExPlas (plasma from exercised individuals) (NCT05068830); multiple plasma proteins to enhance synaptic plasticity and promote neuroprotection; proteostasis agents such as buntanetap/ phenserine may exert effects on multiple proteins including Aß, tau, and alpha-synuclein (NCT06709014)
Traditional medications and remedies	Yangxue Qingnao (NCT04780399); Traditional Chinese Medication
Combinations of an active agent and an agent to reduce peripheral side effects	Xanomeline + Trospium (KarXT; Cobenfy®)(NCT05511363); trospium block the peripheral cholinergic side effects of xanomeline
Combination of an active agent and an agent to reduce peripheral metabolism	Dextromethorphan + Bupropion (NCT04947553)(buproprion blocks peripheral metabolism of dextromethorphan by inhibiting CYP2D6; Auvelity®); dextromethorphan plus quinidine (quinidine blocks peripheral metabolism of dextromethorphan; Nuedexta®)
Combination of agents to enhance blood-brain barrier penetration	Trontinemab (gantanerumab + Brainshuttle™)(NCT04639050); the shuttle interacts with the transferrin receptor to allow passage of gantenerumab across the blood-brain barrier
Combination of a monoclonal antibody and an ultrasound device	Magnetic resonance guided focal ultrasound delivery resulted in local increase in removal of Aß plaques attributed to enhanced blood-brain barrier penetration of the antibody (NCT05469009)
Combination of pharmacotherapy and lifestyle modification	MET-FINGERS (NCT05109169); participants at risk for cognitive decline are randomized to FINGERS intervention vs regular health advice; within the FINGERS arm, those at risk for diabetes are randomized to metformin or placebo
Combination of pharmacotherapy and cognitive stimulation	Participants were treated with pharmacotherapy (rivastigmine) and randomized to cognitive stimulation therapy or standard of care. Those receiving cognitive stimulation benefited more than those receiving only rivastigmine and standard of care[50]
Combination of pharmacotherapy and noninvasive brain stimulation	Repetitive transcranial stimulation is combined with cognitive training during the stimulation period to enhance the effects of either therapy when delivered alone (NCT01504958)

AD — Aß or tau — plus alpha-synuclein or TDP-43[14]. Combination therapies could include combining DTTs with novel cognitive enhancing agents, drugs to treat neuropsychiatric symptoms, or sleep-enhancing/diurnal rhythm agents.

Two active agents of a combination may address the same or overlapping targets. COYA 302, for example, is intended to enhance the anti-inflammatory function of regulatory T cells (Tregs) and suppress the inflammation produced by activated monocytes and macrophages. The combination is comprised of low dose interleukin 2 and abatacept and is being developed for subcutaneous administration for patients with NDDs including frontotemporal dementia (FTD) and AD[15]. The therapeutic hypothesis is that the two agents will have additive or synergistic effects by impacting several elements of the complex inflammatory network.

1.2. Add-on combinations

Add-on therapies have a history in treatment development for AD. Donepezil is a cholinesterase inhibitor approved for treatment of mild to moderate and severe AD. Memantine is an N-methyl-D-aspartate antagonist approved for monotherapy or add-on treatment of moderate to severe AD based on a single monotherapy trial followed by an add-on trial to donepezil[16,17]. The two agents have complementary mechanisms and are commonly used together. These trials represent add-on therapies of cognitive enhancing agents, and, in some cases, synergistic effects may be observed[18]. Nearly all agents in current clinical trials allow the inclusion of participants receiving stable (3–4 months) background standard of care therapy with cholinesterase inhibitors and/or memantine. In such cases the requirement for stable background therapy represents the definition of the control group (e.g., donepezil + placebo) against which the new combination (e.g., donepezil + novel agent).

Namzaric^{R} is a fixed combination of 10 mg of donepezil and 28 mg of memantine. This is a combination of repurposed agents. The efficacy of the donepezil compared to placebo was established in monotherapy trials. In the Namzaric^{R} development program, a single trial of participants on stable doses of 10 mg daily of donepezil were randomized to an add-on of 28 mg of memantine or placebo. Superior efficacy of the combination over donepezil monotherapy was demonstrated and the combination treatment was approved[19]. This is an example of an add-on strategy leading to approved fixed combination based on a single add-on trial.

Combinations of a novel and an approved cognition enhancing agent represent another approach to add-on therapy. Noradrenergic agents may amplify the effects of cholinesterase inhibitors, and one trial design randomizes patients receiving donepezil (a cholinesterase inhibitor) to guanfacine (an α2A adrenergic receptor agonist) or placebo to explore the effects of the combination on cognition enhancement[20].

Add-on combinations will become increasingly common as novel agents are added on to the therapeutic regimen of patients receiving treatment with an anti-amyloid MAB. Lecanemab and donanemab are available by prescription in the US and many other countries. They are indicated for patients with early AD (mild cognitive impairment (MCI) due to AD or early AD dementia) with confirmed amyloid pathology, no excessive cerebrovascular disease as established by magnetic resonance imaging (MRI), and no contraindications to MAB use.

Anti-amyloid MABs produce measurable slowing on global, cognitive, and functional outcome measures of 25 to 40 %[4,5]. Add-on therapies offer the opportunity to further slow disease progression and extend more intact cognitive function for longer periods. An add-on therapy trial would include only patients who met MAB treatment criteria when the MAB therapy was initiated. MAB therapy patients will typically have early AD, be known to be amyloid positive at the time of initiation of the MAB and have limited evidence of cerebrovascular disease. The add-on agent might be developed for monotherapy in patients outside of this narrowly defined range. Anti-amyloid MABs are known to produce amyloid related imaging abnormalities (ARIA) in the first few months of treatment initiation. Most ARIA events are asymptomatic, but a few produce symptoms, and they rarely cause severe injury and death[21,22]. The timing of an add-on intervention must take ARIA into account or risk having ARIA attributed to the novel agent. If the add-on agent has a well-known safety profile without ARIA (i.e., repurposed drugs), then simultaneous initiation of combination therapy can be considered. Anti-amyloid MABs are administered intravenously monthly (donanemab) or twice monthly (lecanemab for the first 18 months) then monthly and the regimen and formulation of a novel add-on must be compatible with adherence to this treatment schedule. Anti-amyloid MAB therapy produces profound changes in AD biomarkers including marked reduction in Aß plaque on amyloid positron emission tomography (PET) and decreased plasma p-tau 181, p-tau 217, and glial fibrillary acidic protein (GFAP)[5,23]. The biomarker profile of the novel agent must be established in monotherapy trials to facilitate interpretation of biomarker changes in the add-on setting. Some patients on MABs do not have complete amyloid clearance and reducing plaque burden to 25 Centiloids or less could be an indication of additional therapeutic response from a co-administered agent. In addition, donanemab is plaque-directed and add-on therapy with agents targeting other species of amyloid may prolong the effects of donanemab or improve the efficacy. An open label lead-in with reduction of plaque amyloid followed by the add-on agent or placebo is a design opportunity to address this type of question. Target engagement biomarkers for the novel treatment might distinguish biomarker effects from those of MABs.

