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.

CSF-1R Inhibitors

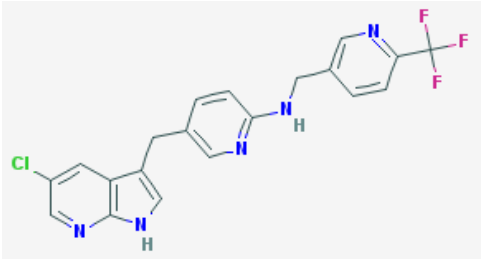
Evidence Summary

Potentially beneficial adjunct to cancer therapy. May either exacerbate or ameliorate brain injury by depleting microglia depending on the inflammatory microenvironment.

Neuroprotective Benefit: CSF-1R inhibition has context dependent effects in the CNS, which can potentially ameliorate or exacerbate neuronal damage and inflammation, depending on environment.

Aging and related health concerns: CSF-1R inhibitors show clinical utility for tenosynovial giant cell tumors, and may be useful as an adjunct to potentiate antitumor responses to immunotherapy in other cancers.

Safety: Clinically tested inhibitors show on-target class effects of increased liver enzymes, which are usually asymptomatic, though pexidartinib contains a black box warning for hepatotoxicity. Other common side effects include fatigue, nausea, and edema.

Availability: Rx for pexidartinib; others are in clinical trials	**Dose**: 250 mg twice per day, orally with a low-fat meal for pexidartinib	Pexidartinib **Chemical formula:** $C_{20}H_{15}ClF_3N_5$ **MW**: 417.82 g/mol  Source: PubChem
Half-life: 26.6 hours (for pexidartinib)	**BBB**: Varies. Pexidartinib has modest penetrance	
Clinical trials: Cancer: >17 trials, primarily small Phase 1 studies. Other tested indications include rheumatoid arthritis, Crohn's disease, and Graft-vs-host disease.	**Observational studies**: None	

What is it?

Colony stimulating factor 1 receptor (CSF-1R), also known as macrophage colony-stimulating factor (M-CSF) is primarily expressed on monocytes and signaling through this receptor regulates the proliferation, survival, and function of a subset of myeloid cells including macrophages, microglia, osteoclasts, and mast cells [1]. It is a tyrosine kinase receptor that acts as receptor for both CSF-1 and IL-34. CSF-1R inhibition results in the loss of CSF-1R expressing myeloid cell populations, and thus has been used preclinically as a strategy to deplete microglia in models of neurodegenerative disease, and clinically to deplete tumor-associated macrophages in cancer. Numerous CSF-1R inhibitors have been developed, including both orally bioavailable small-molecule inhibitors, and monoclonal antibodies administered via intravenous infusion. They have primarily been tested in Phase 1 or Phase 1/2 trials in cancer. Thus far, this class of drugs has shown the greatest clinical utility for tenosynovial giant cell tumors.

Oral CSF-1R Inhibitors

Pexidartinib (PLX3397) is an orally available tyrosine kinase inhibitor that targets CSF-1R (IC_{50} =13 nM), c-Kit (IC_{50}= 27 nM) and FLT3 (IC_{50}= 160 nM). For CSF-1R, it acts as a conformational selective inhibitor, binding the autoinhibited state, rather than as a tyrosine kinase inhibitor per se. It was developed by Plexxikon, Inc. which was acquired by Daiichi Sankyo. Pexidartinib is available from Daiichi Sankyo under the brand name Turalio®, which was FDA approved in 2019 for the treatment of tenosynovial giant cell tumors associated with severe morbidity or functional limitations and not responsive to improvement

with surgery. It contains a black box warning for hepatoxicity and its use is restricted through a Risk Evaluation and Mitigation Strategy Program. It is the first-in-class approved CSF-1R inhibitor.

ARRY-382 (PF-07265804) is an orally available selective CSF-1R inhibitor (IC_{50}= 9nM). It was developed by Array BioPharma, which was acquired by Pfizer in 2019. It was tested in a Phase 1 trial in patients with refractory solid malignancies and in a Phase 1b trial in combination with pembrolizumab in patients with advanced solid tumors. It showed dose-proportional pharmacokinetics and good target engagement, with a half-life of approximately 18 hours.

EI-1071 is an orally bioavailable, BBB penetrant, CSF-1R inhibitor (IC_{50} 3 nM), with selectivity for CSF-1R >100 fold relative to c-Kit, >220 fold relative to PDGFRα, >450 fold relative to FLT3, and >6000 fold relative to PDGFRβ (Poster). It is being developed by Elixiron Immunotherapeutics for Alzheimer's disease and tenosynovial giant cell tumors, and was recently granted Orphan Drug Designation for idiopathic pulmonary fibrosis (Press release). It was recently tested in a Phase 1 study in healthy volunteers.

Edicotinib (JNJ40346527; PRV-6527) is an orally available, BBB penetrant, CSF-1R inhibitor (IC_{50}= 3.2nM), with lower activity at Kit (IC_{50}=20nM), and FLT3 (IC_{50}=190 nM), such that it targets the same kinases, but shows a better selectivity profile toward CSF-1R relative to pexidartinib. It was developed by Janssen Pharmaceuticals, who tested it in a Phase 1 study for Hodgkin's lymphoma. It was licensed to Provention Bio for clinical development in autoimmune conditions, and clinically tested in rheumatoid arthritis in Crohn's disease. Janssen declined the opportunity to reacquire the license following the failure of the drug in these indications, and Provention appears to have discontinued development of the drug (Fierce Biotech article). There is a clinical trial registered for edicotinib in Alzheimer's disease, but the status of the trial and development path of this drug is currently unclear.

Sotuletinib (BLZ945) is a selective, orally available, BBB penetrant CSF-1R inhibitor (IC_{50}=1nM) with over 1000-fold selectivity for CSF-1R relative to other closely related tyrosine kinases. It is under clinical development by Novartis. It was tested in a Phase 1 trial as a monotherapy or in combination with spartalizumab in patients with cancers associated with high levels of tumor associated macrophages, but the trial was terminated by the sponsor. In this study, the half-life of sotuletinib was 15-24 hours. Sotuletinib is also being tested in a clinical trial for ALS.

Vimseltinib (DCC-3014) is an orally available selective CSF-1R inhibitor (IC_{50} = 3nM at 4nM ATP) with greater than 100-fold selectivity for CSF-1R relative to FLT3, KIT, PDGFRα, PDGFRβ, and VEGFR2. It is under clinical development by Deciphera Pharmaceuticals (NASDAQ: DCPH). It is currently being tested in a Phase 1/2 trial in patients with advanced solid tumors, and based on preliminary results in a subset of patients with tenosynovial giant cell tumors, it is also being tested in a Phase 3 trial in patients with tenosynovial giant cell tumors.

Monoclonal antibodies

AMG 820 (AMB-05X) is a fully human IgG2 c-fms monoclonal antibody towards CSF-1R which inhibits the binding of CSF-1 or IL-34 to the receptor, thereby preventing ligand-mediated receptor activation. It was developed by Amgen, and has been licensed for clinical development by AmMax Bio. It was tested in combination with pembrolizumab in patients with advanced, refractory solid tumors, and an open-label study in patients with tenosynovial giant cell tumors. It is currently being tested in a Phase 2 trial in patients with tenosynovial giant cell tumors.

Axatilimab (SNDX6532) is a humanized high-affinity IgG4 monoclonal antibody targeting CSF-1R. It was developed by Syndax Pharmaceuticals and it is under clinical development through a licensing partnership between Syndax and Incyte. It is currently being tested in clinical trials for solid tumors, lymphoma, intrahepatic cholangiocarcinoma, and graft-versus-host disease.

Cabiralizumab (FPA008) is a humanized immunoglobulin G4 (IgG4) monoclonal antibody towards CSF-1R which blocks ligand binding and receptor signaling. It was developed by Five Prime Therapeutics, which was acquired by Amgen. It was clinically tested in combination with nivolumab through a partnership with Bristol-Myers-Squibb. There are additional clinical trials underway for cancer testing cabiralizumab with nivolumab supported by Bristol-Myers-Squibb.

Emactuzumab (RG7155; CXD301) is a humanized monoclonal antibody towards CSF-1R which blocks the receptor dimerization interface and thereby prevents high-affinity binding. It was developed by Roche and was licensed to Celleron Therapeutics in 2020 and is being developed in partnership with SynOx Therapeutics. It was tested in Phase 1 trials in combination with paclitaxel, atezolizumab, or selicrelumab in patients with advanced solid cancers. It is currently being tested in a Phase 3 trial in patients with tenosynovial giant cell tumor.

