Special Report

Drug Repurposing

Repurposing Anti-cancer Drugs for Treatment of Alzheimer's Disease

aranca

April 2023

Alzheimer's Disease (AD) – An Overview

AD is a progressive disease that begins 10–20 years prior to symptoms detection; with ~ 47Mn patients globally, the current therapy options target symptom management

A neurodegenerative disease with slow onset and progressive impairment of behavioral and cognitive functions

Early onset is rarely observed in those below 65 years (account for ~ ≤ 10% AD patients)

Today, more than 25 Mn people globally are affected by dementia, most suffering from AD

There is no cure for AD – treatments currently available only improve some symptoms

Signs, Symptoms and Key Disease Stages

Signs and Symptoms

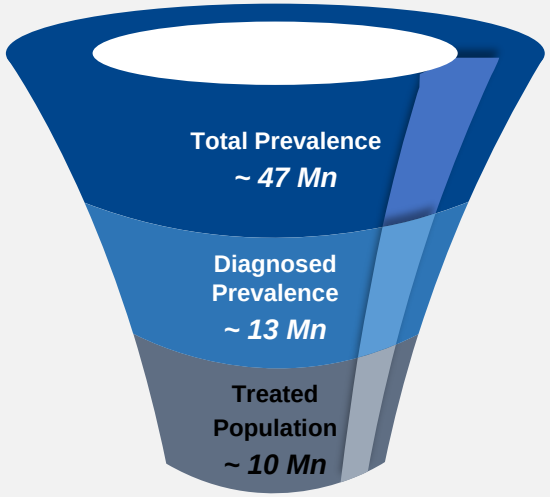
- Memory loss
- Hard to complete familiar task
- Poor judgement
- Changes in mood
- Difficulty in communicating
- Confusion of time & place

Key Disease Stages

Preclinical stage → **Prodromal stage** → **Advanced stage**

Increasing cognitive impairment

Disease Burden across 16 MM



Current Treatment and Key Players

Approved Treatments

Cholinesterase Inhibitors	Donepezil, Rivastigmine, Galantamine
IgG1 Monoclonal antibodies	Memantine
NMDA antagonist	Aduhelm

Key Players

MSD, NOVARTIS, Biogen, AstraZeneca, Roche, Pfizer

Source: *Industry Reports, News Articles, Company Websites, Aranca Analysis*

Current Unmet Needs

The disease has an enormous impact on patients, and especially caregivers; provision of adequate care/support has become a necessity that needs to be addressed

Unmet need

Humanistic burden

- Patients with AD require long-term care, thus causing emotional and psychological distress among family members and caregivers.
- Adult-child caregivers experience higher burden than spousal caregivers despite spending less time caregiving.
- It is among the most pressing issues in healthcare.

~60%

Caregivers with high / very high emotional stress

~40%

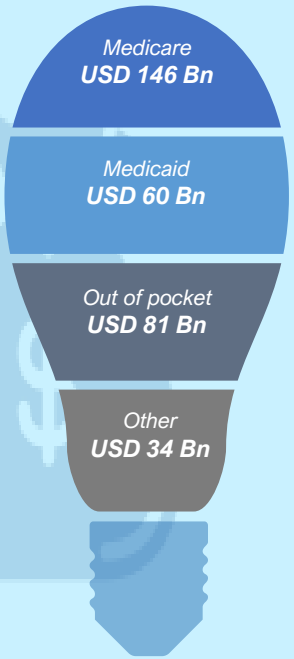
Caregivers that suffer from depression due to AD

~2/3rd

Patients are cared by their spouse

Economic burden

- In the US, the economic burden is expected to increase at an alarming rate in the coming years; treatment costs in 2022 was estimated at ***~USD 321 Bn.***
- Medicare beneficiary patients pay $9,844 out of pocket annually for healthcare and long-term care services.