The Dominantly Inherited Alzheimer's Disease Network Treatment Unit (DIAN-TU) and the Alzheimer Tau Platform are platform trials in which novel agents may be added to anti-amyloid MAB regimens (DIAN-TU) or anti-amyloid MABs may be added on to experimental agents (Alzheimer Tau Platform)[24,25]. These platform trials add valuable information regarding simultaneous or staggered introduction of therapies and involvement of participants with and without cognitive impairment.

Combinations to be considered as add-ons to anti-amyloid MABs include anti-tau agents, anti-inflammatory drugs, and synaptic plasticity/neuroprotective agents. Add-on therapies could involve MABs directed at tau aggregates, alpha-synuclein, or TDP-43 as well as other central nervous system (CNS) targets relevant to AD[26,27]. Additionally, add-on treatments intended to reduce the risk of ARIA and potentially expand the population of patients eligible for MABs may represent opportunities for exploration.

1.3. Combination products

The FDA defines a "combination product" as: 1) a product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are combined or mixed and produced as a single entity; 2) two or more separate products packaged together in a single package and comprised of a drug and device, a device and biological product, or a biological and drug; 3) a drug, device, or biological product packaged separately that is intended for use only with an approved specified drug, device, or biological product; or 4) any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product[28].

Currently, lecanemab is being developed for subcutaneous administration with an autoinjector. This combination of drug and device represents a combination product being assessed for AD therapeutics. Similar approaches for other therapies are anticipated.

1.4. Sequential combinations

Sequential combinations are treatment regimens in which one

specified drug is used and stopped and is then followed by another prespecified drug. For example, an anti-amyloid MAB may be stopped when Aß plaques are no longer detectable by amyloid PET. To extend the period of treatment-related amyloid clearance (TRAC) in the brain, a gamma secretase modulator might be used as a follow up therapy to prevent plaque re-accumulation[29]. This regimen represents an example of a sequential combination aimed at a single therapeutic target, Aß plaques. Sequential treatments could also be directed to non-plaque amyloid species such a protofibrils or oligomers.

1.5. Single agents that have multiple effects

Drugs that are posited to have effects on multiple key nodes of the AD pathophysiological network might be considered as "combinations in a pill". In experimental settings, buntanetap, for example, reduces amyloid precursor protein, tau, alpha-synuclein, and other toxic proteins by suppressing mRNA translation[30]. Interference with proteostasis and the aggregation of multiple types of protein might suppress common pathologies and co-pathologies in AD and be applicable across NDDs.

In a review of the 2025AD drug development pipeline, 4 agents were identified as multi-targeted molecules[31].

1.6. Traditional medications and remedies

Indigenous culture medications such as Indian, Korean, and Chinese traditional medications as well as medications from other healing traditions are usually combinations of herbs or other plants thought to have medicinal effects and represent combination therapies[32]. Yangxue Qingnao is a Chinese traditional medication comprised of an herbal mixture and shown in animal models and preliminary studies in humans to enhance brain circulation and increase Aß degradation in the liver [33]. Yangxue Qingnao is being assessed in a Phase 2 study of patient with mild to moderate AD (NCT04780399).

Bu-Wang San is a Chinese traditional medication that has been assessed for potential multimodal impact[34]. Multiplatform metabolomic studies indicated a primary impact on amino sugar and nucleotide sugar metabolism, as well as on glycine, serine, and threonine metabolic pathways.

Marketing of traditional medications often preceded the development of modern regulatory standards, and not all vendors have advanced quality control standards to ensure product identity, purity, composition, batch consistency, and safety[35,36]. Awareness of these issues is important if traditional medications are being taken by patients who may add on novel therapies to current regimens or participate in trials of experimental agents.

1.7. Combinations of an active agent and a drug to reduce peripheral metabolism of the active agent

One means of optimizing the pharmacodynamic effect of an active agent is to use a combination of approach in which one element of the combination suppresses the peripheral metabolism of the active ingredient. This allows higher peripheral levels and an enhanced ability of the active agent to cross the blood brain barrier (BBB) to achieve greater central effects. Dextromethorphan, for example, a centrally active N-methyl-D-aspartate antagonist and sigma-1 agonist, is peripherally metabolized by cytochrome P450 (CYP) 2D6 liver enzymes. Co-administration of a CYP 2D6 inhibitor allows higher peripheral and higher central levels. The combination of dextromethorphan and quinidine capitalizes on the 2D6 inhibitory properties of quinidine to achieve higher central dextromethorphan levels. This combination is approved, as Nuedexta®, for the treatment of pseudobulbar affect[37]. This combination was also used in preliminary studies to reduce agitation in AD [38].

AXS-05 is a combination of dextromethorphan with bupropion. Bupropion is a CYP 2D6 inhibitor that leads to elevated peripheral and central levels of dextromethorphan. The combination of bupropion and dextromethorphan is approved (as Auvelity ®) for the treatment of major depression and is being assessed for treatment of agitation associated with AD dementia[39].

The combination of two agents, one with central activity and one intended to reduce the peripheral metabolism of the active agent, may have a safety profile that combines adverse events arising with each agent. Vigilance when developing this kind of combination is warranted. If the adverse event profile of each agent is known, checklists of treatment emergent adverse events of special interest may be used for side effect characterization during development.

With this type of combination, co-development of the two agents meets the Food and Drug Administration (FDA) criteria for co-development. Co-development requires that the combination is intended to treat a serious disease or condition; there is a compelling rationale for use of the combination; preliminary clinical data support use of the combination; and there is a compelling reason that the agents cannot be developed individually for this indication[40]. The FDA co-development guidance applies to two or more unmarketed compounds and does not specifically address the development of repurposed agents.