LY3022855 (IMC-CS4) is a human IgG1 monoclonal antibody towards CSF-1R which blocks ligand binding and receptor activation. It was developed by ImClone Systems, which was acquired by Eli Lilly and Co. as a wholly owned subsidiary. It was tested in Phase 1 trials as a monotherapy or in combination with durvalumab or tremelimumab in patients with advanced solid tumors. It is currently being tested in clinical trials in combination with BRAF/MEK inhibitors in melanoma and in combination with cyclophosphamide, GVAX, and pembrolizumab in patients with pancreatic cancer.

Neuroprotective Benefit: CSF-1R inhibition has context dependent effects in the CNS, which can potentially ameliorate or exacerbate neuronal damage and inflammation, depending on environment.

Types of evidence:

- Several laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? None

There is no evidence from human studies to indicate that the inhibition of CSF-1R can prevent cognitive decline, but there is genetic evidence that a lifelong reduction in CSF-1R is associated with rare forms of dementia. Chronically reduced CSF-1R signaling, due to CSF-1R haploinsufficiency leads to a form of dementia called adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) which involves aberrant microglial distribution and white matter degeneration [2; 3]. ALSP is considered a disease spectrum that includes hereditary diffuse leukoencephalopathy with spheroids (HDLS) and familial pigmentary orthochromatic leukodystrophy (POLD). Since CSF-1R signaling is important during brain development [4], it is unclear whether the pathology is related to a neurodevelopmental defect or impaired CSF-1R signaling during adulthood. Due to the typical symptom onset around age 40 [5], the decline in cognitive function may stem from a lifelong accumulation of damage, particularly in the white matter, that manifests after a critical threshold of accumulated damage. Preclinical studies support a role for microglia in myelin maintenance and the homeostasis of oligodendrocyte progenitors in adulthood [6], suggesting that chronic microglial depletion could accelerate white matter damage or inhibit repair.
Gene association studies have also identified the presence of rare pathogenic CSF-1R missense mutations located in or flanking the tyrosine kinase region (p.L868R, p.Q691H, p.H703Y, p.D565N, and p.G957R) in patients with Alzheimer's disease (AD) in a discovery cohort of 332 Caucasian late-onset AD

patients and 676 Caucasian elderly controls and in a validation cohort of 296 AD and 169 mild cognitive impairment (MCI) cases in the UK [7]. These were considered low-frequency-rare variants. The CSF-1R mutation carriers tended to show similar disease phenotypes, which resembles that of hereditary diffuse leukoencephalopathy with axonal spheroids. In postmortem brain tissue from one of the mutation carriers, CSF-1R expression levels were found to be lower in the entorhinal cortex relative to other AD patients or age-matched controls, suggesting these mutations also result in a reduction in CSF-1R. Some of the pathology associated with ALSP could be related to a change in the balance between CSF-1 and CSF-2, as CSF-2 has been shown to be upregulated in the brains of these patients [8].

Human research to suggest benefits to patients with dementia:

There is currently no information on the clinical utility of CSF-1R inhibitors in dementia patients. Two clinical trials testing CSF-1R inhibitors in Alzheimer's disease (AD) have been registered, although one was prematurely terminated, and the status of the other trial is unclear.

A Phase 2a trial registered in 2016 Denmark by Plexxikon (EudraCT: 2016-000429-38) to test the safety, tolerability, and pharmacokinetics of pexidartinib in patients with mild to moderate Alzheimer's disease was prematurely terminated, for reasons that may have been related to the temporary suspension of a Phase 3 trial (ENLIVEN) for pexidartinib in cancer patients in 2016 due to liver toxicity. Due to the very low CSF levels of pexidartinib in non-human primates, stemming from low BBB penetrance [9], pexidartinib is not likely to be the ideal CSF-1R inhibitor for CNS indications.

A randomized, placebo-controlled Phase 1b trial testing the BBB penetrant CSF-1R inhibitor, Edicotinib developed by Janssen Pharmaceuticals, in patients with mild cognitive impairment (MCI) sponsored by Oxford University was registered in 2019 (NCT04121208). However, the last update to Clinicaltrials.gov was in 2020, and the current status of the trial is listed as 'Unknown'. Since Janssen declined the offer to buy back the rights to edicotinib from the biotech, Provention Bio, who was developing it for autoimmune conditions following two failed trials (Fierce Biotech article), the status of both the drug and the trial is unclear.

Elixiron Immunotherapeutics received funding from the Alzheimer's Association to conduct a Phase 2 trial of its oral CSF-1R inhibitor, EI-1071, in patients with Alzheimer's disease (Press release). The trial has not yet been registered, but is anticipated to begin in 2023.

***Mechanisms of action for neuroprotection identified from laboratory and clinical research*:**

Neurogenerative disease: POTENTIAL MIXED (context dependent)
Due to the pleiotropic functions of both microglia and CSF-1R signaling, the inhibition of CSF-1R or depletion of microglia could either be beneficial by reducing neuroinflammation and protecting synapses, or could accelerate neural damage through the loss of neurotrophic support and induction of reactive astrogliosis [1] . **Effects are highly dependent on the brain microenvironment**, which vary based on the mechanism of neuropathology and the stage of the disease.

Alzheimer's disease: POTENTIAL MIXED (preclinical)
The expression of CSF-1 and CSF-1R has been found to be increased in the brain tissue of people with Alzheimer's disease [10], which is hypothesized to contribute to the augmented and aberrant chronic inflammatory microglial activation typically seen in this patient population. Additionally, there is evidence that CSF-1R dynamics may change over the course of the disease, as AD patients were found to have significantly higher levels of CSF-1 in their CSF than those with MCI (441.5 ± 188.6 vs 319.9 ± 71.6 pg/ml; p=0.003) [11]. The differences highlight the changing roles for microglia over the course of disease, and how the timing and nature of any microglial-targeted intervention is likely to be a critical aspect to its potential efficacy. In the periphery, there are some studies showing a connection between AD and lower levels of CSF-1R. In a case-control study (n=222), methylation of the CSF-1R promoter was higher in the peripheral blood of AD patients relative to controls [12]. Blood biomarker analysis from the Framingham Offspring Study (n= 2,134) found that blood CSF-1R levels were generally higher in males, and that CSF-1R mRNA levels were inversely associated with factors linked to increased risk for dementia, including the intake of the saturated fatty acids, total fat, the use of diabetes medication, and cigarette smoking. [13]
The contribution of genetic variants in CSF-1 or CSF-1R to AD risk generally appears to be low, as most gene association studies have not found an association [14]. Rare variants have been identified which produce phenotypes that overlap with dementias such as AD, but could instead be a rare form of adult-onset leukoencephalopathy stemming from chronically low levels of CSF-1R [7]. However, network analysis type studies have implicated CSF-1R in AD, in the hub of dysregulated immune function. These studies suggest that dysregulation of CSF-1R signaling may be a downstream exacerbating effect, indicative of innate immune system dysregulation, rather than a primary cause of neuropathology.

The impact of CSF-1R in AD models is highly context dependent, and largely determined by the characteristics of the predominant cell populations that are expressing CSF-1R in a given context/model. Cognitive enhancing benefits have been demonstrated for both recombinant CSF-1 and CSF-1R inhibitors in various rodent AD models [1]. While primarily expressed on microglia, CSF-1R has been shown to be expressed on a small subset (1-2%) of neurons in the hippocampus and cortex. Expression levels increase in response to neuronal injury. CSF-1R ligands (CSF-1 and IL-34) can enhance neuronal survival through the activation of neuronal CSF-1R. Therefore, augmenting neuronal CSF-1R signaling could be neuroprotective. Meanwhile, activation of CSF-1R on microglia could either contribute to pathological chronic neuroinflammation, or have neuroprotective properties, depending on the subpopulations of microglia present in a given neural environment. Since, the microglia in AD patients appear to be dysfunctional, it has been hypothesized that depleting them would be beneficial [15]. However, there is wide variation in the outcomes of microglial depletion using CSF-1R inhibitors depending on the model, the stage of disease, the sex of the animals, and the dosing regimen. The major driver of these differences appears to be differences in the subpopulations of microglia present coupled with their sensitivity to depletion with CSF-1R inhibitors [16]. In models where microglia sensitive to CSF-1R inhibition are driving pathology, their depletion is neuroprotective, however, in some models there is a preferential depletion of microglia with neuroprotective properties, which can end up exacerbating pathology. It has recently been established that the 'disease-associated' microglia phenotype consists of a heterogenous mix of different subpopulations with different properties, which may be protective in certain contexts and harmful in others. Although some subtypes may be preferentially depleted, there is not a clear trend from preclinical studies regarding the prevalence or contribution of these subtypes in different disease models. Rather, the effect of CSF-1R inhibitors is variable because of the heterogeneity in the composition of microglial subtypes across animals depending on a variety of factors.

