Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Ibrutinib

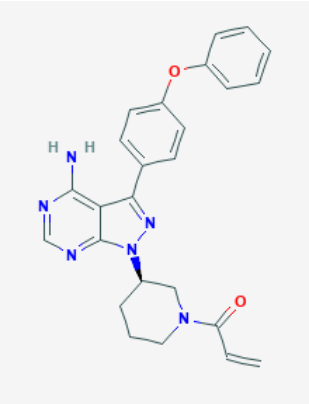
Evidence Summary

While effective in treating B-cell malignancies, ibrutinib is associated with serious adverse events including hematological and cardiovascular toxicities.

Neuroprotective Benefit: BTK is elevated in Alzheimer's disease. While studies in mouse models of AD have shown reduced microglial uptake of synaptosomes with ibrutinib, inhibition of phagocytosis may impair removal of toxic proteins.

Aging and related health concerns: Ibrutinib is effective in treating B-cell cancers. It is also effective against preclinical models of neuroblastoma. But some benefits may be offset by increased risks for hypertension, atrial fibrillation, and others.

Safety: Adverse events, including serious adverse events, are common with ibrutinib, including hematological toxicities, atrial fibrillation, ventricular arrhythmia, hypertension, infections, and bleeding. Other adverse events include diarrhea and rash.

Availability: Rx; used to treat mantle cell lymphoma, lymphocytic leukemia, lymphocytic lymphoma, and others.	**Dose**: In lymphoma patients, the dose is 420 mg orally once a day. Dose adjustments (or discontinuation) are needed for hepatic impairment, hematological toxicity, or nonhematological toxicity.	**Chemical formula:** $C_{25}H_{24}N_6O_2$ **MW**: 440.5  Source: PubChem
Half life: elimination half-life is 4-6 hours	**BBB**: penetrant, but may be effluxed by P-glycoproteins	
Clinical trials: Numerous meta-analyses included over 2,000 patients.	**Observational studies**: N/A	

What is it? Ibrutinib is a small molecule that potently inhibits Bruton's tyrosine kinase (BTK), a cytoplasmic tyrosine kinase that is a critical regulator of B cell development and activation (Keaney et al., 2019). Ibrutinib binds to and irreversibly inhibits BTK activity, preventing B-cell activation and B-cell-mediated signaling (PubChem). Ibrutinib was developed by Pharmacyclics Inc. and FDA-approved for the treatment of mantle cell lymphoma in November 2013, and treatment of chronic lymphocytic leukemia and Waldenström's macroglobulinemia in 2014. Ibrutinib has also been approved by the EMA for the treatment of chronic lymphocytic leukemia and mantle cell lymphoma. Ibrutinib is also approved for use in chronic graft versus host disease.

Neuroprotective Benefit: BTK is elevated in Alzheimer's disease. While studies in mouse models of AD have shown reduced microglial uptake of synaptosomes with ibrutinib, inhibition of phagocytosis may impair removal of toxic proteins.

Types of evidence:

- A few laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:
There have not been any studies to date that tested ibrutinib in dementia patients or people with age-related cognitive decline.

Bruton's tyrosine kinase (BTK) has been implicated in regulating the peripheral innate immune response, NLRP3 inflammasome, and microglial phagocytosis (Ito et al., 2015; Liu et al., 2017). Human genetic studies have identified genes highly expressed in microglia that contribute to Alzheimer's risk, including PLCG2, whose protein product phospholipase gamma 2 (PLCγ2) is a BTK substrate (Watanabe et al., 2001).

In postmortem brains of Alzheimer's disease patients, BTK levels (measured using the Brain Myeloid Landscape platform) were modestly elevated in the temporal cortex and fusiform gyrus relative to age-matched controls in two separate gene expression datasets (Keaney et al., 2019).