1.8. Combinations of an active agent and a drug to reduce peripheral side effects of the active agent

Another type of combination directed to optimizing central effects of an active agent is to co-administer an agent that blocks peripheral side effects that may accompany treatment. For example, the M1M4 agonist xanomeline is associated with peripheral cholinergic effects. In the development program of Cobenfy®, trospium was co-administered to block the peripheral cholinergic effects of xanomeline, allowing increased central exposures to be achieved with acceptable side effects. This combination is approved for treatment of adult with schizophrenia and is in clinical trials for treatment of AD-related psychosis based on observations suggesting that the xanomeline reduces psychotic and agitated behavior in AD[41].

Combination agents of this type may exhibit side effects associated with both agents.

Since these agents are not intended to be used alone for the indication for which they are being developed, FDA guidance for co-development or two or more unmarketed investigational drugs defines the expectations of the FDA for the development program, although this guidance applies to novel agents and not specifically to new uses of repurposed agents[40].

1.9. Combination agents designed to enhance blood-brain barrier penetration

Many drugs are excluded from the CNS environment by the BBB. Barrier mechanisms exclude large molecules (greater than 500 Daltons), hydrophilic drugs, drugs that are metabolized by CYP450 enzymes found in endothelial cells and surrounding astrocytes, and drugs excluded by specific efflux transporters such as P-glycoprotein (P-gp) [42,43]. Combining a large molecule with a receptor mediated BBB transport mechanism may allow entry of agents typically excluded from the brain such as MABs.

Trontinemab is a bispecific fusion molecule comprised of a "cargo" monoclonal antibody (previously being developed as gantenerumab) and a transferrin receptor ligand that interacts with the receptor to allow the MAB to be transported through the BBB via transcytosis and released into the CNS[44]. Trontinemab circulating in the bloodstream binds via the Brainshuttle® to the transferrin receptor on the luminal surface of endothelial cells that comprise the BBB. Receptor binding leads to endocytosis of gantenerumab and release through exocytosis into the intracerebral space. This results in better BBB penetration with higher brain concentrations and lower plasma concentrations. Brain-Transporter™ similarly uses the transferrin receptor to enhance BBB

penetration of MABs. Transferrin receptors are not confined to the brain and vigilance for off target effects is warranted with this approach. Trontinemab is in current clinical trials as a DTT for treatment of AD. If successful, the transferrin receptor technology may be used to enhance brain entry of treatments for non-AD NDDs.

1.10. Combination pharmacotherapy and focused ultrasound

Temporary opening of the BBB can be achieved with focused ultrasound. This technology is being explored in a variety of therapeutic areas including AD, Parkinson's disease, and glioblastoma[45]. The ability of focused ultrasound to temporarily open the BBB creates an opportunity for a drug-device combination with increased CNS penetration facilitated by ultrasound treatment. In a preliminary study of patients with AD receiving aducanumab, focused ultrasound to one hemisphere was associated with greater amyloid plaque removal from that hemisphere compared to the homologous region in the contralateral hemisphere[46]. This study suggests that temporary opening of the BBB by focused ultrasound allowed greater entry of the therapeutic anti-amyloid MAB and greater removal of the amyloid plaque drug target. It is important to demonstrate the safety of long-term use of focused ultrasound as a drug-device combination for the approach to be widely implemented.

1.11. Combination pharmacotherapy and lifestyle intervention

Increasing evidence suggests that lifestyle interventions including physical exercise, healthy nutrition, and control of cardio-cerebrovascular risk factors can improve brain health and delay the onset or slow the progression of cognitive decline[47]. These beneficial activities can be combined with any therapeutic intervention including cognitive enhancing agents, anti-amyloid MABs, or emerging therapies.

One example of a combined lifestyle and pharmacotherapy intervention is the MET-FINGERS study[48]. In this clinical trial, patients are randomized to the FINGERS lifestyle intervention or usual care. Within the FINGERS arm of the trial, those patients for whom metformin is indicated (have risk indicators of type 2 diabetes) are re-randomized to active treatment with metformin or placebo. This design will allow study of the additive or synergistic effects of lifestyle changes and metformin therapy.

1.12. Pharmacotherapy plus cognitive stimulation combinations

Cognitive stimulation such as memory training, decision rehearsal, deficit compensation, and real work practice can benefit patients with MCI or early AD dementia[49]. A combination of cognitive stimulation with pharmacotherapy may enhance the beneficial response. One trial included treating all participants with rivastigmine and randomizing them to either standard of care plus rivastigmine treatment or cognitive stimulation plus rivastigmine. The cognitive intervention included at least 90 min per week of activities directed by a neuropsychologist for a 2-month interval. Patients receiving the combination therapy had significantly better outcomes on cognitive, mood, and functional measures[50].

1.13. Combination noninvasive brain stimulation and cognitive training

Noninvasive brain stimulation plus cognitive training represents an opportunity for device-cognitive training combination therapy. These studies combine regular noninvasive brain stimulation with cognitive training administered simultaneously with the device application. Preliminary evidence suggests a benefit in amnestic MCI and AD dementia [51,52] although not all studies of this combination have shown cognitive benefits[53].

2. Formulations of combination therapies

Considerations of drug formulation may become more complex in the development of combinations compared to monotherapy drug delivery. Patient and caregiver burden associated with combination therapy regimens can be mitigated by considering the administration and adherence requirements for all medications being prescribed for the patient. Taking one pill with two elements or two pills once or twice a day is a convenient mode of administration. Packaging of oral medications must consider the fact that individuals with AD or caring for someone with AD and who are opening bottles of tablets or peeling blister packs to access medications will likely be older may encounter difficulties if they have arthritis, neuropathy, or other physical limitations. Smart pill dispensers, autoinjectors, digital adherence monitors, smartphone reminders, and telehealth availability may reduce the burden of monotherapy and combination therapy on patients and caregivers. More complex regimens such as intravenous infusions once or twice monthly, intrathecal administrations, subcutaneous injections, intramuscular injections, and intranasal administration could adversely affect patient acceptance and adherence. Approaches for promoting patient convenience, encouraging adherence, and assessing acceptability of combination formulations may assist in advancing combination drugs from trials to clinical use. If the patient is on an existing agent such as a MAB and a second agent is to be added, planning for convenience and adherence will facilitate successful treatment initiation. MABs are currently administered intravenously; subcutaneous formulations are being investigated. The FDA has developed human factors guidance for combination product development addressing issues of convenience, safety, and risk[54].

