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.

Troculeucel (SNK01)

Evidence Summary

Early phase trials have shown potential benefits of troculeucel in Alzheimer's disease and lung cancer, but larger, longer trials are needed to fully evaluate its efficacy and safety.

Neuroprotective Benefit: As of August 2025, only a small open-label phase I trial of troculeucel has been completed in AD patients. An ongoing phase I/2a study in moderate AD is testing its efficacy and safety and will be completed in June 2026.

Aging and related health concerns: A few early-phase clinical trials in lung cancer have shown potential benefits of SNK01 when combined with other therapies, but larger, longer trials are needed to evaluate efficacy.

Safety: Phase I trials so far have shown that SNK01 is well tolerated with no adverse events directly related to SNK01. Larger longer trials are needed to fully establish safety.

What is it?

Troculeucel is an immunotherapeutic drug candidate made of patient-specific ex vivo-expanded autologous natural killer (NK) cells under development by NKGen Biotech, a clinical-stage company. Peripheral blood mononuclear cells (PBMCs) are collected from the patient's blood and then the NK cells are expanded (Lim et al., 2013). Once expanded outside the body, troculeucel is reinfused into the same patient.

NK cells are part of the innate immune system and constitute approximately 10-20% of the white blood cells in a healthy body, providing the first line of defense against infections and cancer. Troculeucel is designed to enhance the natural abilities of these cells, allowing them to better target and eliminate toxic proteins or cells (Zuniga et al., 2025).

Troculeucel is the International Nonproprietary Name (INN) for SNK01 assigned by the WHO. Troculeucel is under development for the treatment of neurodegenerative disorders and a broad range of cancers (NKGen pipeline).

In February 2025, NKGen Biotech received US FDA Fast Track Designation for troculeucel for the treatment of moderate Alzheimer's disease (NKGen press release).

Neuroprotective Benefit: As of August 2025, only a small open-label phase I trial of troculeucel has been completed in AD patients. An ongoing phase I/2a study in moderate AD is testing its efficacy and safety and will be completed in June 2026.

Types of evidence:

- 1 clinical trial completed and another ongoing as of August 2025)
- Several laboratory studies

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

No studies have tested whether troculeucel can prevent dementia or age-related cognitive decline.

Human research to suggest benefits to patients with dementia:

In an open-label phase 1 trial that enrolled 11 patients with mild, moderate, or severe Alzheimer's disease, SNK01 treatment (1, 2, or 4 x 10^9 cells, intravenously, every 3 weeks) for a total of 4 infusions resulted in stable or improved cognitive and functional outcomes in 50-70% of enrolled subjects (Zuniga et al., 2025). Four patients received 1 x 10^9 cells per infusion, 4 patients received 2 x 10^9 cells per infusion, and 3 patients received 4 x 10^9 cells per infusion. The primary endpoint was safety. Secondary endpoints included changes in cognitive and functional scores: Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog11), Mini Mental State Examination (MMSE), Clinical Dementia Rating Sum of Boxes (CDR-SB), and the Alzheimer's Disease Composite Score (ADCOMS) score. Other secondary endpoints included biomarker levels (Aβ42, Aβ42/40, α-synuclein, total tau, ptau217, ptau181, NfL, GFAP, and YKL-40).

With regards to cognitive function measured by ADAS-Cog, at week 11 (1 week after final infusion), 3 out of 10 (30%) patients showed an improvement of at least 4 points (1 subject receiving 1 x 10^9 cells, and 2 subjects receiving 4 x 10^9 cells), 5 patients (50%) were stable (3 receiving 1 x 10^9 cells, 1 receiving 2 x 10^9 cells, 1 receiving 4 x 10^9 cells), and the remaining 2 patients showed a decline of more than 3 or 4 points (Zuniga et al., 2025). Amongst the subjects with stable or improved scores, 4 patients had mild Alzheimer's disease, 3 patients had moderate Alzheimer's disease, and 1 subject had severe Alzheimer's at study start, where the 2 subjects with moderate Alzheimer's disease improved the most. At week 22 (12 weeks after final infusion), 2 out of 9 (22.2%) patients improved their final score compared to baseline and 6 out of 9 (66.7%) remained stable. Because of the open-label study design, lack of placebo control, and the short duration of treatment and follow-up, efficacy data are preliminary; practice effects and placebo effects cannot be ruled out.