The transgenic APP knock-in mouse lines, with humanized APP, AppNL-F and AppNL-G-F, show an increase in glutamate release probability, starting prior to the onset of plaques [17]. Partial microglial depletion using PLX5622 (300 mg/kg) resulted in a similar phenotype of increased glutamate release probability in 10 months old wildtype mice, and exacerbated the effect in AD model (AppNL-F) mice, but had no effect on plaque load. The effect was less pronounced with complete microglial depletion, suggesting that the effect may be related to the loss of the microglial subpopulations that are most sensitive to CSF-1R inhibitors, leading to an overall imbalance in microglial activities. In this model, the microglia resistant to depletion were most likely to express the phagocytic marker CD68. In human iPSC-derived microglia, from a male donor, treatment with the CSF-1R inhibitor PLX3397 resulted in a dose-

dependent reduction in microglial survival [18]. At low concentrations, there was a preferential depletion of SPP1+ (osteopontin) microglia, which is consistent with a disease-associated phenotype. In the Tg2541model, which expresses the 0N4R isoform of human tau with the familial frontotemporal lobar degeneration (FTLD)-linked P301S mutation, the effect of microglial depletion with PLX3397 was dependent on sex [19]. While male mice had greater drug exposure, only female mice showed functional improvements and extended survival. In male mice, higher drug levels were associated with higher levels of the neural injury marker neurofilament light (NFL) and worse survival, which was related to the induction of excitotoxicity. The discrepancy appears to stem from differential microglial subpopulation depletion between males and females. In males, the surviving microglia were preferentially of a pathogenic neuroinflammatory subtype, whereas in females, the inflammatory disease-associated microglia were preferentially eliminated, leading to a protective effect.
In a novel tau seeding model (hemizygous 5xFAD mice crossed with hemizygous tau P301S mice), amyloid plaque-associated microglia tended to be the most resistant to PLX3397 (1000 mg/kg), leading to a preferential depletion of microglia associated with tau and neuronal pathology [20].
Disease stage may play a role depending on the degree of neuronal cell death because the interaction between apoptotic neurons and microglia can influence microglial remodeling states. [21] Neuronal apoptosis may drive the induction of microglia phenotypes with high phagocytic capacity that are resistant to CSF-1R inhibition. In the retina, there was a preferential depletion of homeostatic microglia with CSF-1R, leading to a bias toward microglia in disease-associated microglia-like states.

Amyloid: Most studies indicate that microglia depletion with CSF-1R inhibitors has minimal impact to amyloid plaque pathology, however, there is evidence that it may exacerbate cerebrovascular amyloid pathology. Patients with ALSP, who are deficient in CSF-1R, show evidence of cerebrovascular pathology, including cerebral amyloid angiopathy (CAA) [22]. Peripheral macrophages, including perivascular macrophages were found to have reduced phagocytic capacity, which reduces the macrophage response to brain-derived amyloid, leading to the accumulation of amyloid in blood vessels. Additionally, crosstalk between endothelial cells and microglia/macrophages regulates the BBB. CSF-1R signaling is involved in this process, such that the reduction in CSF-1R leads to BBB remodeling in a manner that reduces barrier integrity. Similarly, microglial-deficient FIRE mice, which have a deletion in a regulatory enhancer of CSF-1R, crossed with an AD model (5XFAD), show a shift from parenchymal amyloid plaques toward cerebrovascular amyloid accumulation, intracerebral hemorrhages, increased brain calcification, and premature lethality [23]. A similar increase in brain calcification was seen in postmortem brain tissue from AD patients with concomitant vascular pathology. An increase in calcification is also seen in other models with impaired phagocytic capacity, such as TREM2 deficiency.

This is notable, because there is evidence for a physiological interaction between TREM2 and CSF-1R in which they mutually regulate expression [24]. The administration of CSF-1 was able to partially restore microglial survival, phagocytosis, and Aβ clearance in TREM2 knockout mice. Although not required, the presence of TREM2 enhances CSF-1R-mediated microglial survival.

***Tau*:** The depletion of microglia using CSF-1R inhibitors generally shows greater benefit in the context of tauopathies, relative to mixed pathology models. The primary mechanism of benefit appears to be the reduction in tau propagation via microglial-derived extracellular vesicles. In the 5XFAD, 3xTg, and Tg4510 models, microglial depletion (80-90%) or reduction (30%) with PLX3397 starting before or after the onset of pathology, offered minor cognitive benefits on some memory tasks, and reduced microglial association with plaques, but generally had no effect on Aβ or tau pathology [25; 26; 27; 28]. However, microglial depletion with PLX3397 reduced the transmission of tau in an AAV-mediated rapid tau propagation model [29]. Similarly, in a model where AAV-P301L-tau was injected into medial entorhinal cortex at five months of age, microglial depletion using PLX5622 (1200 mg/kg) from four to six months of age, reduced the propagation of tau, though it increased plaque burden and plaque-associated tau-containing dystrophic neurites in AppNL-G-F mice. Disease-associated microglia (MGnD) were found to hypersecrete extracellular vesicles containing p-tau as well as compact Aβ plaques and phagocytose/clear tau from dystrophic neurites [30]. This microglial uptake of tau then is both neuroprotective in clearing it from dystrophic neurites, and pathological by facilitating tau propagation. In the Tg2541model, intermittent/interventional dosing of PLX3397 was sufficient to reduce pathogenic tau in the forebrain, but continuous dosing was needed to reduce tau in the hindbrain [19].

***Cellular senescen*ce**: Chronic activation and replication of microglia in AD models was shown to induce replicative senescence, as characterized by increased βgal activity, a senescence-associated transcriptional signature, and telomere shortening [31]. Senescent microglia ($P21^{+}IBA1^{+}$) have also been seen in postmortem brain tissue from AD patients. In mice, treatment with a non-depleting dose of the CSF-1R inhibitor GW2580 for four months prior to the onset of plaque pathology, reduced the conversion of microglia to a disease-associated state with senescent properties, and enhanced synaptic preservation.

Overall, there are many remaining questions regarding the potential utility of microglial depletion strategies for AD. It is unclear which populations would be preferentially depleted, and whether this would vary in a sex-dependent, disease-stage, or patient-specific manner. The optimal timing for intervention is also unclear. However, the biggest issue is likely one of dosing. Most rodent studies use

an acute depletion or more continuous depletion lasting several months. With intermittent dosing, populations rebound within 14 to 21 days, along with an increasing degree of resistance with each successive dose [16]. It is unclear whether this is due to the preferential expansion of resistant populations, or whether changes in the environmental milieu stemming from depletion lead to changes in cell dynamics. As a result, it is not clear how long any potential benefits could be sustained. Continuous depletion carries an increased risk for CNS infections, and could lead to other issues, such as the exacerbation of white matter damage, as is seen in patients with CSF-1R haploinsufficiency [5] and some animal models [32].

Parkinson's disease: POTENTIAL MIXED (preclinical)
In a gene association study in Taiwan including 508 PD patients and 511 matched controls, the frequency of the rs1058885 TT genotype in CSF-1 was lower in PD patients (odds ratio [OR]: 0.63, 95% confidence interval [CI] 0.43 to 0.92) [33]. The biological impact of this variant is unclear, though the T allele was also associated a reduced risk for periodontitis in a different study.
Pretreatment with PLX3397 (40mg/kg daily by oral gavage for 21 days) depleted microglia in mice by approximately 90%. The microglia depletion prior to MPTP induced dopaminergic cell damage exacerbated MPTP mediated toxicity [34]. It worsened motor deficits, and enhanced inflammation by promoting the infiltration of leukocytes ($CD4^+$ and $CD8^+$ T cells) and augmenting local inflammatory responses by astrocytes. This work supports the finding of other studies that microglial depletion is detrimental during acute neural injury, but does not indicate whether it may be beneficial in a chronic phase, as has been demonstrated with other neurodegenerative disease models. In male rats injected with the toxin 6-OHDA into the striatum, microglial depletion with PLX3397 (30 mg/kg/day) from day 7 to 28 after surgery led to fewer motor deficits and better neurotransmission in the striatum [35]. The difference across studies highlights the context-dependent nature of microglial depletion.