3. Combination therapy development

Here we consider aspects of the development of combination therapies. Recommendations are made based on published studies, mechanistic information, and experience with other development programs. Judgments about the best possible trial design and development program will vary depending on the combination of molecules of interest, the information needed to advance the program, and guidance from regulatory authorities.

3.1. Non-clinical studies

Assessment of combination treatments can begin in the non-clinical phase of development with studies in animal models of AD or New Approach Methodologies (NAMs) that model aspects of human AD (this initial step is shown in Figures 1-4). The FDA Road Map to Reducing Animal Testing in Preclinical Safety Studies suggests that developers may rely increasingly on NAMs to provide guidance for safety and first-in-human exposures[55]. Animal models of AD have provided systems in which to study the pharmacodynamic impact of treatment on specific molecular pathways that can be reproduced in transgenic animals. These model systems do not recapitulate the complexity of human AD and do not predict trial participant responses to novel medications[56]. Relatively few non-clinical experiments involving combination therapy for AD have been reported. Tested combinations have not succeeded in being advanced to human studies[57,58]. Animal models have contributed importantly to observations regarding pharmacologic toxicity as well as dosing strategies for Phase 1 studies. Non-clinical animal models may provide insight into add-on therapies where rodents receiving anti-amyloid MABs could be exposed to a novel and-on therapy or placebo.

When both elements of the combination are new molecular entities (NMEs), FDA encourages a complete non-clinical evaluation of each NME (e.g., genetic toxicology; pharmacology; safety pharmacology; pharmacokinetics (PK); absorption, distribution, metabolism, excretion (ADME); toxicity; reproductive and developmental toxicity;

carcinogenicity). The agency also recommends the assessment of the combination in non-clinical studies. If the two drugs or biologics will be used only in combination, it is possible that it may be sufficient to conduct toxicology studies only on the combination without assessing each NME independently[59]. Animal studies of efficacy of the combination are not generally needed for the novel agents if they are intended for monotherapy and possible add-on use.

When an NME is to be used in combination with a previously marketed drug or biologic as in the case of add-on therapy with anti-amyloid MABs, the FDA recommends that non-clinical studies be conducted on the NME. Such studies will already have been completed for the previously marketed compound. In chronic conditions such as AD, the FDA recommends that a sponsor conduct a bridging study of up to 90 days with the combination therapy in the most appropriate species[59]. As noted with combinations of two or more novel agents, animal studies of efficacy of the combination are not expected. The final details of the planned non-clinical studies should be reviewed with the FDA or other regulatory agencies to ensure their appropriateness[60].

If one of the agents in the combination is repurposed, electronic medical records (eMRs) can be reviewed to determine if pharmacoepidemiologic agent supports clinical efficacy by showing a decreased incidence in those exposed to the agent compared to those on other agents given for similar periods of time for the same indication[61]. In some cases, trial emulation may be possible with matching of exposed and unexposed groups to assess an outcome that is trial-relevant[62].

3.2. Phase 1 of a combination therapy development program

Combination therapy may pursue a co-development program where the drugs will always be used together and there is a compelling reason that the drugs cannot be developed independently[40]. Combination therapies can also be studied in programs where each efficacious agent may eventually be used independently, and the sponsor is interested in determining the benefit of the proposed combination for efficacy, safety, or commercial purposes.

Phase 1 of a program focused on development of two agents that may eventually be used independently as well as the combination of these two agents will be characterized by standard assessments expected in first-in-human studies including determination of the maximum tolerated dose (MTD), the nature of the dose limiting toxicity (DLT), and PK parameters. Determination of a dose-response for measures such as biomarkers will provide important guidance for dosing in Phase 2. The effects of food on PK characteristics and possible drug interactions should be determined for each agent. CNS penetration should be assessed and the plasma: cerebrospinal fluid (CSF) ratio determined. In most cases, if small molecules are being developed, participants are healthy volunteers. If one or more of the agents being studied is a biologic such as a MAB, trial participants may have AD.

If one agent of the combination is marketed and an add-on approach is anticipated, Phase 1 will have been completed for the marketed agent and Phase1 can focus on the novel agent.

Studies of the drug combination should be pursued in Phase 1 if drug interactions or additive or synergistic toxicities are anticipated[12]. If there suspected interactions or additive toxicity, combination studies will be required whether both agents are novel, or one is marketed and one novel.

Open label assessments of combination therapies to build confidence in safety and collect directional efficacy information may be considered in Phase 1b studies. This course was taken in the SToMP-AD program assessing the combination of dasatinib and quercetin for treatment of AD [63]. An important learning from this trial and a demonstration of the importance of preliminary studies of this type was that quercetin was undetectable in CSF suggesting that it was not contributing to the potential efficacy of the senolytic combination[64].

3.3. Phase 2 of a combination therapy development program

A 2-by-2 factorial study with four arms comprised of drug A, drug B, the combination AB, and placebo is a preferred Phase 2 design (Figure 3). This design allows exploration of the contribution of each drug to the efficacy of the combination treatment, facilitates assessment of the efficacy and safety of each of the component drugs, and provides insight into any drug interactions or additive toxicity. Early assessment of the combination has an advantage for program or element termination if the combination has no effect or if the combination effect is not greater than one of the elements. If the combination is of an add-on therapy to a marketed agent such as an anti-amyloid MAB, the combination must perform better than the anti-amyloid MAB by itself for the novel therapy to warrant continued development. In the design and reporting of trials with factorial designs, the reasons for using the factorial design, the justification of the agents included, the main comparisons to be analyzed, and the anticipated interaction effects should be specified[65].

A trial of vascular cognitive impairment proposed a 2-by-2 factorial design of isosorbide mononitrate that augments the phosphodiesterase 5 (PDE5)-inhibitor pathway, and cilostazol, a PDE3 inhibitor that enhances the prostacyclin-cyclic adenosine monophosphate pathway. Both these pathways modulate endothelial function and combination therapy is hypothesized to improve cognition in patients with vascular dementia. These are repurposed agents approved for treatment of vascular diseases; have no known interactions; and have adverse event profiles that support their safe use in combination[66]. The design planned 100 patients per arm with feasibility and safety being the primary outcomes. Data on death, vascular events, and cognition are collected.

An adaptive trial design that modifies the factorial approach can be used to determine if the single agents have less activity than the combination. If the individual agents fail to show efficacy but the combination is efficacious, development of the individual agents can be suspended and development can concentrate on the combination treatment. This outcome can occur if the interaction of the contributing agents is synergistic rather than additive. If either agent performs like the combination, development of the combination therapy may be unnecessary. Adaptive designs may save time and require fewer participants to guide development decisions[12,67].