With regards to CDR-SB, at week 11, 7/10 (70%) patients showed an improvement or remained stable (3 subjects receiving 1 x 10^9 cells, and 1 subject receiving 2 x 10^9 cells, 3 subjects receiving 4 x 10^9 cells) (Zuniga et al., 2025). The remaining 3 subjects showed an increase in the sum of scores of 2.0 points and were considered to decline in function. Among the patients with stable or improved scores, 3 patients had mild Alzheimer's, 2 had moderate Alzheimer's, and 1 had severe Alzheimer's disease at baseline, with one patient with moderate Alzheimer's disease improving the most.

With regards to cognitive function measured by MMSE, 5 out of 10 (50%) patients were stable or improved (2 subjects receiving 1 x 10^9 cells, and 1 subject receiving 2 x 10^9 cells, and 2 subjects receiving 4 x 10^9 cells) (Zuniga et al., 2025). Five patients showed a decline in MMSE. Of the 5 subjects with stable or improved scores, 2 patients with moderate Alzheimer's disease at baseline improved the most.

ADCOMS is a composite measure composed of items from the ADAS-Cog, MMSE, and CDR-SB scales. It is thought to be sensitive to changes in cognition in the preclinical and early stages of Alzheimer's disease. At week 11, 3 out of 10 (30%) of patients showed an improved change score of ≥ 0.100, and 6 patients appeared to be stable (change score < 0.100), while 1 patient showed clear worsening (increase by 0.205) (Zuniga et al., 2025). The subject with the most improved scores at week 11 and week 22 had moderate Alzheimer's disease at baseline. This patient had an ADCOMS value of 1.054 at baseline, which dropped to 0.810 at week 11 and 0.846 at week 22, which would be classified as mild (range: 0.615-0.901).

With regards to biomarkers, at week 11, an increase in cerebral spinal fluid (CSF) Aβ42 and Aβ42/40 was seen in 40% and 50% of subjects, respectively, suggesting decreased amyloid levels in the brain (Zuniga et al., 2025). For the other proteins where a decrease in the CSF is thought to be beneficial, 50% of subjects (5/10) had a decrease in CSF ptau217, 70% (7/10) had decreased CSF ptau181, and 60% (6/10) had a decrease in CSF α-syn compared to baseline values. With regards to neuroinflammation biomarkers, 60% (6/10) had a decrease in GFAP and YKL-40 at week 11.

A larger randomized placebo-controlled study of troculeucel is ongoing as of August 2025. At the ADPD conference in April 2025, NKGen Biotech presented data from the phase 1 part of the phase 1/2a trial of troculeucel in moderate Alzheimer's disease (NKGen press release; ADPD slide presentation). Troculeucel was administered intravenously at a dose of 6 $x10^9$ cells every 3 weeks to 3 patients with moderate Alzheimer's disease for up to 1 year. The primary endpoint was safety, monitored for 21 days after the first dose for each patient. Patients were treated every 3 weeks, with 2 patients having completed 17 doses and 1 patient completed 10 doses. Efficacy measures included cognitive and functional scores: CDR-SB, MMSE, Activities of Daily Living Scale (ADCS-ADL-Severe), ADAS-Cog-11, and the ADCOMS score. Secondary endpoints included changes in protein aggregate and neuroinflammation biomarker levels in the CSF and blood at 6 and 12 months.

At 3 months, all 3 patients showed stable or improved cognitive scores on CDR-SB and ADCOMS (NKGen press release; ADPD slide presentation). Two of the 3 patients improved on all cognitive scales and ADCOMS score and were downgraded from moderate to mild Alzheimer's disease stage based on the CDR-SB score. At 6 months, all 3 patients were stable or improved on CDR-SB, ADAS-Cog11, and ADCOMS, with 2 of the 3 patients stable/improved on all cognitive scales and ADCOMS score. At 12 months, the 2 patients who completed the 17 doses continued to show stable or improved CDR-SB, ADAS-Cog-11, ADCS-ADL-Severe, and ADCOMS scores, with 1 patient reaching a CDR-SB of 4.5

(considered the cutoff between mild cognitive impairment and mild Alzheimer's disease). The third patient withdrew from the trial prior to reaching 12 months, for reasons other than adverse events or drug-related issues. Because this phase of the study employed an open-label design, practice effects and placebo effects cannot be ruled out.

With regards to blood and CSF biomarkers, at 6 months, all 3 patients showed decreased levels of the inflammation marker, GFAP, in the CSF and plasma. At 12 months, the CSF and plasma Aβ42/40 ratio improved in both patients, while the CSF p-tau181 and p-tau217 levels remained relatively stable.