Human research to suggest benefits to patients with dementia:
None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
In mouse models of Alzheimer's (5xFAD and Thy1-hTau mice), BTK levels were elevated in the brains compared to littermate controls, and BTK immunoreactivity colocalized with Iba1-positive microglia (Keaney et al., 2019). *In vitro* studies in rodent microglia and human monocyte-derived macrophages have shown that ibrutinib treatment decreased phagocytosis and microglial uptake of synaptosomes (Keaney et al., 2019). However, it is not clear how ibrutinib-induced inhibition of phagocytosis would impact the ability of microglia to phagocytose toxic proteins like Aβ and tau.

APOE4 interactions: Unknown.

Aging and related health concerns: Ibrutinib is effective in treating B-cell cancers. It is also effective against preclinical models of neuroblastoma. But some benefits may be offset by increased risks for hypertension, atrial fibrillation, and others.

Types of evidence:

- 1 case study
- 1 systematic literature review
- Numerous laboratory studies

Ibrutinib is approved for the treatment of mantle cell lymphoma, chronic lymphocytic leukemia, lymphocytic lymphoma, Waldenström's macroglobulinemia, and graft versus host disease.

Chronic lymphocytic leukemia: SUPERIOR TO COMPARATOR MEDICATIONS
In a systematic literature review of 10 comparative trials in patients who were previously treated for chronic lymphocytic leukemia, a strong and consistent trend of superiority for ibrutinib was observed when it was indirectly compared using treatment comparison (ITC) models with idelalisib plus ofatumumab and physician's choice (Sorensen et al., 2017). Ibrutinib had prolonged progression-free survival (HR = 0.06; 95% CI, 0.04-0.11) and overall survival (HR = 0.25; 95% CI, 0.12-0.54) versus comparators. Ibrutinib also had prolonged progression-free survival (HR = 0.41; 95% CI, 0.25-0.66) and overall survival (HR = 0.50; 95% CI, 0.23-1.08) versus physician's choice. These findings were robust and favored ibrutinib even after adjusting for underlying differences in patient population between the trials.

Optic neuropathy: UNKNOWN
A case study of a 45-year old man with chronic lymphocytic leukemia who developed bilateral optic disc edema experienced visual recovery after treatment with ibrutinib and intrathecal methotrexate (Khan et al., 2016). The patient was believed to be in clinical remission but presented with vision loss and bilateral optic disc edema, and based on an optic nerve sheath biopsy, his optic neuropathy was confirmed to be due to chronic lymphocytic leukemia. Histopathology confirmed a perivascular B-cell lymphocytic infiltrate, with more than 90% of cells staining positive for CD20. CNS involvement in chronic lymphocytic leukemia is rare and has been reported in 0.8%–2% of antemortem studies. Optic neuropathy in chronic lymphocytic leukemia has been typically treated with optic nerve irradiation and high-dose corticosteroids, intrathecal methotrexate, or a combination of the two. Further studies are needed to determine whether ibrutinib is efficacious in treating patients with chronic lymphocytic leukemia and optic neuropathy.

Neuroblastoma: BENEFIT IN PRECLINICAL MODELS

Bruton's tyrosine kinase is expressed in neuroblastoma cell lines and tumor tissues, and its high expression correlates with poor relapse-free survival probability of neuroblastoma patients (Li et al., 2018). In nude mice with neuroblastoma xenograft, ibrutinib treatment (20 mg/kg, i.p.) attenuated the growth of neuroblastoma xenografts, suggesting a key role of BTK in the carcinogenesis of neuroblastoma. In tumor tissues, ibrutinib treatment increased levels of cleaved caspase-3 and PARP. In neuroblastoma cell lines, ibrutinib inhibited cell proliferation and induced significant cell apoptosis.

Safety: Adverse events, including serious adverse events, are common with ibrutinib, including hematological toxicities, atrial fibrillation, ventricular arrhythmia, hypertension, infections, and bleeding. Other adverse events include diarrhea and rash.

Types of evidence:

- 6 meta-analyses or systematic reviews
- 3 reviews

Numerous meta-analyses and systematic reviews have reported that ibrutinib is associated with significantly increased risks for adverse events, including serious adverse events (Caron et al., 2017; Tillman et al., 2018; Ball et al., 2019; Zhou et al., 2019; Caldeira et al., 2019; Hou et al., 2020).

The discontinuation rate due to adverse events with ibrutinib monotherapy increases over time and ranged from 11% to 51% in real-world evaluation (de Weerdt et al., 2017). The most frequent reasons for discontinuation or dose reduction varied between the studies and included: arthralgia, atrial fibrillation, bleeding, second malignancy, general debility, infection, and pneumonitis. Fatal adverse events have been reported in 1–9% of patients on single-agent ibrutinib treatment.

In the latest 2020 meta-analysis of 13 clinical studies comprising a total of 1,445 patients with diffuse large B-cell lymphoma (DLBCL), ibrutinib treatment was associated with adverse events in 98.3% of people and 25.2% of patients discontinued ibrutinib due to these adverse events (Hou et al., 2020). Grade 3 or worse adverse events occurred in 70.7% of patients during the ibrutinib therapy, and 4.1% patients experienced grade 5 adverse events. More than half of the patients (52.6%) developed serious adverse events. The most common hematologic toxicities of ibrutinib in patients with DLBCL were anemia (44.6%), neutropenia (36.0%), and thrombocytopenia (35.2%). Fatigue and gastrointestinal adverse events, such as diarrhea, nausea, and vomiting, developed in more than 20% of the patients.

Moreover, 17.0 % of patients developed infection of any grade, and 7.6% of patients had infection of grade 3 or worse. Atrial fibrillation of any grade was experienced by 3.4 % of patients with DLBCL using ibrutinib.

In a 2019 meta-analysis of 7 studies randomizing 2,167 patients with B-cell malignancies, ibrutinib was associated with a significantly increased risk of infection of any grade (RR=1.34, 95% CI, 1.06 to 1.69, p= 0.015) and infection of grades 3-5 (RR=1.35; 95% CI, 1.05 to 1.74, p=0.018)(Ball et al., 2019). In patients with chronic lymphocytic leukemia, a significantly increased risk of grade 3-5 infection was noted in the ibrutinib group (RR=1.24; 95% CI, 1.02 to 1.50, p=0.028). However, incidences of pneumonia and upper respiratory tract infections were not significantly different between groups. A 2018 meta-analysis reported more serious findings on infections; it included 48 trial cohorts that tested ibrutinib in hematologic malignancies, and infectious complications were common, occurring in 56% of patients taking single-agent ibrutinib and 52% of those on combination therapy (Tillman et al., 2018). Approximately 1 in 5 patients developed pneumonia, which was the major contributor to a 2% rate of death from infections. Many of the cases of pneumonia were due to opportunistic pathogens.

In a 2019 meta-analysis including 5 randomized controlled trials totaling 2,456 elderly patients with chronic lymphocytic leukemia, ibrutinib was not associated with significantly higher risk of anemia (RR=0.90), thrombocytopenia (RR=0.61), neutropenia (RR=0.50), or febrile neutropenia (RR=0.89), but ibrutinib was associated with a higher risk of diarrhea (RR=2.14; 95% CI, 1.44 to 3.17; p=0.0002)(Zhou et al., 2019). Diarrhea occurs most often during the first 6 months of treatment, and its median duration is 20 days and is usually self-limiting (de Weerdt et al., 2017)..

Another 2019 meta-analysis of 8 randomized controlled trials totaling 2,580 patients with chronic lymphocytic leukemia, mantle cell lymphoma, or Waldenström's macroglobulinemia reported that ibrutinib significantly increased the risk of hypertension (RR=2.82; 95%CI, 1.52 to 5.23) with moderate quality evidence, and significantly increased the risk of atrial fibrillation (RR=4.69; 95%CI, 2.17 to 7.64) with high quality evidence (Caldeira et al., 2019).

