*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.*

# Trametinib

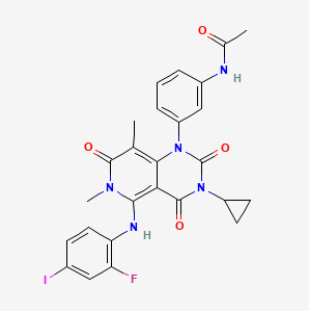
**Evidence Summary**

Trametinib is a targeted therapy for specific cancers. Preclinical work suggests it may increase autophagy and neurogenesis in AD and ALS, but there is currently no in-human data to suggest benefit in dementia.

**Neuroprotective Benefit:** Some preclinical work reports that trametinib is neuroprotective in models of ALS and AD. The drug is currently in trial for ALS in one of the first in human, non-oncological indication for this medication.

**Aging and related health concerns:** Trametinib provides some benefit in certain subtypes of advanced cancers but is less effective than combination treatment of trametinib + dabrafenib.

**Safety:** At oncological doses, trametinib's side effects can include serious rash and serious cardiovascular, ocular, and GI adverse events. These effects may be mitigated at lower doses for neurodegenerative indications, but human data on this is not yet available.

| | | |
|---|---|---|
| **Availability**: Rx | **Dose**: For melanoma, non-small cell lung cancer, thyroid cancer, and solid cancers: 2 mg daily, orally. | **Chemical formula:** $C_{26}H_{23}FIN_5O_4$<br>**MW**: 615.4<br>  <br>Source: PubChem |
| **Half-life**: 3.9 – 4.8 days | **BBB**: Limited penetrance | |
| **Clinical trials**: Largest meta-analysis included 1,449 patients on trametinib or trametinib + dabrafenib | **Observational studies**: Largest observational study was a retrospective chart review including 499 patients who received trametinib + dabrafenib | |

**What is it?**

Trametinib (brand name Mekinist) is a cancer drug. It is a small molecule reversible allosteric inhibitor of MEK1 and MEK2, which are proteins in an important signaling cascade known as the Ras-Raf-MEK-ERK pathway. This signaling pathway is also sometimes referred to as the MAPK/ERK pathway, as it is a branch of MAPK signaling. A stimuli – often growth factors – activate Ras, which in turn activates Raf, which activates MEK, which then activates ERK. ERK then translocates to the nucleus where it activates transcription factors, thus directing gene expression (Khunger et al., 2018). Mutations in this pathway can cause cancer. For instance, mutations in BRAF, one of the Raf family members, is a driving mutation in approximately 40% of melanomas. An overwhelming majority of BRAF mutations in melanoma are a single amino acid mutation of valine 600, known as BRAF V600. Targeted therapies have been developed to address these mutations, including BRAF inhibitors such as dabrafenib, and downstream MEK inhibitors like trametinib (Knispel et al., 2018).

Trametinib is approved for use as a monotherapy for certain cancers with BRAF V600 mutation, including unresectable / advanced metastatic melanoma, or as a combination therapy with dabrafenib, a BRAF inhibitor, for the same indication. The combination of trametinib and dabrafenib is also approved for treatment of BRAF V600 metastatic non-small cell lung cancer, BRAF V600 metastatic

anaplastic thyroid cancer with no other treatment options, and BRAF V600 pediatric gliomas (Dabrafenib + Trametinib Patient Website), and has FDA approval to treat almost any kind of metastatic or unresectable solid tumor with a BRAF V600E mutation (NCI Press Release).

Genuv, a biotech company, has a proprietary drug discovery platform called ATRIVIEW. According to a pre-print that has not yet been published in its final peer-reviewed form, ATRIVIEW uses neural stem cells from a mouse model of Alzheimer's Disease (Tg2576) to assess whether candidate compounds have neuroprotective effects and/or otherwise promote neurogenesis or neural-homeostasis. Their most potent FDA-approved hit was trametinib (Yoon et al., Preprint). Their preclinical data in an ALS and an AD model have both served as rationale for their ongoing Phase 1/II trial in ALS and their ongoing IND-enabling study for AD (Genuv Pipeline).