Safety and efficacy of troculeucel in moderate Alzheimer's disease patients will be evaluated in the ongoing phase 2a part of the study, which is a randomized placebo-controlled trial.

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

A cell culture study of NK cells investigated the ability of these cells to internalize and degrade Aβ aggregates (Zuniga et al., 2025). SNK01 cells were treated with varying concentrations of Aβ aggregates for 1 hour and SNK01 cells internalized Aβ in a concentration-dependent manner. When SNK01 cells were treated with 5 µM of Aβ aggregates for up to 24 hours, SNK01 cells internalized Aβ in a time-dependent manner. When Aβ aggregates that remained in media were removed, SNK01 cells showed gradually decreased levels of internalized Aβ aggregates, suggesting that the aggregates were degraded intracellularly.

Similarly, SNK01 cells were able to internalize and degrade α-syn aggregates (Zuniga et al., 2025). The amount of internalized α-syn aggregates gradually decreased and was rarely detectable after 6 hours of incubation, suggesting that SNK01 cells degraded α-syn aggregates.

APOE4 interactions:

It is currently unknown whether troculeucel has differential effects in APOE4 carriers versus noncarriers.

Aging and related health concerns: A few early-phase clinical trials in lung cancer have shown potential benefits of SNK01 when combined with other therapies, but larger, longer trials are needed to evaluate efficacy.

Types of evidence:

- 2 phase 1/2a trials in cancer
- Some laboratory studies

NK cells play an important role in tumor immunosurveillance and participate in the immune response against cancer cells by recognizing molecular patterns characteristic of stressed cells (reviewed in Wang et al., 2024).

In a phase 1/2a randomized controlled trial of 18 patients with stage IV non-small cell lung cancer (with a history of failed frontline platinum-based therapy), the efficacy and safety of pembrolizumab (anti-PD-1 antibody; every 3 weeks) alone versus combined with 6 weekly infusions of SNK01 (either 2 or 4 $x10^9$ cells per infusion) were compared (Kim et al., 2022). The objective response rate (ORR) and the 1-year survival rate in the pembrolizumab plus SNK01 combination group were numerically (but not statistically significantly) higher than those who underwent pembrolizumab monotherapy (ORR=41.7% in combination therapy vs ORR=0% in monotherapy, p=0.11; 1-year survival rate of 66.7% in combination therapy vs 50.0% in monotherapy, p=0.39). The median progression-free survival (PFS) was also higher in the pembrolizumab plus SNK01 combination group (6.2 months vs 1.6 months, p=0.001) with a median follow-up duration of 17.5 months. Efficacy outcomes were numerically higher for patients administered the higher dose (4 $x10^9$ cells per infusion) compared to the lower dose (2 $x10^9$ cells per infusion) of SNK01, but the difference was not statistically significant. ORR, PFS, and 1-year survival rate were significantly higher in patients with immune-related adverse events compared to those without these events (ORR=80.0% vs. 7.7%, p=0.008; median PFS=not reached vs. 1.7 months, p=0.005; 1-year survival rate=100% vs. 44.9%, $p < 0.001$). While the results are encouraging with regards to combining SNK01 with pembrolizumab, the authors noted a few limitations to the study, including the small number of patients, and the baseline tumor characteristics (e.g., EGFR mutation status, number of previous therapies, and PD-L1 expression) not balanced across the groups, possibly contributing to the poorer response in the pembrolizumab monotherapy group.

In a 2-year follow-up of the above phase 1/2a trial, the estimated 2-year survival rate was 58.3% in the pembrolizumab plus SNK01 combination versus 16.7% in the pembrolizumab monotherapy group (Park et al., 2022). Among the 11 patients who died, 5 were from the combination therapy groups (41.6%, 5

out of 12), and 6 received pembrolizumab monotherapy (100%, 6 out of 6). Although the median PFS was significantly higher in the pembrolizumab plus SNK01 combination therapy group than in the pembrolizumab monotherapy group, overall survival and PFS did not differ statistically between patients who received low dose SNK01 and those who received high doses SNK01.

In a phase 1/2a trial of 12 patients with EGFR-mutated recurrent or metastatic non-small cell lung cancer who failed prior tyrosine kinase inhibitor treatment, safety and efficacy of 7-8 weekly SNK01 treatment (either 4 or 6 x10^9 cells per infusion) in combination with chemotherapy (gemcitabine/carboplatin) and SNK01 treatment in combination with cetuximab (anti-EGFR antibody) and chemotherapy were compared (Choi et al., 2024). For the SNK01/cetuximab/chemotherapy treatment, the ORR was 50%, disease control rate was 100%, and the median PFS was 145 days. For the SNK01/chemotherapy treatment, the ORR was 25% and the median PFC was 143 days. The overall survival did not reach the median survival. CD56+ cells from the peripheral blood drawn from the enrolled patients showed variable proportions of NK cells (CD56+CD3-), but the final SNK01 products were mainly composed of NK cells (99.81%±0.22%) with minimal contamination of CD3+ T cells (0.15%±0.20%), CD14+ monocytes (0.32%±0.10%), and CD20+ B cells (0.01%±0.01%). In the expansion culture, the NK cells were significantly expanded (4,462,189±2,063,228-fold) with viability of 98% and was sufficient for multiple infusions. Limitations of this study is its small sample size resulting in limited statistical power. Longer-duration clinical studies are needed to confirm these initial findings, including how efficacies compare with other therapies.

In a mouse model of Osimertinib-resistant lung cancer, treatment with NK cells resulted in less tumor growth compared to cetuximab treatment and the control group (Choi et al., 2024). The volume of tumor after treatment was the smallest in the NK cell plus cetuximab treatment group.

Safety: Phase I trials so far have shown that SNK01 is well tolerated with no adverse events directly related to SNK01. Larger longer trials are needed to fully establish safety.

Types of evidence:

- 3 phase 1/2a clinical trials

In an open-label phase 1 trial that enrolled 11 patients with mild, moderate, or severe Alzheimer's disease, SNK01 treatment (1, 2, or 4 x 10^9 cells, intravenously, every 3 weeks) for a total of 4 infusions did not result in any drug-related adverse events (Zuniga et al., 2025). One subject died before the

completion of the study due to multiple organ dysfunction syndrome, but this was deemed unrelated to study drug. The subject died 5 days after the second infusion of 2 x 10^9 cells. The investigator cited the underlying diabetes mellitus, hypertension, and hypercholesterolemia as the etiology, and the event was deemed not related to SNK01. There were no dose-limiting toxicities at any of the doses tested. The proportion of subjects who experienced at least one adverse event was comparable in all cohorts: 3 subjects (75%) receiving 1 x 10^9 cells/infusion experienced at least one adverse event; 4 subjects (100%) receiving 2 x 10^9 cells/infusion experienced at least one adverse event; 3 subjects (100%) receiving 4 x 10^9 cells/infusion experienced at least one adverse event. Overall, 90.9% of subjects (n=10) experienced at least one adverse event. The proportion of subjects who experienced at least one treatment-emergent adverse event was 75%, 100%, and 66.7% of subjects receiving 1, 2, and 4 x 10^9 cells/infusion, respectively. The most common treatment emergent adverse events experienced by subjects were puncture site pain (63.6%, 7 subjects), vessel puncture pain (36.4%, 4 subjects), anemia (36.4%, 4 subjects), and hypertension (18.2%, 2 subjects). The majority of treatment emergent adverse events were of grade 1 severity, related to the procedures (e.g., blood and CSF collection), and were transient in nature. No interruption of infusion or treatment with other medications were required. There were 2 events of grade 2 severity: localized edema and urinary tract infection. There were no serious adverse events related to SNK01. None of the treatment emergent adverse events were thought to be related to SNK01 and none of these led to SNK01 discontinuation.

At the ADPD conference in April 2025, NKGen Biotech presented data from the phase 1 part of the phase 1/2a trial of troculeucel in moderate Alzheimer's disease (NKGen press release). After up to 12 months of treatment of 6x10^9 cells every 3 weeks, the 3 patients had no drug-related adverse reactions.

In a phase 1/2a randomized controlled trial of 18 patients with stage IV non-small cell lung cancer (with a history of failed frontline platinum-based therapy), safety of pembrolizumab (anti-PD-1 antibody; every 3 weeks) alone versus combined with 6 weekly infusions of SNK01 (either 2 or 4 x10^9 cells per infusion) were evaluated (Kim et al., 2022). For SNK01, there was no dose-limiting toxicity observed, and the maximum tolerated dose was determined to be 4 x10^9 cells per infusion. There were no new safety signals when SNK01 was combined with pembrolizumab. Immune-related hyperthyroidism (n=3), hypothyroidism (n=3), and pneumonitis occurred in the SNK01/pembrolizumab combination group. There were no grade 3-5 immune-related adverse events. The median time to the occurrence of immune-related adverse events was 2.7 months after the first pembrolizumab infusion. Patients receiving the SNK01/pembrolizumab combination tended to experience more immune-related adverse events than those receiving pembrolizumab monotherapy (35.7% vs. 0%, p=0.26), but this was not statistically significant. Part of this numerical difference may be explained by the longer progression-free

survival in the SNK01/pembrolizumab combination group compared to the pembrolizumab monotherapy group, and therefore, more pembrolizumab was administered (mean of 5.4 times vs 3.5 times) and the follow-up period was longer (median of 14.6 months vs 11.0 months). In a 2-year follow-up of the phase 1/2a trial, 2 patients were excluded due to side effects of pembrolizumab (Park et al., 2022). One of the patients in pembrolizumab + low-dose SNK01 group showed grade 3 arthralgia (joint pain) and myalgia (muscle pain), and the other patient in the pembrolizumab + high-dose SNK01 group experienced grade 2 pneumonia.

In a phase 1/2a trial of 12 patients with EGFR-mutated recurrent or metastatic non-small cell lung cancer who failed prior tyrosine kinase inhibitor treatment, 7-8 weekly SNK01 treatment (either 4 or 6 $x10^9$ cells per infusion) in combination with cetuximab (anti-EGFR antibody) and chemotherapy (gemcitabine/carboplatin) was well tolerated (Choi et al., 2024). Grade 3 or higher adverse events occurred in 5 patients (5 neutropenia, 1 anemia) but all of them were related to cytotoxic chemotherapy. No grade 3 or higher SNK01-related adverse events were reported. No dose-limiting toxicities were observed. The maximum dose tested (6 $x10^9$ cells per infusion) was found to be tolerable, so the maximum tolerated dose was not determined.

Drug interactions: Drug interactions with troculeucel has not been documented.

Sources and dosing:

Troculeucel is an immunotherapeutic drug candidate made of patient-specific ex vivo-expanded autologous natural killer (NK) cells under development by NKGen Biotech, a clinical-stage company.

Peripheral blood mononuclear cells (PBMCs) are collected from 300-350 mL of the patient's blood and then the NK cells are expanded (Lim et al., 2013). Once expanded outside the body, troculeucel is reinfused into the same patient. Each blood draw is sufficient to produce 1-4 doses of troculeucel (Zuniga et al., 2025). Criteria for troculeucel include: the absence of microbial contamination (bacteria, fungus, and mycoplasma), ≥ 80% viability in a trypan blue exclusion assay, ≥ 50% cytotoxicity against K562 target cells at the effector to target cell (E:T) ratio of 10:1, ≤ 0.5 EU/mL endotoxin level, and immune phenotyping via flow cytometric analysis proving the expression of the NK cell markers (CD56+ /CD3–) (≥ 80%) and the absence of CD14, CD3, and CD20 (< 5% each). Troculeucel that met the criteria are shipped at 2-8°C and administered via intravenous injection over 45 ± 15 min/100 mL (2×10^9 cells). Cells need to be used within 42 hours from the time of manufacture. Doses tested to date are up to 6 x 10^9 cells per infusion (Choi et al., 2024; NKGen ADPD slide presentation).

Research underway:

Based on ClinicalTrials.gov, a phase 1/2a study is evaluating the safety, tolerability, and efficacy of SNK01 in 36 patients with moderate Alzheimer's disease (NCT06189963). SNK01 will be administered as an IV infusion every 3 weeks for up to 1 year. Placebo is sodium lactate Hartmann's solution. Primary outcomes include safety outcomes as well as cognitive/function measures (CDR-SB, MMSE, ADCS-ADL, ADAS-Cog). Secondary outcomes include CSF and plasma biomarkers (ptau-181, Aβ42/40, GFAP, NfL). This trial is scheduled to be completed in June 2026.

NKGen Biotech also announced the administration of the first dose of troculeucel to a frontotemporal dementia patient under compassionate use investigational new drug (IND) cleared by the FDA (Nasdaq.com). The patient carries the C9orf72 gene mutation.

In March 2025, NKGen Biotech administered its first troculeucel dose to a stroke patient under an FDA-cleared compassionate use IND (clinicaltrialvanguard.com). The treatment is aimed to address the chronic neuroinflammation observed post-stroke.

Search terms:

Pubmed, Google: SNK01, troculeucel

Websites visited for SNK01, troculeucel:

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

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