Amyotrophic lateral sclerosis: POTENTIAL MIXED (etiology dependent, rodents)
Patients with sporadic ALS have less spinal microglia than those with the familial SOD1 driven disease, which may explain the disparate effects of CSF-1R inhibitors in different models of the disease. In the classic SOD^{G93A} familial mouse model, use of the selective CSF-1R inhibitor, GW2580, reduced microglial proliferation, attenuated motor neuron death, and extended survival [36]. In contrast, in a mouse model of sporadic ALS (rNLS8) involving prominent hTDP-43 mediated pathology, microglial activity was necessary for the clearance of neuronal TDP-43, and microglial depletion with PLX3397 (1000 mg/kg) resulted in worse motor function [37]. The discrepancy may also be related to the differential effects of the two CSF-1R inhibitors in terms of timing and potency. GW2580 primarily affected proliferation, only

leading to a 30% reduction in microglial number, which was restricted to the chronic phase, whereas PLX3397 produced a substantial depletion of microglia starting in the acute phase. The selective CSF-1R inhibitor, sotuletinib, is currently being tested in a Phase 2 trial for patients with ALS (NCT04066244).

Stroke: POTENTIAL MIXED (context dependent, rodents**)**
Modulation of microglial numbers and/or function has been shown to either ameliorate or exacerbate neural injury in various stroke models. In the brains of patients, there is an increase in the level of pro-inflammatory (IL-1β+) microglia 24 hours after intracerebral hemorrhage. In a mouse model of intracerebral hemorrhage, pre-treatment with PLX3397 (40 mg/kg by oral gavage for 21 days) reduced microglia by 90%, reduced neuroinflammation, prevented brain edema, and attenuated neurological deficits [38]. However, the same pretreatment regimen augmented the production of inflammatory mediators, leukocyte infiltration, stroke severity, and worsened neurological deficits in an ischemic stroke model (MCAO) [39]. These studies suggest that the effects of microglial modulation therapy could greatly vary from patient to patient, but it is unclear whether these studies are even relevant to humans, who likely would not receive treatment until after stroke onset.

Radiation protection: POTENTIAL BENEFIT (rodents)
Microglial activation has been implicated in the induction of cognitive function-related side effects of cancer treatments, such as radiation therapy. Mice treated with PLX3397 (1.2 mg per day) while undergoing whole brain irradiation (IRR 3.3 Gy) were spared from radiation induced monocyte accumulation, declines in synaptic spine density, and cognitive deficits [40]. In a hippocampal-dependent novel object recognition task, PLX3397 treated mice performed similarly to non-radiated sham controls (sham = 30.34 ± 5.67 %; PLX IRR = 27.37 ± 4.50 %; $p > 0.05$; control IRR = 1.145 ± 4.24 %; $p < 0.05$). Since PLX3397 treatment has also been shown to potentiate the antitumor response to radiation therapy in preclinical models [41], it may be particularly useful in boosting the benefit-to-side effect profile in cancer treatment.

APOE4 interactions: Unknown

Aging and related health concerns: CSF-1R inhibitors show clinical utility for tenosynovial giant cell tumors, and may be useful as an adjunct to potentiate antitumor responses to immunotherapy in other cancers.

Types of evidence:

- 5 clinical trials for Pexidartinib
- 3 clinical trials for Edicotinib
- 1 clinical trial for Sotuletinib
- 1 clinical trial for Vimseltinib
- 1 clinical trial for ARRY-382
- 2 clinical trials for AMG 820
- 2 clinical trials for Axatilimab
- 2 clinical trials for Cabiralizumab
- 2 clinical trials for Emactuzumab
- 3 clinical trials for LY3022855
- Numerous laboratory studies

Cancer

Immunosuppressive (M2-like) tumor associated macrophages are linked with poor outcome in various cancers. They can modulate the tumor microenvironment in a manner that limits the ability of the immune system to remove the cancerous tissue. Cancer patients with the CSF-1R c.1085A>G SNP have less M2-like tumor associated macrophages and better disease-free survival [42]. The production of CSF-1 by tumor cells promotes the infiltration and proliferation of these immunosuppressive macrophages, therefore CSF-1R inhibitors, such as pexidartinib, have been proposed as a method of preventing/relieving this immunosuppression. Since tumor-mediated immunosuppression involves multiple mechanisms, targeting the macrophages alone is insufficient. With the exception of tenosynovial giant tumor, CSF-1R inhibitors show marginal to no benefit as a monotherapy, and preclinical studies suggest they are most likely to show benefit when used in combination with other immunosuppressive targets such as checkpoint inhibitors, which remove co-inhibitory molecules (i.e. PD-1) on anti-tumor T cells, or chemotherapeutics [43] [44; 45] [46; 47; 48; 49; 50].

Monotherapy

Tenosynovial giant cell tumor: BENEFIT

Pexidartinib: Tenosynovial giant cell tumor (TGCT) is a type of cancer of the joints (synovium) in which mass formation is driven by the recruitment of macrophages to the joint [51]. It can be localized or diffuse, and occurs around the knee in approximately 75% of cases. The diffuse form is also called Pigmented Villonodular Synovitis (PVNS). In many cases surgical resection would worsen joint function. TGCT is considered one of the most promising indications for CSF-1R inhibitors because it is

characterized by a pathological upregulation of CSF-1, leading to a massive infiltration of CSF-1R expressing macrophages into the tumor.
Pexidartinib (oral 1000 mg daily) was demonstrated to have clinically beneficial effects in Phase 1, 2, and 3 trials for TGCT. In a Phase 1/2 trial (NCT01004861) 23% of patients had disease stabilization and 1 patient had a partial response in the dose-escalation study (n=41), while 52% had a partial response and 31% had disease stabilization in the Phase 2 extension study (n=23) [52]. In the recent 25-week Phase 3 ENLIVEN trial (n=120) (NCT02371369), pexidartinib (a loading dose of 1000 mg/day for 2 weeks: 400 mg in morning plus 600 mg in evening, followed by 400 mg BID for remainder of study) significantly reduced tumor size with a 39% overall tumor response rate by RECIST criteria (39% vs 0%; P<0.0001). By 22 months, the overall response rate by RECIST was 53% (95% CI 40 to 64%), with a durable response throughout the monitoring period in the majority of responders [53]. Significant improvements were also seen with range of motion (+15% vs +6%), physical functioning (+4.1% vs -0.9%), and stiffness (-2.5% vs -0.3%). Based on data from this trial pexidartinib (Turalio®) was approved by the FDA for adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not responsive to improvement with surgery in August 2019 (Fda.gov). Turalio® has Orphan Drug designation for this indication.

Vimseltinib (DCC-3014): The orally bioavailable selective CSF-1R inhibitor, vimseltinib is currently being tested in a Phase 1/2 trial (NCT03069469). The Phase 1 dose escalation study included patients with advanced solid tumors and TGCT (n=39), while the ongoing Phase 2 will only include patients with TGCT [54]. Three patients with TGCT were enrolled in the Phase 1 study and received a loading dose of 30 mg (orally) daily for five days followed by 30 mg twice weekly in 28-day cycles. All three patients showed a reduction in tumor burden, quantified as -84% after nine cycles, -67% after 12 cycles, and -24% after two cycles, respectively. Participants also experienced improvement in pain, joint swelling, and range of motion. The treatment course led to dose-dependent increases in CSF-1 and IL-34, as well as decreased numbers of $CD16^+$ monocytes, which are pharmacodynamic markers indicative of target engagement.

AMG 820 (AMB-05X): The monoclonal antibody directed towards CSF-1R, AMG 820, was tested in an open-label Phase 2 trial in patients with TGCT of the knee (n=11) via intra-articular injection (NCT04731675). Improvement in terms of tumor reduction and functional outcomes were improved in all eight patients who completed the 12-week treatment course according to released topline results (Press release).

Glioblastoma: NO BENEFIT WITH PEXIDARTINIB

Pexidartinib: Although pexidartinib (oral 1000 mg daily) could successfully cross the blood-tumor barrier, it showed no efficacy in the treatment of patients with recurrent glioblastoma (n=61, average age 58.5 years) [55]. Only 8.8% (90% CI, 3.5%–21.6%) of patients reached the primary endpoint of 6-months progression-free survival in the multicenter Phase 2 RCT. In patients with surgical resection, 58% (7/12) were found to have a decrease in the number of tumor localized Iba1+ microglia, but across all patients there was no overall difference in tumor microglia in the treated population. While it is unclear whether the lack of efficacy was related to the incomplete microglial depletion, preclinical studies suggest that PLX3397 is only likely to offer clinical benefits when used in combination with immunotherapy and checkpoint inhibitors (i.e. anti-PD-1) [49; 56].