**Neuroprotective Benefit:** Some preclinical work reports that trametinib is neuroprotective in models of ALS and AD. The drug is currently in trial for ALS in one of the first in human, non-oncological indication for this medication.

*Types of evidence:*

- 5 review articles
- 9 laboratory experimental studies
- 2 conference presentations

***Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function***:

No studies in humans have evaluated whether trametinib may assist in prevention of dementia, decline, or improvement of cognitive function.

***Human research to suggest benefits to patients with dementia***:

No studies in humans have evaluated whether or not trametinib has any benefit for dementia patients.

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

Genuv identified trametinib using ATRIVIEW, a proprietary phenotypic drug discovery platform that screens compounds using neural stem cells for neuroprotective, neurogenesis, or neural-homeostasis effects. Part of their approach rests on the apparent perturbation of adult neurogenesis in AD patients; by screening FDA- approved compounds for their efficacy in promoting neural differentiation of neural stem cells, the company hopes to identify novel, promising targets. Trametinib was their most potent hit. They also discuss prior papers that report Aβ interferes with neurogenesis through MEK/ERK signaling (Yoon et al., Preprint).

One theory of a neuroprotective potential mechanism of action of trametinib comes from a recent paper from Chun and colleagues from Genuv. In a thorough paper utilizing cell and animal models, the authors report that trametinib reduces synapse loss, improves neural functioning, and mitigates cognitive impairment in a mouse model of AD. They found that through MEK1/2 and ERK1/2 inhibition, and subsequent disinhibition of transcription factor EB (TEFB), trametinib increases autophagic lysosome activity, thus improving clearance of Aβ and reducing cell death in cell studies (Chun et al., 2022).

Trametinib is currently being assessed in a Phase 1/II clinical trial for safety, tolerability, and efficacy in ALS patients (See "Research Underway" section for more details). Genuv presented some preclinical data at a conference that underlies their ongoing clinical trial. The authors report that ERK levels are increased in an ALS mouse model as well as cell models expressing SOD1 G93A, a common genetic model of ALS. The authors reported that trametinib treatment of the ALS mouse models improved survival, muscle strength, and motor performance. Trametinib treated mice also had reduced loss of spinal motor neurons. The authors found that trametinib treatment increased autophagic lysosome activity and enhanced degradation of mutant protein in this model, and hypothesize that this is a main mechanism of action for benefit in this model (Genuv Publication Page; PDF Link).

Genuv has presented preclinical data in conference presentations along with a pre-print article detailing another potential mechanism of action. They report finding that trametinib induced neuronal differentiation in neural stem cells from adult AD model mice. Moreover, they found that treatment with trametinib increased neurogenesis in several brain regions, including the hippocampus and cortex, in mouse models of AD. Trametinib also mitigated neuronal loss and morphology defects, and improved cognitive function in these AD mouse models (Yoon et al., Preprint).

The MAPK/ERK pathway is involved with many cellular processes and has potential links to neurodegeneration beyond modulation of autophagy and apoptosis / neurogenesis, such as phosphorylation of tau and Aβ and regulation of β- and γ-secretase (Kim & Choi, 2010). In cell culture models MEK has also been suggested to phosphorylate TDP-43, a protein involved in ALS, and through this phosphorylating activity may modulate TDP-43 function. However, the effect of this activity has yet to be determined (Li et al., 2017).