A "fast fail" strategy may be desirable in some circumstances. For novel combinations, the combination would be compared with placebo, possibly with biomarker readouts (Fig. 1). If there is no drug placebo difference, the program can be stopped or substantially reconsidered. An absence of effect of the combination suggests an absence of effect of either agent unless the agents are somehow antagonistic. If a drug-placebo difference is observed, further testing of A and B is warranted to determine if one or both are responsible for the observed efficacy. This approach was used for the development of COVID therapies, where accelerating testing of combinations allowed the greatest chance of discovering efficacy without waiting for the conclusion of monotherapy trials[68]. For add-on therapy, the" fast fail" approach would compare combination therapy to the standard of care (e.g., treatment with an anti-amyloid MAB only) (Fig. 2). If the novel agent shows no effect beyond that observed with the MAB, the program can be stopped or reconsidered (e.g., is the dose optimized). If the add-on is superior to the MAB-only arm, then further development of the novel agent is warranted.

Phase 2 decisions may depend primarily on the biomarker outcomes observed in both monotherapy and combination therapy trials. Knowing the biomarker outcome profile of each agent of a combination is the basis for interpreting the biomarker changes observed in the combination therapy setting. Assessment of clinical outcomes in Phase 2 may depend on effect size calculations, consistency across measures, directionality and magnitude of response without necessarily achieving a conventional threshold of statistical significance[69].

Determination of dosing of a combination builds on information

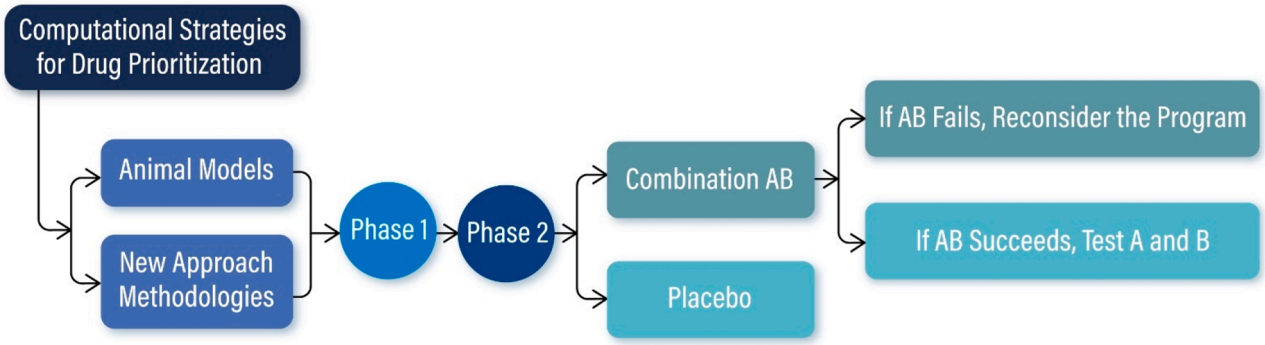

Fig. 1. "Fast fail" approach for novel combination with advancing of the novel agents only the novel combination performs better than placebo.

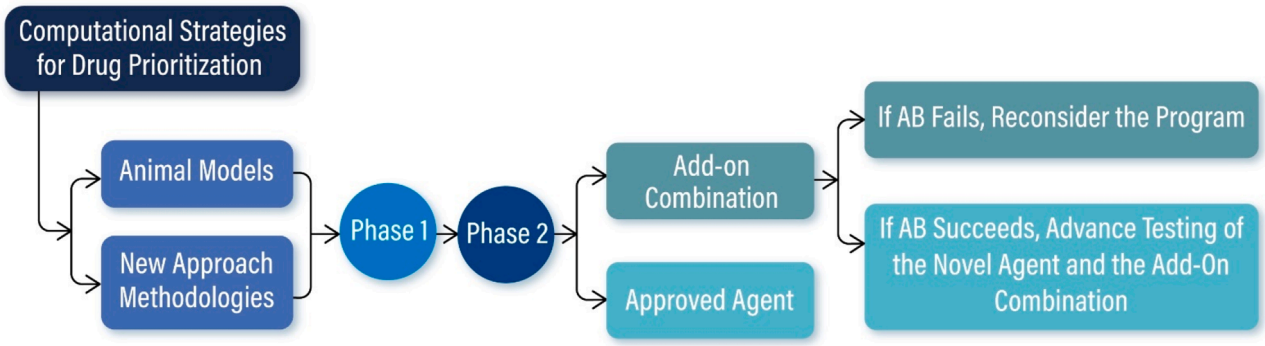

Fig. 2. "Fast fail" approach for add-on combination with advancing of the novel agent only if it succeeds in performing better than approved agent without the novel agent.