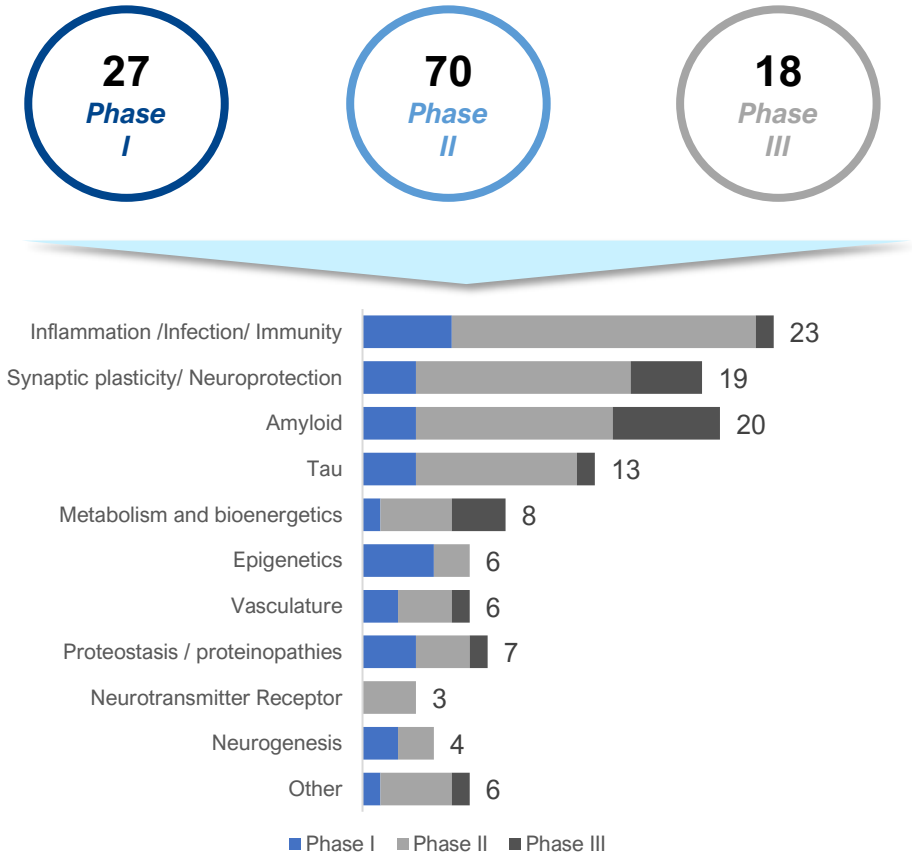
Clinical burden

- Need to improve validation of potential drug targets
- Lack of better understanding of why some neurons die and others are resistant to cell death to identify novel drug targets
- Challenges in translating newly identified genetic risk factors and lack of approaches to assess drug-target engagement in humans
- Inappropriate choice of subject populations for proof-of-concept clinical trials
- Lack of proof of target engagement demonstration in early clinical development

Source: *Industry Reports, News Articles, Company Websites, Aranca Analysis*

Current Clinical Trial landscape for Alzheimer's Disease

Innovators are trying to address another significant unmet need – lack of disease-modifying therapies (DMT) in the current regimen; although multiple candidates reach the late-stage, failure rates remain high