Acute myeloid leukemia: POTENTIAL BENEFIT WITH PEXIDARTINIB AS FLT3 INHIBITOR
Pexidartinib: Mutations in the FLT3 gene are common in acute myeloid leukemia. Pexidartinib was tested in a Phase 1/2 trial in patients with relapsed/refractory FLT3-ITD–mutant acute myeloid leukemia (n=90) (NCT01349049) for its ability to act as a FLT3 inhibitor [57]. The overall composite complete response rate in this study was 11%. The median survival of responders was 265 days (90% CI 170 to 422 days).
Edicotinib: A Phase 2 trial for edicotinib in acute myeloid leukemia was terminated due to low enrollment (NCT03557970).

Hodgkin lymphoma: POTENTIAL BENEFIT
Edicotinib: In an open-label Phase 1/2 trial in patients with relapsed or refractory Hodgkin lymphoma (n=21) (NCT01572519), the orally bioavailable CSF-1R inhibitor, edicotinib, showed dose-proportional exposure over a range of 150 to 450 mg per day (orally) and showed target engagement based on a greater than 80% inhibition of CSF-1R phosphorylation [58]. One patient, treated at the 150 mg per day dose, achieved a complete response, with progression free survival for at least 352 days. Eleven patients had disease stabilization that ranged from 1.5 to 8 months.

Adjunct therapy
Combination with Chemotherapy: POTENTIAL MINOR BENEFIT
Pexidartinib: In a Phase 1b open label trial (NCT01525602), patients with advanced solid tumors (n=54) were treated with between 600-1600 mg of oral pexidartinib per day in conjunction with paclitaxel (80 mg/m^2 i.v.) [59]. Efficacy was evaluated based on 38 patients, of which one had a complete response, five had a partial response, 13 had stable disease, and 17 had disease progression. Pharmacodynamic target engagement biomarkers indicated a compensatory 1.6- to 53-fold increase in

plasma CSF-1 levels, along with a 57-100% reduction in $CD14^{DIM}/CD16^{+}$ monocyte levels, indicative of CSF-1R inhibition.

Emactuzumab: The monoclonal antibody directed towards CSF-1R, emactuzumab (100 to 3000 mg i.v. q2w) was tested as a monotherapy (n=99) and in combination (n=54) with paclitaxel (80 mg/m^2 i.v. weekly) in an open-label, phase Ia/b trial in patients with advanced/metastatic solid tumors (NCT01494688) [60]. There were no objective responses with monotherapy, and the objective response rate with combination therapy was 7%, indicative of a lack of clinically significant antitumor activity in this population. Treatment was associated with a reduction in nonclassical $CD14^{DIM}/CD16^{BRIGHT}$ monocytes in peripheral blood, without significant effects on other monocyte subsets. While there was a reduction in M2-like tumor-associated macrophages, it was not accompanied by an enhancement in the immunostimulatory properties of the remaining tumor macrophages. Emactuzumab was also tested in a Phase 2 trial in combination with paclitaxel and bevacizumab (n=9) in patients with platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer (NCT02923739).

Combination with Immunotherapy: POTENTIAL BENEFIT

Cabiralizumab: The monoclonal antibody directed towards CSF-1R, cabiralizumab, has been tested in combination with other immunotherapies in clinical trials in patients with solid tumors. Cabiralizumab (4 mg/kg i.v. q2w) was tested in combination with the PD-1 inhibitor nivolumab (480 mg i.v. q4w) and stereotactic body radiotherapy in patients with advanced solid tumors (n=37) in a phase 1 trial (NCT03431948) [61]. Based on RECISTv1.1 response criteria, there was one complete and four partial responses. Cabiralizumab (4 mg/kg i.v. q2w) was also tested in combination with the CD40 agonist APX005M (0.3 mg/kg i.v. q2w) with or without nivolumab (240 mg i.v.) in patients with either melanoma, kidney cancer, or non-small cell lung cancer (NSCLC) resistant to anti-PD-1/PD-L1therapy (n=26) (NCT03502330) [62]. There was one unconfirmed partial response and eight patients with stable disease, but there were no obvious changes in tumor macrophage density or T-cell infiltration following treatment.

AMG 820: The monoclonal antibody directed towards CSF-1R, AMG 820 (1100 mg or 1400 mg q3w), was tested in combination with the anti-PD-L1 antibody pembrolizumab (200 mg i.v. q3w) in patients with advanced, refractory mismatch repair-proficient colorectal cancer, pancreatic cancer, anti- PD-1/PD-L1 naïve NSCLC with low (<50%) PD-L1 expression, or relapsed/refractory NSCLC after anti-PD-1/PD-L1 treatment with low or high (≥50%) PD-L1 expression (n=116) in a Phase 1b/2 trial (NCT02713529) [63].

There were three immune-related partial responses that lasted for 9.2, 10.0, and 12.5 months, respectively, but none of the patient cohorts in the Phase 2 study met the predefined threshold for efficacy. Target engagement biomarkers revealed an increase in serum CSF-1 and IL-34 along with a decrease in $CD16^+$ monocytes, indicative of CSF-1R inhibition.

ARRY-382: The selective CSF-1R inhibitor, ARRY-382 (200–400 mg QD orally) in combination with the anti-PD-L1 antibody pembrolizumab (Phase 1b: 2 mg/kg i.v./Phase 2: 200 mg/kg i.v. q3w) was tested in an open-label Phase 1b/2 trial (n=76) in patients with advanced solid tumors in the Phase 1b, and with pancreatic ductal adenocarcinoma, PD-1 resistant tumors, or platinum-resistant ovarian cancer in the Phase 2 study (NCT02880371) [64]. Limited clinical efficacy was seen, with two partial responses, lasting 29.2 and 3.1 months, respectively, in the Phase 1b, and one partial response lasting 2.4 months in the Phase 2 study.

Emactuzumab: The monoclonal antibody directed towards CSF-1R, emactuzumab (500–1350 mg i.v. q3w) was tested in combination with the anti-PD-L1 antibody atezolizumab (1200 mg i.v. q3w) in an open-label Phase 1 trial in patients with advanced solid tumors (n=221) (NCT02323191) [65]. The objective response rate of the study was 7.7%, including three complete responses and 14 partial responses. In a separate cohort of 40 metastatic urothelial bladder cancer (UBC) patients naïve to immune checkpoint therapy, there was one complete and three partial responses, with response duration ranging from 2.8 to 8.4 months. In a third cohort of patients with melanoma (n=18), NSCLC (n=40), or UBC (n=12) with prior immune checkpoint therapy, partial responses were seen in one, five, and one patient, respectively. $CSF\text{-}1R^+$ and $CD163^+$ tumor associated macrophages were reduced in tumor biopsies following treatment. Patients with prior immunotherapy had higher levels of tumor infiltrating macrophages at baseline, and showed a lower level of reduction, in comparison to those who were immunotherapy naïve. Emactuzumab was also tested in a Phase 1trial in combination with selicrelumab in patients with advanced solid tumors (n=38) (NCT02760797).

LY3022855: The monoclonal antibody targeting CSF-1R, LY3022855 (25-100 mg weekly), was tested in combination with the anti-PD-1 antibody durvalumab (750 mg i.v. q2w) or the anti- CTLA-4 antibody tremelimumab (75 mg i.v. q4w) in a Phase 1a/b trial in patients with advanced solid tumors, NSCLC, or ovarian cancer (n=72) (NCT02718911) [66]. Overall response rates were low in this population. There were three responders in the LY3022855 (100 mg) plus durvalumab group, including one complete response and two partial responses. Anti-drug antibodies were present in 21.2% of treated patients. No responses were seen with LY3022855 monotherapy in a phase 1 dose-escalation trial in patients with

advanced solid tumors (n=52) (NCT01346358)[67]. Additionally, no objective responses were seen with LY302285 monotherapy in a Phase 1 study in patients with advanced refractory metastatic breast cancer or metastatic castration-resistant prostate cancer (n=34) (NCT02265536) [68].

Sotuletinib: A Phase 1/2 trial testing the orally available CSF-1R inhibitor, sotuletinib, alone (300–1600 mg/d weekly; or 4 days on/10 days off at 300–1200 mg/d) or in combination (150-1400 mg/d weekly; or 4 days on/10 days off at 300–1200 mg/d) with the anti-PD-1 antibody sotuletinib (400 mg i.v. every 4 weeks) in patients with advanced solid tumors (n=146) (NCT02829723), was terminated by its sponsor (Novartis). There were two partial responses in patients with relapsed/refractory glioblastoma (n=18).

Axatilimab (SNDX6532): The monoclonal antibody targeting CSF-1R, axatilmab was tested in a Phase 1a/b trial in patients with advanced solid tumors (NCT03238027). It was tested as a monotherapy (1, 2, 3, 6 mg/kg every 2 weeks, and 6 mg/kg every 4 weeks) or in combination (1, 2, or 3 mg/kg q2w) with the anti-PD-1 antibody durvalumab (1500 mg q4w) (n=32) [69; 70]. Treatment resulted in plasma elevations of CSF-1 and IL-34 as well as depletion of circulating non-classical monocytes ($CD14^{+}CD16^{hi}$), but there were no objective responses.

Chronic Graft-Versus-Host Disease: POTENTIAL BENFIT FOR AXATILIMAB
Axatilimab: The monoclonal antibody targeting CSF-1R, axatilimab, was tested in a Phase 1/2 trial in patients with recurrent or refractory chronic graft-versus-host disease (cGVHD) (n=40) (NCT03604692). In the Phase 1 study, patients were dosed at 0.15, 0.5, 1, or 3 mg/kg q2w or 3 mg/kg q4w. In the Phase 2 study, they were dosed at 1 mg/kg q2w. The overall response rate by cycle 7 day 1, was 82% (95% CI 60 to 95) in the Phase 2 cohort and 67% (95% CI 50 to 81) in the total cohort [71]. There was a sustained response lasting over 20 weeks in 33% of patients. Biomarker analysis indicated a reduction in CSF-1R+ macrophages in skin biopsies following treatment.

Rheumatoid arthritis: NO BENEFIT WITH EDICOTINIB
Edicotinib: The oral CSF-1R inhibitor, edicotinib (100 mg BID for 12 weeks) was tested in a double-blind, placebo-controlled Phase 2 RCT in patients with active rheumatoid arthritis that is not well managed on current disease-modifying antirheumatic therapies (n=95) (NCT01597739) [72]. The primary endpoint of a change in the 28-joint Disease Activity Score with CRP (DAS28-CRP) from baseline to week 12 was not met. The changes in DAS28-CRP were 1.15 for the edicotinib group and 1.42 for the placebo group. Target engagement was demonstrated based on an increase in CSF-1 levels and a decrease in $CD16^{+}$ monocytes, suggesting that the lack of efficacy was not due to a lack of adequate CSF-1R inhibition. The

CSF-1R inhibitor PLX5622 was also tested in a clinical trial in patients with rheumatoid arthritis (NCT01329991), but no results are available and development has been discontinued.

Crohn's disease: NO BENEFIT WITH EDICOTINIB
Edicotinib: The orally active CSF-1R inhibitor, edicotinib (orally BID for 12 weeks) was tested in a Phase 2a double-blind, placebo-controlled RCT in patients with moderately to severely active Crohn's disease (n=93) (NCT03854305). This study failed to meet its primary endpoint of the change from baseline to week 12 in Crohn's Disease Activity Index score, which the investigators attributed to a higher-than-expected placebo response rate. Following this study, Janssen declined their right to buy back the drug from Provention Bio, and Provention noted that it would discontinue in-house development and instead focus on other assets in its autoimmunity pipeline (Fierce Biotech article).

Regeneration/Healing: POTENTIAL HARM (preclinical)
Monocyte (macrophage/microglial) mediated processes have been shown to be important for the proliferation of precursor cells associated with regenerative processes[73; 74]. In a zebrafish model, phagocytic monocytes were found to be necessary for cardiac cell proliferation and heart regeneration following injury [74]. Therefore, chronic microglial depletion may impair healing processes following acute tissue damage.

Safety: Clinically tested inhibitors show on-target class effects of increased liver enzymes, which are usually asymptomatic, though pexidartinib contains a black box warning for hepatotoxicity. Other common side effects include fatigue, nausea, and edema.

Types of evidence:

- 5 clinical trials for Pexidartinib
- 2 clinical trials for Edicotinib
- 1 clinical trial for Sotuletinib
- 1 clinical trial for Vimseltinib
- 1 clinical trial for ARRY-382
- 3 clinical trials for AMG 820
- 2 clinical trials for Axatilimab
- 2 clinical trials for Cabiralizumab
- 2 clinical trials for Emactuzumab

- 3 clinical trials for LY3022855
- Numerous laboratory studies

CSF-1R is expressed on Kupffer cells in the liver, which is a macrophage-lineage cell that plays a role in filtration of particulate matter from the blood [59]. The loss of these cells with CSF-1R inhibition leads to a reduction in filtration, which can lead to asymptomatic elevations in circulating liver enzymes that are not tied to organ damage. The increase in liver enzymes is an on-target class effect of CSF-1R inhibitors. A major function of the Kupffer cells is to remove pathogens from the blood, thus chronic depletion of these and other tissue resident macrophages could potentially pose an increased risk for infection.

***Pexidartinib**:* The short-term safety of pexidartinib has been tested in several RCTs involving cancer patients, primarily those with TGCT. In all trials the most common adverse events were fatigue (48%-65%), change in hair color, nausea, anemia, and decreased white blood cell counts [52; 75]. Fatigue was the most common reason for dose reduction. The FDA prescribing label lists increased lactate dehydrogenase, increased aspartate aminotransferase (AST), hair color changes, fatigue, increased alanine aminotransferase (ALT), decreased neutrophils, increased cholesterol, increased alkaline phosphatase, decreased lymphocytes, eye edema, decreased hemoglobin, rash, dysgeusia, and decreased phosphate as the most common (>20%) adverse reactions. In the Phase 3 trial for TGCT (n=120), the most common treatment-related grade 3 or 4 adverse events were increased AST (10% vs 0%), increased ALT (10% vs 0%), increased alkaline phosphatase (7% vs 0%), and hypertension (5% vs 0%)
[53]. Hair color changes were also common with pexidartinib (67% vs 3%), which is attributable to c-KIT inhibition. The most common serious adverse event was liver toxicity. The Data Monitoring Committee stopped enrollment of the trial due to the emergence of mixed and cholestatic hepatotoxicity. Three patients taking pexidartinib had levels of transaminases (ALT and AST) ≥3 times the upper limit of normal along with increased levels of total bilirubin and alkaline phosphatase that were ≥2 times the upper limit of normal. Evidence for hepatoxicity was also seen with the use of pexidartinib in other cancers, including a case requiring a liver transplant and another was associated with death. The cases of hepatotoxicity emerged within the first two months of use and was associated with increased alkaline phosphatase. This pattern does not fulfill Hy's law criteria, but is consistent with mixed and cholestatic hepatotoxicity. As a result of these findings, pexidartinib (Turalio®) is only available through a Risk Evaluation and Mitigation Strategy Program and contains a **black box warning** for hepatotoxicity (FDA label). Liver test monitoring is required at initiation and at specified intervals. A study assessing longer-

term safety, based on data from open-label extension studies (n=130) found that most cases of liver toxicity developed within the first two months and no cases emerged after 24 months [76]. There were no new cases of hepatotoxicity in the long-term (up to 76 months) follow up.
Drug interactions: Pexidartinib has drug interactions with CYP3A inhibitors, inducers, or substrates, UGT Inhibitors, proton-pump inhibitors, and high-fat meals. It should not be used in combination with other drugs known to cause hepatotoxicity (FDA label).

Edicotinib: In a Phase 1/2 trial, edicotinib was tested at oral doses ranging from 150 to 600 mg per day or 150 mg twice per day in patients with relapsed or refractory Hodgkin lymphoma (n=21) [58]. The most common adverse events considered drug related were nausea (n = 6), headache (n=5), and pyrexia (n = 5). Grade 3 treatment-related adverse events included were anemia and lymphopenia, gastric obstruction, peripheral edema, abnormal hepatic function, hyperlipasemia, and hypoalbuminemia. There was also a case of grade 4 laryngeal inflammation and a case of grade 5 oropharyngeal pain.
In a Phase 2 RCT in patients with active rheumatoid arthritis (n=95), edocitinib (100 mg BID) treatment for 12 weeks resulted in increases in creatine kinase (138%), lactate dehydrogenase (48%), AST (33%), and ALT (24%) relative to placebo, as is consistent with other CSF-1R inhibitors [72]. The most common (>5%) adverse event that was more frequent in the edicotinib group was an elevation in lactate dehydrogenase. Four participants had ALT elevations >3 times the upper limit of normal, but they were not accompanied by increases in bilirubin. Consistent with its mechanism of action, edicotinib was also associated with mild decreases in levels of neutrophils and monocytes.