MAPK signaling pathways also play complex roles in immunity, many of which are not fully understood or explored in a neurodegenerative context. MEK can be activated by proteins other than Raf, and MEK/ERK are part of signaling cascades downstream of several immune receptors (Reviewed by Arthur & Ley 2013; Zarrin et al., 2020). One preclinical paper found that trametinib treatment mitigated cognitive dysfunction in a mouse model of traumatic brain injury (TBI) as compared to vehicle-treated mice, and they suggest this is in part due to immune modulation. The authors reported that mice with TBI and treated with trametinib had decreased brain TNF-α levels compared to TBI mice with vehicle treatment, and that treating cells with trametinib blunted microglial response to the proinflammatory compound LPS as compared to no trametinib treatment (Huang et al., 2020). Another preclinical paper also found that trametinib treatment of cells resulted in an attenuated response to LPS and reduced TNF-α levels as compared to cells treated just with LPS (Shi-lin et al., 2015). The relevance of these findings to neurodegeneration in humans does not appear to have been explored in published papers.

One caveat to any direct neuroprotective effects that trametinib may have is the extent of its brain distribution. Trametinib is an in vitro substrate for both P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), both of which are efflux pumps that can affect drug concentration in the brain. In vivo studies indicate that P-gp rather than BCRP is primarily responsible for efflux of trametinib from the brain in mice, though the authors caveat that the relative contribution of the two efflux pumps may be different in human patients (Vaidhyanathan et al., 2014),

***APOE4 interactions***: Unknown.

**Aging and related health concerns:** Trametinib provides some benefit in certain subtypes of advanced cancers but is less effective than combination treatment of trametinib + dabrafenib.

*Types of evidence:*

- 1 Cochrane meta-analysis
- 5 systematic reviews & meta-analyses
- 2 randomized controlled trials
- 3 open label studies
- 1 observational study
- 1 review
- 1 laboratory experimental paper

**Cancer:** BENEFIT IN SPECIFIC SUBTYPES

Trametinib is approved as a monotherapy to treat patients with unresectable or metastatic melanoma with mutations of BRAF V600E or V500K. It is also approved in combination with dabrafenib to treat this subtype of melanoma as well as other cancers with BRAF V600 mutations, including metastatic non-small cell lung cancer, metastatic anaplastic thyroid cancer, and metastatic solid tumors. For the latter two cancer subtypes, this combination therapy is specifically indicated when there are no other treatment options.

A 2019 systematic review and meta-analysis assessed progression-free survival (PFS) and overall survival (OS) for up to 19 different treatments or combinations for advanced melanoma as compared to the then-standard melanoma treatment, dacarbazine. They concluded that combination therapies or therapies other than trametinib alone were more likely to be more favorable treatment options. The meta-analysis did report their analysis of trametinib monotherapy. They found that compared to dacarbazine, trametinib had favorable outcomes for PFS (HR=0.55; 95% CI 0.41 – 0.72), trended towards favorable outcomes for OS (HR=0.85; 95% CI 0.63 – 1.11). This can be compared to their more favorable options for each category: dabrafenib + trametinib for PFS (HR=0.21; 95% CI 0.17 – 0.27) and nivolumab + ipilimumab for OS (HR=0.39; 95% CI 0.27 – 0.54). (Franken et al., 2019).

The above meta-analysis included studies on a variety of targeted therapies. One study followed the 322 patients in the Phase III METRIC Study to assess 5-year outcomes. These patients had BRAF V600 advanced or metastatic melanoma. The study was an open-label study comparing trametinib to

chemotherapy. Patients who progressed were allowed to crossover to the trametinib arm. The authors found that the median progression free survival (PFS) was 4.9 months in the trametinib group vs. 1.5 months in the chemotherapy arm (HR=0.54; 95% CI 0.41 – 0.73). Overall survival rates for trametinib vs. chemotherapy at 1 year, 2 years and 5 years were 60.9% versus 49.6%, 32.0% versus 29.4% and 13.3% versus 17.0%, respectively. 65% of patients in the chemotherapy arm did cross-over to the trametinib group, which may obscure a greater survival benefit. Many patients also received other anti-cancer treatments after disease progression as well (Robert et al., 2019).