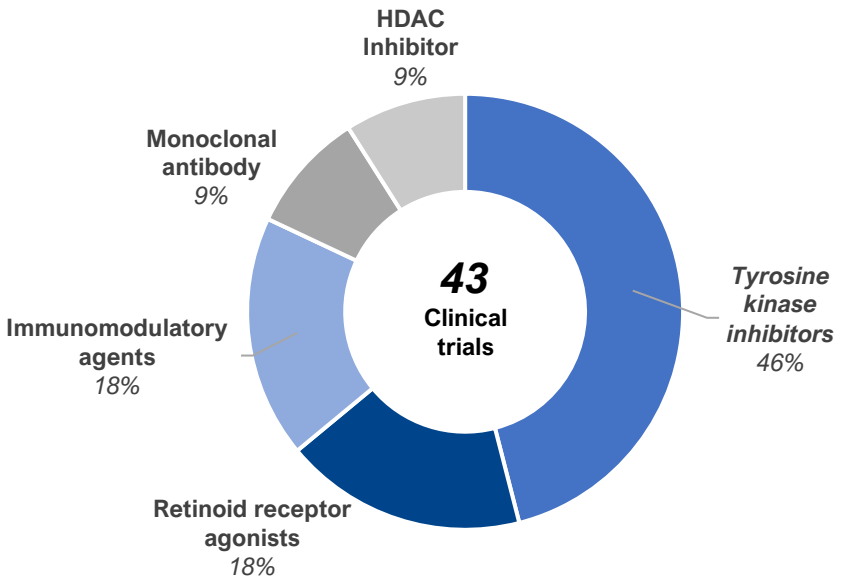
1. Several symptomatic therapies currently exist in the market. However, there are no disease-modifying therapies to cure AD
2. To address this issue, innovators are exploring multiple DMTs. Many promising DMTs are currently in the late-stage of development
3. These therapies are vying to reach breakthrough status post Biogen's Aduhelm (aducanumab), which became the first DMT to reach the AD market in early June 2021
4. However, despite the investigation of novel molecules, ~200 candidates have either been abandoned or failed in late-stage clinical trials in 3 years.
5. The high rates of failure can be attributed to the unpredictability of the symptoms (which emerge after a decade)

AD drug candidates have one of the highest failure rates of any disease area – 99.6%, compared with 81% for cancer.

Source: *Industry Reports, News Articles, Company Websites, Aranca Analysis*

FDA approved anticancer drugs in trials for Alzheimer's disease

Recent research regarding approved anticancer drugs demonstrating promising effects for AD has triggered interest among innovators in the context of repurposing these therapies



1 **Considering the impending challenge of DMT unavailability, innovators are exploring repurposing anticancer drugs for AD treatment.**

- Studies suggest that cancer and AD share some familiar biological hallmarks, and a significant link exists between cancer history and AD neuropathology.
- A study established an interrelationship between cancer and AD at the transcription level.
- The studies compared differentially expressed genes between AD and nine different cancers, and found that glioblastoma multiforme shared a strong correlation with AD.

2 **This interplay between cancer and AD will help in shortening the clinical development by years.**

"We are really very excited, because these findings suggest we can repurpose approved anti-cancer drugs for use as treatments for Alzheimer's disease. It could shorten the clinical development by years." – Researcher, Centre for Blood Research, Vancouver.

Source: *Industry Reports, News Articles, Company Websites, Aranca Analysis*

Anticancer drug class, mechanism of action and therapeutic rationale for repurposing in AD

Studies suggest that dementia and many site-specific cancers share one or more common molecular mechanisms, such as signaling pathways and Pin enzyme…

Molecule	Company name	Drug class	Role in cancer	Rationale for therapeutic purpose in AD
Bosutinib	Pfizer	Tyrosine kinase inhibitor	The primary target is the BCR-ABL kinase. Inhibition of several tyrosine kinases	Increase in blood and brain IL-10 and soluble CX3CL1 protein
Masitinib	AB Science		Inhibits the receptor tyrosine kinase c-Kit. Inhibition of PDGFR, Lck, FAK, and FGFR3	Inhibits c-Kit receptor in mast cells. It is capable of blocking Fyn that is involved in tau phosphorylation. Cognitive improvements as a result of Fyn inhibition
Dasatinib	Bristol-Myers Squibb		Inhibits BCR-ABL, SRC family kinases, c-Kit, EPHA2, and PDGFRβ	Removal of senescent cells from the plaque environment Inhibits amyloid-dependent microgliosis
Nilotinib	Novartis		Antiproliferative effects through inhibition of several kinases (BCR-ABL, c-Kit and PDGF, PI3K-Akt, JACK-STAT)	Abl inhibition facilitates amyloid clearance and reduces inflammation. Upregulation of soluble CX3CL1
Pexidartinib	Daiichi Sankyo		Inhibits the colony-stimulating factor (CSF1)/CSF1 receptor pathway	Reduction in microglial neuroinflammation
Axitinib	University of British Columbia (UBC)		Inhibits tyrosine kinase receptors, including VEGFR-1, VEGFR-2, and VEGFR-3	Blocks a receptor in the brain called a tyrosine kinase receptor, which is partly responsible for spurring blood vessel formation

Source: *Industry Reports, News Articles, Company Websites, Aranca Analysis*

Anticancer drug class, mechanism of action and therapeutic rationale for repurposing in Alzheimer's disease.

…also suggest that anticancer drugs may act as disease-modifying therapies once the AD-related neurodegenerative process starts

Molecule	Company name	Drug class	Role in cancer	Rationale for therapeutic purpose in AD
Vorinostat	German Center for Neurodegener-ative Diseases	HDAC inhibitor	Antiproliferative effect through modulation of histone acetylase activity	Restoration of synaptic plasticity Improved memory long-term potentiation, reduction in Aβ and tau pathology
Bexarotene	Ligand Pharmaceutical	Retinoid X receptor agonist	Inhibition of cell cycle progression, prevention of multidrug resistance, inhibition of angiogenesis and metastasis	Alter CSF levels of ApoE Inhibition of Aβ42 aggregation
Tamibarotene	Osaka City University		Specific agonist for retinoic acid receptor alpha/beta with possible binding to retinoid X receptors (RXR)	Decreased insoluble Aβ 42 deposition and increased VAChT and ACh in the brain and reduction of neuroinflammation
Thalidomide	Celgene Corporation	Immuno modula-tory agent	Possible anti-TNF-α effects May act as a VEGF inhibitor	Reduction of Aβ, inhibition of the expression of BACE1 enzyme. Reduction of proinflammatory TNF-α
Lenalidomide	Celgene Corporation		Tumor cell apoptosis by inhibition of bone marrow stromal cell support, by anti-angiogenic, anti-osteoclastogenic effects, and immunomodulatory activity	Reduction of the expression of TNF-α, IL-6, IL-8 Increase the expression of anti-inflammatory cytokines
Daratumumab	Marc L Gordon, MD	mAB	Targeting and induction of apoptosis in cells that highly express CD38	AD pathology is attenuated in CD38-deficient mouse model

Source: *Industry Reports, News Articles, Company Websites, Aranca Analysis*

Investing in emerging areas of healthcare – How can Aranca help?

For more information on this space or any other research needs, Aranca can prove to be a suitable partner

Research, consolidation, and insightful analysis to aid in-depth understanding of therapy and effective decision-making

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In-depth understanding of various fundamental therapy parameters

Epidemiology
Identification of patient opportunity in key markets across the globe

Market Analysis
Assessment of current competitive landscape and available treatment options

Pipeline Analysis
Competitor asset evaluation across various clinical trial phases

Pricing and Access
Evaluation of various competitor pricing and market access models

Disease Burden and Unmet Need
Evaluation of economic and humanistic burden of disease and key unmet needs

COMMERCIAL OPPORTUNITY

Mapping key differentiators | Identifying key market unmet needs | Framing a strong value proposition

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Healthcare companies leverage our services for various business needs

Our point solutions across the product lifecycle:

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Enabling clients to explore market opportunity for novel drugs, formulations and indications	Supporting clients on queries regarding running their business operations efficiently	Managing the product through different stages of its lifecycle by deploying specific strategies that ensure maximum ROI and profitability	Identifying collaboration opportunities that enable clients to enter new therapy areas or markets through successful partnerships

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