Sotuletinib: In a Phase 1 trial in patients with advanced solid tumors (n=146) as monotherapy (300–1600 mg/d weekly; or 4 days on/10 days off at 300–1200 mg/d) or in combination (150–1400 mg/d weekly; or 4 days on/10 days off at 300–1200 mg/d) with spartalizumab, there were seven dose limiting toxicities in seven patients with monotherapy, which included increased in amylase, increased lipase, increased AST, increased alkaline phosphatase, and sudden death [77]. There were also seven dose limiting toxicities in the combination arm, which included increased amylase, increased AST, increased ALT, dizziness, and hyperuricemia. There were grade 3 treatment-related adverse events in 25% of patient with monotherapy and 33% with combination therapy. The most common treatment-related adverse events were increased AST (35%), nausea (29%), and vomiting (23%) with monotherapy, and a similar profile with combination therapy. Similar to other CSF-1R inhibitors, sotuletinib resulted in cases of asymptomatic elevations in liver enzymes in Phase 1 trials [78]. Since similar elevations have been seen in preclinical studies with rats and monkeys, a study was conducted testing sotuletinib (150 mg/kg/day for 43 days) in male rats to determine whether these elevations were reflective of organ

toxicity [78]. The use of labeled ALT indicated that the elevation in circulating levels was not due to damage in the skeletal muscle, heart, fat tissues, brain or the gastrointestinal system. Histopathological analysis confirmed that there was no clinical pathology in the liver, and that the increase in circulating ALT and AST was due to a reduction in Kupffer cells and other CSF-1R expressing monocyte lineage cells in the liver, an established on-target effect of CSF-1R inhibition.

Vimseltinib: In a Phase 1 dose escalation trial vimseltinib (starting at 10 mg orally per day) was tested in patients with advanced solid tumors (n=39) [54] (Poster). There were three grade 3 treatment-related adverse events, including increased AST, increased amylase, and colitis, as well as one grade 4 increase in lipase. There were two dose-limiting toxicities at the 10 mg daily dose, which were grade 4 increased lipase, and grade 3 hypocalcemia.

ARRY-382: In an open-label Phase 1b/2 trial in patients with advanced solid tumors testing ARRY-382 in combination with pembrolizumab (n=76), 300 mg per day (orally) was identified as the maximum tolerated dose for ARRY-382, as dose-limited toxicities were identified in two patients at the 400 mg dose, which included a grade 2 increase in blood creatine phosphokinase, and grade 3 increase in liver enzymes ALT, AST, and bilirubin, and in one patient at the 300 mg dose, which was grade 3 acute pancreatitis [64]. The increase in liver enzymes, typically asymptomatic and reversible, is an on-target class effect of CSF-1R inhibitors. Correspondingly, the most common ARRY-382-related adverse events were increased transaminases (10.5%–83.3%) and increased creatine phosphokinase (18.2%–50.0%). One patient at the 300 mg dose experienced a serious adverse event, a grade 3 elevation in ALT and AST.

EI-1071: EL-1017 was tested in a Phase 1trial in healthy volunteers (n=58) (NCT04238364). Elixiron indicated that the compound was found to be relatively safe in this study, but further details have not yet been made available.

AMG 820: In a Phase 1 dose escalation trial, AMG 820 was tested at doses ranging from 0.5 mg/kg i.v. qw to 20 mg/kg i.v. q2w in patients with advanced solid tumors (n=25) [79]. There was one dose limiting toxicity of nonreversible grade 3 deafness at the highest dose in a patient who had previously been treated with a chemotherapeutic with the potential for ototoxicity. The most common treatment-related adverse events were periorbital edema (44%), increased AST (28%), fatigue (24%), nausea (16%), increased blood alkaline phosphatase (12%), and blurred vision (12%). Grade 3 treatment-related adverse events included increased AST, hypertension, and periorbital edema. Liver enzyme elevations

resolved with the discontinuation of AMG 820. AMG 820 (1100 or 1400 mg iv. q3w) was tested in a Phase 1b/2 trial in combination with pembrolizumab in patients with select types of solid tumors (n=116) [63]. Over half (58.6%) of patients experienced a grade ≥3 treatment-related adverse event. The most common were increased AST (27.6%), anemia (17.2%), increased lipase (12.9%), rash/maculopapular rash (11.2%), and hypophosphatemia (10.3%). There were two fatal events that were considered treatment related, which included a tumor flare and pneumonitis. The dose of AMG 820 was reduced from 1400 to 1100 mg during the study due to safety signals, including elevated ALT and AST and periorbital edema, which are effects that have been attributed to CSF-1R inhibitors in other studies. In a Phase 2 trial in patients with TGCT (n=11), AMG 820 was administered via intra-auricular injection. Although the full safety profile has not yet been reported, topline results indicated that only grade 1 transaminase elevations were present following this route of administration (Press release).

Axatilimab: In a Phase 1 dose-escalation trial in patients with advanced solid tumors (n=32), ataxilimab was dosed at 1, 2, 3 and 6 mg/kg i.v. q2w or 6 mg/kg qw4 as a monotherapy or 1, 2, and 3 mg/kg i.v. q2w in combination with durvalumab. The most common treatment-related adverse events were fatigue (31%), periorbital edema (31%), increased AST (22%), increased blood creatinine phosphokinase (22%), nausea (13%), and decreased appetite (13%). Grade 3 or 4 treatment-related adverse events included increased creatinine phosphokinase, increased amylase, increase AST, and increased lipase [69]. There was one serious adverse event of pneumonitis at 6 mg/kg q2w that was considered possibly drug related. Dose limited toxicities included grade 3 fatigue in two participants at 2 mg/kg and a case of grade 3 pneumonitis at 6 mg/kg q2w. Despite asymptomatic increases in liver enzymes, there was no evidence of hepatotoxicity. With combination therapy the common treatment-related adverse events were peripheral edema (33%), fatigue (25%), periorbital edema (25%), and hypothyroidism (25%) [70]. In a Phase 1/2 trial in patients with chronic graft-versus-host disease (n=40), there were two dose limiting toxicities at the 3 mg/kg q2w dose including an increase in creatinine phosphokinase from grade 2 to grade 4 coupled with evidence of inflammatory myopathy, as well as a case of grade 3 lipase elevation without evidence of pancreatitis [71]. On-target, grade 3 treatment-related adverse events included increased ALT, AST, GGT, creatinine phosphokinase, lipase, and periorbital edema.

Cabiralizumab: In a Phase 1 trial in patients with melanoma, kidney cancer, or NSCLC (n=26), cabiralizumab (4 mg/kg i.v. q2w) was tested in combination with APX005M and nivolumab. All patients experienced at least one treatment-related adverse event [62]. The most common were asymptomatic elevations of lactate dehydrogenase (n = 26), creatine kinase (n = 25), AST (n = 25), and ALT (n = 19); periorbital edema (n = 17), and fatigue (n = 13), which were anticipated with CSF-1R inhibition, and

attributable to cabiralizumab. Around half of the creatine kinase and aminase elevations were grade 3. There was one asymptomatic grade 4 increase in creatine kinase, and one dose limiting toxicity of acute respiratory distress syndrome. Periorbital edema was grade 1-2 and resolved upon discontinuation of cabiralizumab. Cabiralizumab (4 mg/kg i.v. q2w) was also tested in a Phase 1 trial in combination with stereotactic body radiotherapy and nivolumab in patients with advanced solid tumors (n=37) [61]. There were seven dose limiting toxicities, which included three grade 4 creatine phosphokinase elevations, a grade 3 maculopapular rash, grade 3 periorbital edema, grade 3 colitis, and a case of grade 4 hyperglycemia/diabetic ketoacidosis. Notably, this study had a separate arm including radiotherapy and nivolumab with a different immunotherapy (urelumab), in which there were no dose limiting toxicities, suggesting that these adverse events were attributable to the presence of cabrilizumab. These are also the types of toxicities that are consistent with other CSF-1R inhibitors.

Emactuzumab: In a Phase 1 trial, emactuzumab was tested as a monotherapy (n=99) or in combination with paclitaxel (n=54) in patients with advanced/metastatic solid tumors at doses ranging from 100 to 3000 mg i.v. every two or three weeks [60]. The maximum tolerated dose was not reached, and there were no dose limiting toxicities with monotherapy. There were four treatment-related adverse events that led to discontinuation, including grade 2 asthenia (weakness), grade 4 increased blood creatine phosphokinase, grade 4 hematoma, and grade 2 laryngeal edema. There were 14 treatment-related grade ≥3 adverse events, including asthenia and anemia, which were the most common, followed by fatigue, hypophosphatemia, nausea, and hypertension. There were two dose limiting toxicities with combination therapy. One patient experienced grade 4 hypokalemia and grade 3 gastrointestinal inflammation and hemorrhagic enterocolitis, while another patient experienced a grade 5 gastrointestinal perforation, that was ultimately fatal. Grade 3 or 4 adverse events occurred in 69% of patients taking emactuzumab in combination with paclitaxel, with anemia and hypophosphatemia as the most common. Emactuzumab (500–1350 mg i.v. q3w) was also tested in a Phase 1 trial in combination with atezolizumab (n=221) [65]. Treatment-related grade ≥3 adverse events were common (50.2% of patients). The most common were fatigue (6.3%), rash (6.3%) each), asthenia (5.9%), anemia (3.6%) and increased AST (3.6%). Relative to what is typically seen with atezolizumab, the combination with emactuzumab resulted in higher rates of fatigue and skin rash. Based on these studies the optimal dose for emactuzumab was determined to be 1000 mg i.v. (q2w or q3w, depending on combination drug). However, a PK/PD modeling study suggests that the optimal biological dose is actually ≥ 900 mg iv. q2w, which allows for target saturation over the entire dosing cycle of greater than 90% [80].

LY3022855: In a Phase 1 dose escalation trial, LY3022855 was tested with both weight-based and non-weight-based dosing in patients with advanced solid tumors (n=52) [67]. The highest weighted dose of 2.5 mg/kg i.v. qw led to drug-related adverse events in all patients tested at that dose. The most common treatment-related adverse events included increased AST levels (42.3%), increased blood creatine phosphokinase levels (36.5%), fatigue (30.8%), nausea (25.5%), asymptomatic increased lipase (21.2%), diarrhea (17.3%), anorexia (13.5%), increased ALT (11.5%), increased amylase (11.5%), increased blood lactate dehydrogenase (11.5%), muscular weakness (11.5%), pyrexia (11.5%), and vomiting (11.5%). Treatment-related serious adverse events included acute kidney injury, delirium, headache, hypotension, injection site reaction, left ventricular dysfunction, nausea, pancreatitis, pyrexia, rhabdomyolysis, sudden death, tachycardia, and urticaria. The non-weight-based 100 mg i.v. qw dose was selected for further study based on this trial. In a Phase 1 trial in which LY3022855 was tested at doses of 1.25 mg/kg q2w, 1.0 mg/kg on weeks 1, 2, 4, and 5, and 100 mg weekly or q2w in patients with advanced breast cancer or prostate cancer (n=34), treatment-related grade 3 adverse events included increased blood creatine phosphate, increased alkaline phosphatase, increased lipase, increased ALT, nausea, and fatigue [68]. Treatment-related grade 4 adverse events included increased gamma-glutamyl transferase (GGT), increased AST, and increased amylase. Other treatment-related adverse events included decreased appetite, vomiting, and periorbital edema. In another Phase 1 trial, LY3022855 (up to 100 mg i.v. qw) was tested in combination with durvalumab or tremelimumab (n=72) [66]. Grade 3 treatment-emergent adverse events occurred in 69.4% of patients, including anemia (13.9%), increased blood creatine phosphokinase (11.1%), hyponatremia (9.7%), increased AST (8.3%), fatigue (6.9%,), hypertension (6.9%), increased lipase (5.6%), and lymphopenia (5.6%). Treatment-related face edema was observed in 26.4% patients, which is a common feature of CSF-1R inhibitors.

Sources and dosing:

Pexidartinib (Turalio®) is marketed by Daiichi Sankyo, and is available for patients with tenosynovial giant cell tumors associated with severe morbidity or functional limitations and not responsive to improvement with surgery, though its use is restricted through a Risk Evaluation and Mitigation Strategy Program due to the potential for hepatotoxicity. The recommended dose is 250 mg orally twice daily with a low-fat meal (FDA label). Currently, none of the other CSF-1R inhibitors have been approved for any indication, and are available as part of clinical trials. The small molecule CSF-1R inhibitors are all administered orally, while the CSF-1R monoclonal antibodies are administered intravenously. One of the antibodies, AMG 820 (AMB-05X), is also being administered via intra-auricular injection in patients with TGCT.

Research underway:

Clinical trials

Pexidartinib: According to Clinicaltrials.gov, there are currently six active trials for pexidartinib. These include trials for patients with TGCT, children and young adults with refractory leukemias and refractory solid tumors, and patients with unresectable or metastatic KIT-mutated melanoma.

Edicotinib: According to Clinicaltrials.gov, there is currently one active Phase 1 trial testing edicotinib in patients with high-risk, resectable localized or locally advanced prostate cancer. There is also one clinical trial testing edicotinib in patients with Alzheimer's disease, but the status of this trial is listed as unknown.

Sotuletinib: According to Clinicaltrials.gov, there is currently one active Phase 2 trial testing sotuletinib in patients with ALS.

Vimseltinib: According to Clinicaltrials.gov, there are active Phase 1/2 and Phase 3 trials in patients with TGCT as well as a Phase 1 trial of vimseltinib in combination with avelumab in patients with advanced/metastatic sarcomas.

AMG 820 (AMB-05X): According to Clinicaltrials.gov, there are three active trials for AMB-05X in patients with TGCT.

Axatilimab: According to Clinicaltrials.gov, there are five active trials for axatilamab in patients with relapsed/refractory classical Hodgkin lymphoma, high risk triple-negative breast cancer, intrahepatic cholangiocarcinoma, or graft vs host disease.

Cabiralizumab: According to Clinicaltrials.gov, there are currently six active clinical trials for cabiralizumab in combination with nivolumab (and other drugs) in advanced melanoma, non-small cell lung cancer or renal cell carcinoma, relapsed/refractory peripheral T cell lymphoma, advanced pancreatic cancer, head and neck cancer, hepatocellular carcinoma, and localized triple negative breast cancer.

Emactuzumab: According to Clinicaltrials.gov, there is currently one active Phase 3 trial for emacuzumab in TGCT.

LY3022855: According to Clinicaltrials.gov, there are currently two active clinical trials testing LY3022855 in patients with melanoma in combination with MEK/BRAF inhibitors, and in patients with borderline resectable adenocarcinoma of the pancreas in combination with cyclophosphamide, GVAX, and pembrolizumab.

Preclinical development

There are numerous groups working on developing CSF-1R inhibitors with improved selectivity profiles [81; 82; 83].

PET development

Several groups have been working on trying to develop PET ligands for CSF-1R, which would be useful for monitoring microglia, neuroinflammation, and for target engagement with CSF-1R inhibitors. The major issue has been with non-specific binding. The most extensively tested CSF-1R PET tracer is [^{11}C]CPPC, which showed binding in postmortem brain tissue from AD patients and binding in the non-human primate brain which increased with an inflammatory stimulus and decreased with blocking [84]. However, tracer uptake was similar between wildtype and CSF-1R mice, suggestive of a degree of non-specific binding. Additionally, the [^{3}H]CPPC labeled version of the tracer showed a high degree of non-specific binding in the CNS in rodents [85]. The [^{11}C]GW2580 tracer showed higher sensitivity toward changes in CSF-1R in rodent and non-human primate models of neuroinflammation in a head-to-head study [86]. A group in Japan developed [^{11}C]NCGG401, which is based off of the selective CSF-1R inhibitor BLZ945 (sotuletinib) with an IC_{50} of 27.1 nM for CSF1R [87]. But its utility in the CNS is limited because it is a substrate for efflux transporters. A group from Stanford also tried to radiolabel BLX945 ([^{11}C]BLZ945), which had an IC_{50} of 6.9 ± 1.4 nM, but was similarly a substrate for efflux transporters and brain binding was largely non-specific [88]. The same group at Stanford developed a series of tracer compounds based off compound 18b from Roche [89]. The most promising was [^{11}C] labeled compound 4 (4-((5-Methoxy-6-((4-methoxybenzyl)oxy)pyridin-3-yl)oxy)-N-methylpicolinamide), which showed an IC_{50} of 12 ± 3 nM for CSF-1R, without appreciable affinity for related kinases c-KIT and PDGFRβ. In mice, the tracer showed good brain uptake, which was reduced by the use of blockers, good metabolic stability, without strong evidence of efflux. A group in Korea developed a novel tracer based on CPPC, [^{18}F]1 (5-cyano-N-(4-(4-(2-[18F]fluoroethyl)piperazin-1-yl)-2-(piperidin-1-yl)phenyl)furan-2-carboxamide), which had an IC_{50} of 3.42 ± 0.33 nM [90]. It showed increased brain binding in a model of

inflammation, which was reduced with blocking using CPPC, but more work is needed to confirm specificity for CSF-1R relative to related kinases.

Search terms:

Pubmed, Google: Pexidartinib or PLX3397 +
Alzheimer's disease, dementia, neuroprotection, aging, cancer, clinical trials, safety

Websites visited for CSF-1R inhibitors:

- Clinicaltrials.gov (Pexidartinib; ARRY-382; Edicotinib; Sotuletinib; Vimseltinib; AMG 820; AMB-05X; Axatilimab; Cabiralizumab; Emactuzumab; LY3022855)
- PubChem
- DrugBank.ca

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