A 2018 network meta-analysis compared treatments for non-small cell lung cancer in patients who had received treatment previously and had advanced and unresectable disease. The treatments were compared to docetaxel, the comparator arm in all studies except the single-arm trial for dabrafenib + trametinib. To include this combination, the authors performed an externally controlled comparison between the dabrafenib + trametinib trial and a trial of nivolumab using a matching-adjusted indirect comparison. The study using dabrafenib + trametinib enrolled 57 patients. The authors found that compared to docetaxel, dabrafenib + trametinib was associated with a 12.2 times higher odds of a response to treatment during study follow up (OR=13.2; 95% CI 5.5 - 33.0). Trametinib was associated with higher odds of progression free survival at 12 months (HR=0.32; 95% CI 0.16 – 0.59) and of overall survival at 24 months (HR=0.41; 95% CI 0.11 – 1.41. (Li et al., 2018).

The dabrafenib + trametinib combination has been evaluated in trials like NCI-MATCH and ROAR, known as 'basket' or 'bucket' trials, wherein they enroll patients with different cancers but a mutation in common. These trials led to approval for treatment of solid tumors harboring a BRAF V600 mutation (National Cancer Institute). One example is the approval for anaplastic thyroid cancer (ATC). Anaplastic thyroid cancer has a median survival of 5 to 12 months, with a 1-year overall survival rate of 20% to 40%. The ROAR trial's ATC cohort enrolled 36 patients, all of whom took dabrafenib + trametinib until disease progression, unacceptable toxicity, or death. The study recruited from 2014 to 2018, and continued patient follow up. The authors published an update in 2022 with data up to 2020. They found that the median PFC was 6.7 months (95% CI 4.7 - 13.8 months), and median overall survival was 14.5 months (95% CI 6.8 - 23.2 months). The 24-month survival rate was 31.5% (95% CI 16.3% - 47.9%) (Subbiah et al. 2018; Subbiah et al,. 2022).

Trametinib has also been evaluated for other cancer types. A 2022 study randomized 260 patients with low grade serous carcinoma of the ovary and peritoneum (LGSC) to standard of care or trametinib. The authors found that median progression-free survival in the group treated with trametinib was 13.0

months (95% CI 9.9 – 15.0) compared with 7.2 months (95% CI 5.6 – 9.9) in the standard-of-care group (HR=0.48; 95% CI 0.36 – 0.64; p<0.0001) (Gershenson et al., 2022).

**Lifespan**: POTENTIAL BENEFIT IN LABORATORY MODELS

A 2015 experimental paper in fruit flies found that treatment with trametinib extended lifespan through its action in the Ras-ERK pathway. Perturbations to this pathway, such as Ras deletion, have been reported to extend lifespan in other model systems, including yeast and mice. The authors reported that the extension in lifespan did not appear to be because of anti-cancer effects in their fruit fly model They hypothesize that this may in part be due to the MAPK pathway being downstream of insulin signaling, which may play a role in animal lifespan (Slack et al., 2015).

**Diabetes & Obesity:** THEORETICAL POTENTIAL BENEFIT

As insulin signaling can activate the MAPK pathway, there is some theoretical and/or preliminary preclinical work indicating that modulation of the MAPK pathway may affect conditions like diabetes and obesity. For instance, ERK inhibition in mice, including through MEK inhibition, has been reported to improve insulin sensitivity, and basal activation of ERK is elevated in patients with diabetes (Reviewed by Hall et al., 2020).

**Safety:** At oncological doses, trametinib's side effects can include serious rash and serious cardiovascular, ocular, and GI adverse events. These effects may be mitigated at lower doses for neurodegenerative indications, but human data on this is not yet available.

*Types of evidence:*

- 5 systematic reviews & meta-analyses
- 1 clinical trial
- 2 observational studies
- 2 review papers

Trametinib is commonly prescribed as a combination therapy with dabrafenib, and so much of the safety data is reported for the two-drug regimen. Where possible, this report includes either data from monotherapy or data comparing dabrafenib + trametinib to dabrafenib alone, such that the picture of

trametinib's adverse effects may be more clear. It does not appear that trametinib has been tested in non-cancer populations in any published study; thus, the dosing and side-effects must be considered in that light.