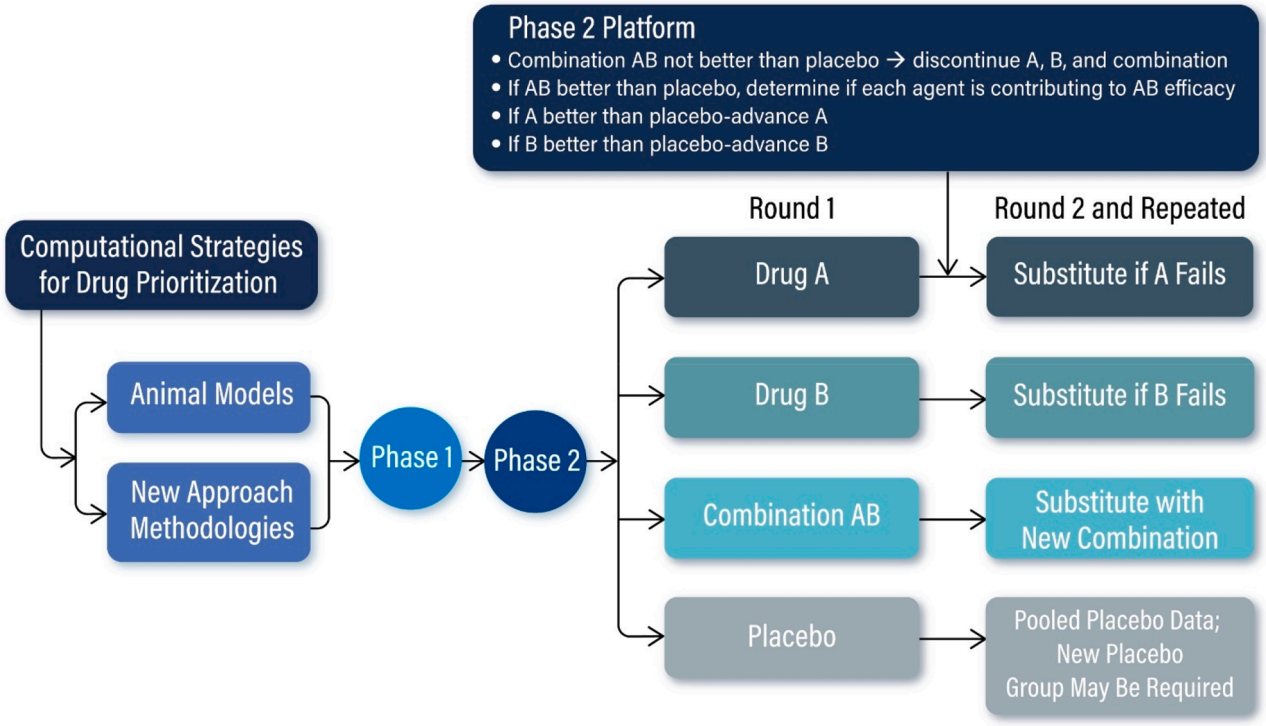

Fig. 3. Factorial 2 × 2 combination platform design with Bayesian analysis and progression to 2nd round agents and combinations if the first candidates and candidate combinations do not show efficacy.

derived in Phase 1 regarding escalating doses of each agent in the combination. Assessment of multiple dose combinations may be required to establish an optimal dose or doses for combination drug testing in Phase 3. Doses of combination treatments may be lower than those required for monotherapy of the individual agents if synergistic efficacy is demonstrated. Such combinations may have less toxicity than monotherapy alone.

3.4. Phase 3 of a combination therapy development program

Biomarkers have a key role in Phase 2 and may inform the decision to progress a compound to Phase 3. In Phase 3 programs, demonstration of clinical efficacy will be required for drug approval. Exceptions might include situations where biomarkers can inform regulatory decisions such as in prevention trials or in accelerated approval.

The design of Phase 3 clinical trials will depend on information derived from Phase 2 and the nature of any remaining questions regarding efficacy and safety of novel agents or the combination. If Phase 2 trials demonstrate the contribution of each novel agent or the contribution of a novel agent as an add-on to standard of care such as an anti-amyloid MAB, then Phase 3 may be a two-arm study comprised of a combination of the novel agent and the anti-amyloid MAB compared to the anti-amyloid MAB by itself. This design would establish the efficacy of the combination and of the contribution of the novel agent to the combination[12].

If substantial questions remain after Phase 2 regarding a novel combination, a 2-by-2 factorial design may be required[70] (Fig. 3). Adaptive modifications of the factorial design may be applicable. A three-arm design comparing drug A and drug B to the combination AB may be appropriate in some circumstances (Fig. 4). If the combination AB is superior to drug A, then drug B must be contributing, and if the combination AB is superior to drug B, then drug A must be contributing [12]. Other types of factorial designs such as a 2-by-2-by-2 where two dose levels of each agent are assessed or factorial designs allowing three interventions to be studied can be considered. Fractional and nested factorial designs can be used when they best meet the needs of the development program[71].

Other designs may be possible and will be negotiated with the FDA or other regulatory agencies prior to trial initiation[60].

3.5. Analytic and planning strategies for combination trials

There are analytic and planning challenges unique to combination therapies. For example, adverse events may now occur from two or more therapies included in the combination therapy, and this may increase attrition rates. Prediction of attrition and adjustment of sample size will be important preemptive strategies to preserve the power of analyses.

Drug interactions must be anticipated in combination trials. Combinations therapy therapies may show synergistic effects, additive effects, or antagonistic effects. At the non-clinical level (in vitro or in vivo) these can be experimentally characterized allowing simulations of human data and analytical planning for combination trials[72].

Clinical trial designs (discussed above), clinical observations collected in the trial, and biomarkers all contribute to the weight of evidence that will determine whether an agent should be progressed, stopped, or directed to trials where critical missing data can be generated. Pre-specification of decision rules based on the sponsor's model of AD and expected biomarker and clinical outcomes gives increased credibility to the conclusions drawn from the trial and the derived action plan. Bayesian adaptive designs may offer advantages in combination trials where there are uncertainties in terms of responsive population, dose, or best outcome. Adaptive designs require greater pre-specification but allow adjustment of key trial features based on data collected during the trial[73].

4. Platform trial designs for combination therapies

Platform trials are governed by a master protocol that allows for the evaluation of multiple therapies that enter the platform and may matriculate to further trials or be discontinued based on the trial data collected (Figures 3 and 4). Platform trials have operational efficiencies such as a standing network of participating sites, shared placebo data, and seamless progression for testing one agent or combination to another. Data on novel biomarkers and clinical outcomes across a variety of trials and types of interventions can be accrued. Trial learnings are incorporated into trial decisions as the trial proceeds. The flexibility of platform trials requires extensive pre-trial specification of trial operations. Analytic approaches and decision rules must be prospectively determined. Trial simulations may be used to explore the likely outcomes of trials using different types of decision rules[74]. The DIAN-TU and the Alzheimer Tau Platform are examples of applying the platform approach to the development of combination therapies[24,25].

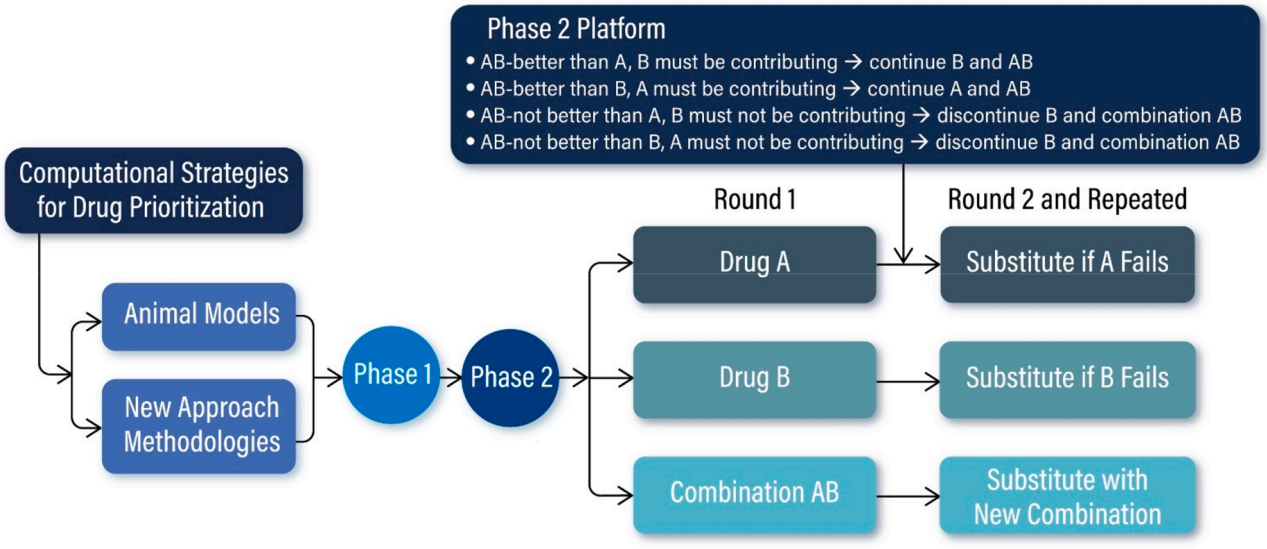

Fig. 4. Three arm combination therapy platform design comparing each drug to the comparison to determine if the comparison is superior to each drug alone and progression to substitute agents if the original candidates do not show efficacy.

5. Biomarkers in clinical trials of combination agents

Biomarkers guide clinical trial decision making and have become a key aspect of successful drug development[9,75]. The FDA-NIH Biomarker Work Group has defined the context of use for biomarkers in clinical trials[76]. The specified roles include diagnosis, risk determination, prognostic forecasting, pharmacodynamic response, monitoring, benefit or harm prediction, and safety. Table 2 shows each of the contexts of use and the role they may play in trials of combination therapies.

In AD clinical trials, diagnostic biomarkers detect or confirm the presence of AD. Confirmation of the presence of amyloid pathology with amyloid PET, CSF AD signature studies, or plasma p-tau 217 are used to establish the diagnosis of AD in both monotherapy trials and trials for combination treatments. Conduct of trials for treatments of AD, monotherapy or combination treatments, should confirm the diagnosis of AD as a requirement for trial participation.

Risk biomarkers may differ in monotherapy and combination therapy trials if one of the disease targets influences the risk for AD. For example, diabetes is a risk factor for AD and a combination containing a drug repurposed from the treatment of diabetes might perform differently in a population enriched for this risk state.

Prognostic biomarkers may assist in identifying populations that are more likely to decline during a trial, optimizing the opportunity to observe a drug-placebo difference. Higher levels of p-tau 217 are associated with a greater likelihood of progression to AD dementia in individuals with MCI due to AD[77].

Two types of pharmacodynamic response biomarkers are of value in AD clinical trials. Target engagement biomarkers measure the degree to which the drug interacts with the pharmacologic or mechanistic target. For example, anti-amyloid MABs are directed at fibrillar plaque amyloid detected by amyloid PET. Target engagement with reduction in plaque burden is reflected by diminished plaque burden revealed by this imaging biomarker. Target engagement biomarkers that are unique to each member of a combination therapy would be particularly valuable to establish the independent biological effects of the combination elements.

Disease impact pharmacodynamic biomarkers report on the degree to which the therapy changes the underlying biology of the disease. For example, removal of amyloid plaque is accompanied by changes in downstream biomarkers including p-tau 217, GFAP, and neurogranin[4,5,78]. The importance of these biomarker changes is supported by their relationship to slowing of the progressive decline of AD. In trials of combination therapies, it may be difficult to discern the independent impact of each agent on biomarkers if they have similar downstream effects. The impact of the combination on the timing, trajectory, or magnitude of response may be informative if these parameters differ from that observed in trials for each of the contributing agents of the combination.

There are few predictive biomarkers for AD clinical trials. The presence of the apolipoprotein E ε4 (*APOE*4) gene predicts an increased risk of ARIA. In studies of donanemab, high levels of neurofibrillary tangles observed on tau PET predicted a failure of response to the anti-amyloid MAB[4]. As more predictive biomarkers are discovered, they may have an increasingly important role in trials of combination therapies.

Monitoring biomarkers are collected serially to determine the effects of treatment. Plasma biomarkers lend themselves to this context of use. In AD trials of anti-amyloid MABs, serial measures of p-tau 217, p-tau 181, Aß 42/40, and GFAP have proven to be useful in monitoring the therapeutic response[5,23,78]. Serial measurement of any biomarker that is uniquely or disproportionately related to the impact of each agent in the combination will be helpful in determining the contribution of the component aspects of the combination therapy.

Safety biomarkers include MRI for the detection of ARIA in trials of anti-amyloid MABs as well as blood tests monitoring for drug induced liver injury (DILI), treatment-related cardiac irregularities, or other laboratory abnormalities[79]. MRI may play a key role in combination trials that include anti- amyloid MABs. Safety biomarkers may help understand adverse events associated with each element of the combination. ARIA occurring in patients on anti-amyloid MABs are most likely to be due to the MAB, but ARIA can occur spontaneously in patients with cerebral amyloid angiopathy (CAA) and rarely occurs in response to other types of treatment[80]. Similarly, monitoring liver function tests will be helpful, particularly if liver abnormalities have been observed with one of the agents in preparatory monotherapy trials.

Biomarker-based analytic and trial design strategies can be used to answer questions central to drug development. Populations can be stratified based on biomarkers to allow pre-specified analyses of biomarker subgroups in a trial (e.g., *APOE4* carriers vs noncarriers; those with higher levels of inflammatory markers at baseline compared to those with lower levels; those with higher vs lower levels of tau as demonstrated on tau PET at baseline). Prognostic factors may be used to enrich populations to ensure decline in the placebo group (e.g., p-tau 217, tau PET)[81,82]. Biomarkers might be used for interim analyses of early-stage trials to assess target engagement, adjust sample sizes, or declare futility if no or little biomarker change confidently predicts an absence of potential clinical benefit. Pharmacokinetic/pharmacodynamic modeling of biomarkers may inform understanding of treatment effects on biomarkers and relationships among biomarkers in combination treatments trials[83].

Table 2
Context of use of biomarkers in combination and add-on trials.