A 2017 meta-analysis of 22 clinical studies including 2,152 ibrutinib recipients (mostly with chronic lymphocytic leukemia and small lymphocytic lymphoma, a few with mantle cell lymphoma, or Waldenström's macroglobulinemia) reported that the relative risk of overall bleeding was significantly higher in ibrutinib recipients (RR=2.72; 95% CI, 1.62 to 6.58), but major bleeding did not show a significant difference (RR=1.66; 95% CI, 0.96 to 2.85; p=0.07)(Caron et al., 2017). The incidences of major bleeding and any bleeding were 3.0 (95% CI, 2.3 to 3.7) and 20.8 (95% CI, 19.1 to 22.1) per 100 patient-

years, respectively. There are safety concerns for using ibrutinib with anticoagulant/antiplatelet therapies, but even in patients not on these therapies, ibrutinib treatment resulted in lower grade (<3) bleeding in 28% of patients (de Weerdt et al., 2017). Grade ≥3 bleeding occurred in 2–4% of patients on ibrutinib who were not on anti-platelet or anti-coagulant therapy.

A review discussing the cardiovascular toxicities of BTK inhibitors noted that the incidence of atrial fibrillation as been reported in up to 16% of patients treated with ibrutinib (Pineda-Gayoso et al., 2020). But it is important to note that these cardiovascular toxicities do not appear to be a drug class-related toxicity, as low rates are observed with other BTK inhibitors. In the RESONATE trial for chronic lymphocytic leukemia, 3% of patients developed grade 3 or higher atrial fibrillation, while another 2% of patients developed grade 1 or 2 atrial fibrillation (Byrd et al., 2014). After a median of 19-month follow-up, a total of 7% of patients developed atrial fibrillation with a 5.1-month median time to onset (Brown et al., 2018). In the phase 3 RESONATE-2 trial, 269 patients age 65 years or older with previously untreated chronic lymphocytic leukemia or small lymphocytic leukemia were randomized to receive either ibrutinib or chlorambucil, with 6% of ibrutinib-treated patients developing atrial fibrillation after a median exposure of 17.4 months in contrast to only 1 patient in the chlorambucil group (Burger et al., 2015). The 5-year follow-up of the RESONATE-2 trial reported that a total of 16% of patients developed atrial fibrillation at any time, with 5% having experienced a grade 3 event.

In a retrospective study, 137 patients diagnosed with B-cell malignancies treated with ibrutinib were compared with 106 patients treated with cytotoxic chemotherapy for the same cancers. The incidence of atrial arrhythmias was 14% in the ibrutinib group, compared with 3% in patients treated with cytotoxic chemotherapy (p= 0.009). In multivariable analysis, patients treated with ibrutinib had a 5-fold increased risk of developing atrial arrhythmias (OR=5.18; 95% CI, 1.42 to 18.89) and ibrutinib was an independent risk factor for developing atrial arrhythmias (Fradley et al., 2019).

Although the actual mechanism of ibrutinib-related atrial fibrillation is still not clear, it is thought to be related to the inhibition of cardiac PI3K-Akt signaling (Pineda-Gayoso et al., 2020). In mouse models, ibrutinib-associated atrial fibrillation has been associated with atrial structural remodeling and fibrosis, dysregulated calcium handling in atrial myocytes, enhanced delayed afterdepolarization, and increased activity of CaMKII, a kinase implicated in many cardiac pathologies. In patients, once atrial fibrillation has developed, ibrutinib withdrawal does not change its course, and therefore appropriate treatment of atrial fibrillation needs to be started (de Weerdt et al., 2017).

Ibrutinib use has been associated with ventricular arrhythmias but with less frequency than atrial fibrillation. The incidence of ibrutinib-associated ventricular arrhythmias in a study of 582 patients was 1% after a median follow-up of 32 months (Pineda-Gayoso et al., 2020). In the HELIOS study, a randomized, double-blind, phase 3 study that assessed the safety of adding ibrutinib to bendamustine plus rituximab for previously treated chronic lymphocytic leukemia or small lymphocytic leukemia, 2% of patients developed grade 3 or higher ventricular arrhythmias, cardiac arrests, and sudden deaths in the ibrutinib-containing arm.

Ibrutinib is also associated with hypertension. In the RESONATE trial, with up to 71 months of follow-up after the initiation of ibrutinib therapy, 21% of patients developed hypertension of grade 3 or higher (Munir et al., 2019).

A review of a retrospective observational study at a single institution reported case series of unique adverse events related to ibrutinib (Shaikh et al., 2019). Ten patients experienced unique adverse events and they included: palindromic rheumatoid arthritis, diffuse spongiotic dermatitis, bullous pemphigoid, recurrent hemorrhagic stroke, peripheral neuropathy, recurrent paronychia, intramedullary fibrosis, recurrent joint pains, pulmonary aspergillosis, dyspnea with exacerbation of atrial fibrillation, and resolution of autoimmune hemolytic anemia.

Ibrutinib also frequently causes a rash, but it is generally classified as grade 1 or 2 and often improves spontaneously without any treatment (de Weerdt et al., 2017).

Drug interactions: There are 170 major, 191 moderate, and 3 minor drug interactions with ibrutinib (Drugs.com). Ibrutinib is metabolized by CYP3A (and CYP2D6) to the active metabolite PCI-45227. Therefore, CYP3A4 inducers may decrease serum levels of ibrutinib while CYP3A4 inhibitors may increase serum levels of ibrutinib (Drugs.com). Ibrutinib may also enhance the adverse/toxic effects of anticoagulants and antiplatelet agents.

Bioavailability and blood-brain barrier penetrance: P-glycoproteins restrict brain penetration of ibrutinib while CYP3A limits its bioavailability (van Hoppe et al., 2018). *In vitro* and mouse studies have shown that, ibrutinib is transported moderately by multidrug efflux transporters, human ABCB1 and mouse Abcg2, but not detectably by human ABCG2 (van Hoppe et al., 2018). In mice, Abcb1 markedly restricted the brain penetration of ibrutinib and its metabolite (ibrutinib-DiOH, 10-fold reduced BTK inhibitory activity), either alone or in combination with Abcg2. Transport of ibrutinib by human ABCB1 and mouse Abcg2 had efflux ratios or 2.33 and 1.93, respectively, well above the often-used cutoff value

of 1.5. However, the human blood-brain barrier expression of ABCB1 is 2.3-fold lower than that of the mouse Abcb1a expression. Thus, the effect of ABCB1 in human brain penetration of ibrutinib might be relatively smaller than that of mice. Ibrutinib is also extensively metabolized by CYP3A in the intestine and liver, restricting its oral bioavailability (van Hoppe et al., 2018).

Sources and dosing: Ibrutinib (marketed as Imbruvica®) is a prescription medication used to treat mantle cell lymphoma, chronic lymphocytic leukemia, lymphocytic lymphoma, Waldenström's macroglobulinemia (a type of non-Hodgkin lymphoma), and others. In lymphoma patients, the dose is 560 mg orally once a day (Drugs.com). In patients with chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and graft versus host disease, the dose is 420 mg orally once a day. Dose adjustments (or discontinuation) are needed for hepatic impairment, hematological toxicities, and nonhematological toxicities.

Research underway: Based on ClinicalTrials.gov, there are over 200 ongoing clinical trials testing ibrutinib, mostly for cancers (ClinicalTrials.gov).

Search terms:
Pubmed, Google:

- + cognitive, + APOE, + dementia, + Alzheimer, + neuropathy, + atherosclerosis, + cardiovascular, + clinical trial, + meta-analysis

Websites visited for ibrutinib:

- Clinicaltrials.gov (200+)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com (0)
- PubChem
- DrugBank.ca
- Cafepharma
- Pharmapro.com (0)

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