The 2019 systemic review and meta-analysis from Franken and colleagues that compared up to 19 different treatments for advanced melanoma as compared to the then-standard medication, dacarbazine, assessed the relative risks of serious (Grade III/Grade IV) adverse events. They found that compared to dacarbazine, trametinib had a higher risk of serious adverse events (RR=1.38; 95% CI 1.04 – 1.83) (Franken et al., 2019).

A 2022 study of patients with LGSC treated with trametinib or standard of care found that the most frequent grade 3 or grade 4 adverse events in the trametinib group were rash (13%), anemia (13%), hypertension (12%), diarrhea (10%), nausea (9%), and fatigue (8%). The most frequent grade 3 or 4 adverse events in the standard of care group were abdominal pain (17%), nausea (11%), anemia (10%), and vomiting (8%). There were adverse events of special interest in the trametinib group, including decrease in ejection fraction (8%), pneumonitis (2%), QTc prolongation (2%), left ventricular systolic dysfunction (2%), and retinal adverse events (2%). In the standard of care group, 1% of patients experienced left ventricular systolic dysfunction and 1% had decreased ejection (Gershenson et al., 2022).

A 2019 systematic review and meta-analysis assessed the cardiovascular adverse effects associated with MEK inhibition therapy by comparing results from trials of just BRAF inhibitors such as dabrafenib as compared to combination therapy of BRAF + MEK inhibitors such as dabrafenib + trametinib. These cardiovascular events are thought to arise from the oxidative stress, myocyte apoptosis, and decreased angiogenesis that arises from the negative regulation of the MAPK pathway of the therapeutics. This study included 2317 patients with melanoma. The authors found that compared to monotherapy with just dabrafenib, the combination therapy significantly increased the risks of pulmonary embolism (RR=4.36; 95% CI, 1.23 - 15.44; P = 0.02), decrease in left ventricular ejection fraction (RR=3.72; 95% CI, 1.74 - 7.94; P < 0.001), and arterial hypertension (RR=1.49; 95% CI, 1.12 - 1.97; P = 0.005). It is not certain whether these effects are due to a more complete inhibition of the MAPK pathway or if it is due to MEK inhibition, and the options are not mutually exclusive (Mincu et al., 2019).

The 5 year follow up to the Phase III METRIC Study of 322 patients with unresectable / advanced melanoma found that adverse events were in line with their early analyses and other clinical trials. Rash

(57% vs 3%), acneiform dermatitis (19% vs 0%), diarrhea (33% vs 12%), and peripheral edema (16% vs 0%) were the most common side effects in the trametinib group vs. the chemotherapy group, respectively. Fatigue was also common but similarly present in both groups (20% vs 22%) (Robert et al., 2019).

A 2015 systematic review and meta-analysis examined the risk of skin toxicities in cancer patients treated with MEK inhibitors. The authors included RCTs that compared MEK inhibitors to a placebo or standard of care medication that did not target the Ras-Raf-MEK-ERK pathway. They found that as compared to control treatment, treatment with MEK inhibitors lead to a higher risk of any grade skin rash and acneiform dermatitis (RR=1.71; 95% CI 1.07 – 2.72; p = 0.02 and RR=6.55; 95% CI 3.42 – 12.56; p < 0.00001, respectively). The authors also found that the risk of high-grade skin rash and acneiform dermatitis was also higher with MEK inhibitor treatment as compared to control treatment (RR=2.64; 95% CI 1.42 – 4.91; p = 0.002, and RR=8.44; 95% CI 2.39 – 29.81; p = 0.0009). The authors included multiple kinds of MEK inhibitors, but in a subgroup analysis did not find any difference in relative risk between different drugs in this class (Abdel-Rahman et al., 2015)