Context of Use	Combination and Add-on Therapy Trials
Diagnosis	Diagnostic standards will be similar or identical for monotherapy and combination therapy trials
Risk	Might differ from monotherapy trials if the add-on agent or novel combination has potential impact based on the specific indicator of risk (e.g., the presence of diabetes in an AD population)
Prognosis	Prognostic biomarkers might differ in combination trials from monotherapy trials if the members of the combination have differential impacts on populations on different disease trajectories
Pharmacodynamic: target engagement	Target engagement biomarkers would be of use for all members of a combination therapy to provide insight into the pharmacological impact of each agent
Pharmacodynamic: disease impact	Biomarkers of disease impact may differ depending on the targeted processes of the members of the combination
Monitoring	Monitoring biomarkers may differ in combination trials and monotherapy trials if a biomarker of disease impact differs for the combination therapy compared to immunotherapy approach
Predictive	Predictive biomarkers of efficacy may differ when combination therapies address multiple biologies compared to a single biology addressed by monotherapy. Predictive safety biomarkers may differ for a combination with multiple components compared to monotherapy
Safety	Safety biomarkers may differ for monotherapies and combination therapies. Components of combination therapies might have corresponding safety liabilities involving liver dysfunction, ARIA, etc.

APOE4 - apolipoprotein E ε 4; ARIA - amyloid related imaging abnormalities.

6. Choosing agents for combination therapies

It is a challenge to decide how best to construct a combination therapy whether two novel interventions are being considered or an add-on therapy with a novel agent and an anti-amyloid MAB is planned. AD is a complex disorder with core features including amyloid and tau

protein abnormalities, non-specific pathophysiological changes that accompany the core features including inflammation and neurodegeneration, and co-pathologies such as alpha-synuclein and TDP-43 [3]. In addition, mitochondrial abnormalities, oxidation, synaptic plasticity alterations, epigenetic changes, and lipid and lipoprotein abnormalities are present in AD and may comprise therapeutic targets[84]. Choosing among these targets for development of combination therapies depends on the body of information justifying the target, the availability of biomarkers to monitor a therapeutic response, and the characteristics and developmental stage of candidate agents for the potential use in combination therapies.

Computational strategies are emerging that may assist in identifying the highest priority agents for use in the combination therapy setting. Network medicine approaches are becoming increasingly sophisticated and incorporate an expanding universe of informative data sets. Genome wide association studies (GWAS) and "omic" databases increasingly inform disease network mapping. Known drug networks can be explored to determine their proximity to disease networks and the relative likelihood of an impact on disease processes[85]. Candidate therapies can be assessed in animal models, organoids, or IPS cells to validate their biological effects. In the case of repurposed drugs, electronic medical records can be studied to determine if drug exposure resulted in decreased disease incidence. Clinical trial emulation can be conducted on electronic medical record data to determine if virtual trial data support efficacy of an agent or a combination[62]. The convergence of multiple types of information using computational strategies would support prioritizing some agents over others[86]. These strategies have been used to predict the likely efficacy and risk of side effects of combination therapies for AD[87,88]. These approaches have not yet predicted a successful AD therapy, but the advances in computational approaches suggest that they will become a valuable part of combination treatment development.

7. Discussion and conclusion

Combination add-on therapies with anti-amyloid MABs are being conducted in DIAN-TU and the Alzheimer Tau Platform and more add-on combinations are anticipated[24,25]. In some cases, anti-amyloid MABs will be allowed in trials but not required, creating subpopulations on combination therapies. In others, anti-amyloid MABs may be the standard of care to which novel interventions are added. A wide array of combinations of therapeutic types are being studied including combinations of drugs, MABs and other biological therapies, devices, gene therapies, cell therapies, and lifestyle interventions. Progress in understanding the neurobiology of AD facilitates more cogent choice of elements of a combination therapy, and emerging computational strategies may play an increasingly important role in prioritizing candidates for combinations.

While the logic of combination therapies is compelling, there are substantial hurdles to combination drug development[89] . Two novel agents may not be available in the same company or may be at different phases of development, making testing in a single trial difficult. A consensus strategy for prioritizing compounds or pathways that are most promising to address in combination trials has not been achieved. Clinical trials of combination therapies are complex and may require unrealistically large number of numbers of patients to demonstrate differences between combination therapies and monotherapies particularly if one of the agents in the combination is accounting for most of the therapeutic response. Repurposed agents may lend themselves to combination trials but lack of resources for late-stage development limits the likelihood that such treatments will become approved therapies. The "right" population may differ for the agents in the combination diminishing the effectiveness of the combination in trials involving single populations of the AD continuum are conducted.

A variety of clinical trial designs with two, three, and four arms are feasible depending on the type of information required. It is important for sponsors to thoroughly characterize the individual agents of a planned combination prior to assessing the agents together in a combination approach or add-on trial. Interpretation of clinical effects, biomarker effects, and adverse events depends on thorough understanding of each agent in the combination.

Creating a trial infrastructure to support combination trials is needed. Platform trials have been used to develop combination therapies in oncology and lessons from this experience can be applied to platform trials in AD and NDDs. DIAN-TU and the Alzheimer Tau Platform represent progress in developing platform trials for add-on drug combinations[24,25].

Treatment with MABs requires substantial practitioner and health care resources. Many countries currently cannot divert funding from other high priority areas to these emerging therapies. Add-on therapies to MABs may make regimens more complex and further decrease accessibility. Combination therapies consisting of agents that are easier to administer may improve global access to effective therapies.

The new therapeutic era introduced by anti-amyloid MABs creates new opportunities and new challenges. Add-on therapy to MABs may further slow disease decline and produce greater patient benefit. The landscape of anti-amyloid MAB use is evolving rapidly. Progression in understanding of AD pathophysiology requires a therapeutic response that reflects the complexity of the illness. New therapies are emerging, and new combinations will be identified. The goal of preventing, arresting, or substantially slowing the progression of AD will depend on resolving the issues involved in developing combination therapies. Precision medicine addressing AD and co-pathologies will depend on combinations of biomarkers guiding a corresponding regimen of therapies. The implementation of precision medicine requires understanding the risk and resilience factors of individual patients and choosing combinations of medicines with low likelihood of interactions and harm and high likelihood of benefit.

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CRediT authorship contribution statement

Jeffrey L Cummings: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Aaron H Burstein:** Conceptualization, Writing – review & editing. **Howard Fillit:** Conceptualization, 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

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