Another 2015 meta-analysis from the same group assessed the risk of gastrointestinal toxicities in patients treated with MEK inhibitors. This study also included RCTs that compared MEK inhibitors to control treatment and included a total of 3,204 patients. The authors found that compared to control, treatment with MEK inhibitors increased risk of all-grade stomatitis (RR=2.03; 95% CI 1.41 – 2.96; p = 0.002), diarrhea (RR=1.92; 95% CI 1.48 – 2.50; p < 0.00001), and vomiting (RR=1.35; 95% CI 1.0 6– 1.71; p = 0.01). MEK inhibitor treatment also was associated with significantly increased risk of high-grade diarrhea (RR=2.69; 95% CI 1.55 – 4.65; p = 0.0004). When the authors performed subgroup analysis to assess whether there was a difference between the specific MEK inhibitors in the study, they found no significant differences between drugs (Abdel-Rahman et al., 2015).

A 2017 systematic review and meta-analysis looked at the risk of peripheral edema in 1,931 MEK inhibitor treated patients as compared to control treatment in RCTs. The authors found that treatment with MEK inhibitors was associated with an increased risk of peripheral edema (RR=3.05; 95% CI 1.98 – 4.70; p < .00001). They did not find a significant difference of effect between MEK inhibitors (Yang et al., 2017).

Ocular side effects are also a concern for MEK inhibitors, including trametinib. The Phase III METRIC study that enrolled 322 patients in a 2:1 trametinib : standard care medication reported ocular side

effects, mostly Grade I/II, in 9% of patients. One patient had reversible chorioretinopathy (Flaherty et al., 2012). A Phase I dose-escalation study assessing trametinib for use in advanced solid tumors enrolled 206 patients and reported 2 cases of central serous retinopathy (Infante et al., 2012). Other ocular events such as retinal vein occlusion and uveitis have been reported after combination therapy of trametinib and dabrafenib (Stjepanovic et al 2016).

***Drug interactions***:

Trametinib has 20 known drug interactions, all of which are moderate. Most of these drug interactions involve altering the absorption or the metabolism of either trametinib or the other medications, thus affecting the concentration in the body. Some examples include the tetracycline antibiotic sarecycline; kinase inhibitors like abrocitinib for atopic dermatitis; oncological medications (e.g.,brigatinib, encorafenib, erdafitinib, gilteritinib, idelalisib, midostaurin, pacritinib, pirtobrutinib, pralsetinib, and tucatinib); medications that target sex hormone pathways like anti-androgens or anti-estrogens, some of which are also used as oncological treatments (e.g., apalutamide, elacestrant, elagolix, enzalutamide),; fostamatinib for chronic immune thrombocytopenia; lasmiditan for migraines; and isavuconazonium, which is an anti-fungal (Drugs.com)

Trametinib is commonly co-prescribed with dabrafenib, an inhibitor against another member of the Ras-Raf-MEK-ERK pathway, but the combination can lead to more severe side effects, and so patients should be carefully monitored.

Food is also known to affect trametinib absorption. Patients are therefore instructed to take trametinib either 1 hour before or 2 hours after eating.

**Research underway:**

There are more than 130 ongoing trials registered on clinicaltrials.gov and/or the EU clinical trials registry involving trametinib. Essentially all are for the treatment of various kinds and stages of cancer. There is one ongoing trial exploring the use of trametinib in ALS.

NCT04326283 is a Phase 1/2a study investigating the safety, tolerability, and efficacy of trametinib in ALS patients as compared to riluzole. The study is currently enrolling. The study plans to enroll 30 patients with ALS and randomize 4:1 to trametinib or riluzole. The first 8 trametinib patients will start at

0.5 mg daily. Pending safety assessment of the first group, an Independent Data Monitoring Committee will initiate a 1 mg dose of trametinib for further groups. Their primary outcome measure is safety and tolerability as measured by adverse events. Their secondary outcome measures include an ALS functional rating score, forced vital capacity, and plasma and CSF concentrations of trametinib.

**Search terms:**

Pubmed, Google: trametinib, MAPK

- +ALS, +dementia, +GENUV,+ ocular, +APOE4, +inflammation, +neuroinflammation, +brain metasteses

Websites visited for trametinib:

- Clinicaltrials.gov
- Geroprotectors
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma