Cancer Research Consortium of West Michigan
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# FAST FACTS

**WF 97116: A Phase 3 Randomized Placebo Controlled Clinical Trial of Donepezil in Chemotherapy Exposed Breast Cancer Survivors with Cognitive Impairment**

**Inclusion Criteria**

1. Women ≥18 years old with history of invasive breast cancer
2. Must have completed at least 4 cycles of adjuvant/neo-adjuvant cytotoxic chemotherapy between 1 and 5 years prior to enrollment **(**Ongoing herceptin or other chronic HER 2 directed therapies are allowed).
3. Patients receiving ongoing hormonal therapy for breast cancer must be on the same hormonal agent for at least 3 months prior to study enrollment and plan to continue for the duration of the study (9 months)
4. Use of psychotropic medications (anti-depressants, anxiolytics, sleeping aids, narcotics) is permitted if the patient whose eligibility is being assessed has been on the medication for at least 12 weeks. The dose of this medication must be stable for at least 4 weeks prior to enrollment.
    a. Patients who were previously on one of these psychotropic medications and have subsequently discontinued the drug must have been off the medication for at least 4 weeks prior to enrollment.

    b. Patients who have been on a psychotropic medication for at least 12 weeks but have recently switched to a medicine in the same class (for example, switching from one SSRI antidepressant to a different SSRI antidepressant) need to be on a stable dose of the new medication for at least 4 weeks prior to enrollment to be eligible.
5. Self-reported cognitive problem plus a measured memory deficit (score ≤ 7 on single trial of Eligibility Pre-screen HVLT-R Form 3).
6. ECOG performance status 0-2
7. Able to understand and willing to sign a written informed consent document.
8. Must be able to speak English.
9. Patients currently taking a moderate risk QTc prolongation medication (see Appendix A) are allowed if one of the following criteria are met:
    a. The moderate risk QTc prolongation medication is stopped. The patient should be off the moderate risk QTc prolongation medication for at least 5 half-lives before starting study drug.
    b. Patients that continue using a moderate risk QTc prolongation medication must have a normal QTc interval (≤ 460 milliseconds) on a screening ECG following informed consent and prior to study enrollment. These patients will also be monitored at designated study follow-up visits per Section 7.5 (monitored 3-7 days after initiating study drug, at week 3, and 3-7 days after the study drug dose increase with ECG's to assess the QTc interval; the QTc level must be ≤ 500 milliseconds at these time points in order to continue on the study drug).
    c. Moderate risk QTc prolongation medications that are only taken occasionally may be stopped at the discretion of the treating site physician. Patients must be off medication for at least 5 half-lives prior to starting study drug to be eligible.

10. Patients currently taking a moderate risk bradycardia-causing agent (see Appendix B) are allowed if one of the following criteria are met:
    a. The moderate risk bradycardia-causing agent is stopped. The patient should be off the moderate risk bradycardia-causing agent for at least 5 half-lives before starting study drug.
    b. Patients that continue using a moderate risk bradycardia-causing agent must have a resting heart rate ≥ 55 beats per minute at screening following informed consent. These patients' resting heart rate will be monitored 3-7 days after initiating study drug, at week 3, and 3-7 days after the study drug dose increase per Section 7.5.
    c. Moderate risk bradycardia-causing agents that are only taken occasionally may be stopped at the discretion of the treating site physician. Patients must be off medication for at least 5 half-lives prior to starting study drug to be eligible.

**Exclusion Criteria**

1. Evidence of or suspected recurrent or metastatic disease.
2. Prior brain irradiation.
3. Planned therapy (surgery, radiation, chemotherapy, or immunotherapy) while on the study for brain and/or extracranial primary/metastatic disease.
4. Hypersensitivity to donepezil or piperidine derivatives
5. Current use of ceritinib
6. Current use of Succinylcholine/Acetylcholinesterase Inhibitors as listed in Appendix C. For patients who have used these medications, they must not have used them within 4 weeks prior to enrollment.
7. Current use of high-risk QTc prolonging medication(s). See Appendix D.
8. Current use of quinidine or systemic ketoconazole (topical ketoconazole is acceptable to use while on study).
9. History of dementia, Alzheimer's disease, multi-infarct dementia or clinically significant Cerebrovascular Accident (history of transient ischemic attack (TIA) is allowed).
10. Current use of donepezil, galantamine, rivastigmine, tacrine, memantine, methylphenidate, dextroamphetamine, or any other specific cognition enhancing drug(s). For patients who have used these medications, they must not have used them within 4 weeks prior to pre-screening. Patients who plan to start taking a cognition enhancing drug while on this study are also excluded.
11. History of allergic reactions attributed to compounds of similar chemical or biologic composition to donepezil. Hypersensitivity to donepezil.
12. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, recent myocardial infarction, or cardiac arrhythmia.
13. Major medical conditions that affect cognition, traumatic brain injury, multiple sclerosis, acute severe fatigue, chronic fatigue syndrome or fibromyalgia.
14. Psychiatric illness/social situations that would limit compliance with study requirements including but not limited to a history of schizophrenia, psychosis or substance abuse.
15. Untreated current severe depression. Currently treated depression is permitted if treatment is stable
16. Patients with a resting heart rate less than 55 beats per minute, seizure disorder or peptic ulcer disease (PUD).
17. Screening QTc of > 460 milliseconds will make the patient ineligible.
18. History of congenital long QT syndrome or torsades de pointes.

19. Pregnant women are excluded from this study. Following informed consent, women of child-bearing potential will be screened with a serum or urine pregnancy test within 10 days of enrollment. The effects of donepezil on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because donepezil is known to be teratogenic, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.
20. It is unknown whether donepezil is excreted in breast milk, for this reason women who are currently breast-feeding are not eligible for this study.
21. On another intervention study involving medication at the time of enrollment or during participation in this study. (Exception: Patients will remain eligible for this study if they are also enrolled on the Alliance for Clinical Trials in Oncology study (NCT02927249): Aspirin in Preventing Recurrence of Cancer in Patients with HER2 Negative Stage II-III Breast Cancer After Chemotherapy, Surgery, and/or Radiation Therapy. Studies that involve only blood draws or questionnaires are also permitted.)
22. Use of investigational drugs likely to affect cognition within 30 days prior to pre-screening visit.

## SCHEMA

Pre-Screening: Verbal consent for Eligibility:
Self-reported cognitive symptoms; poor memory performance (Hopkins Verbal Learning Test-Revised (HVLT-R)-Form 3 Score ≤7)

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Informed Consent / Screening

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Enrollment / Randomization

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**Baseline Data Collection**

- Clinic visit for medical history and study assessments.
- Baseline Assessment Booklet:
  - Neurocognitive test battery: HVLT-R-Form 1, Digit Span Backwards, Digit Symbol Coding, Trail Making Test, Controlled Oral Word Association Test
  - Patient-Reported Outcomes: Functional Assessment of Cancer Therapy-Cognition (v3), PROMIS Fatigue scale, PROMIS Sleep Disturbance scale, Patient Health Questionnaire-9.
  - Cognitive Reserve: Shipley-2 Vocabulary Test

| Donepezil tablets x 24 weeks<br>Weeks 1-6: one 5mg tablet orally once a day<br>Weeks 7-24: two 5mg tablets (10mg total) orally once a day | Placebo tablets x 24 weeks<br>Weeks 1-6: one tablet orally once a day<br>Weeks 7-24: two tablets orally once a day |
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**Intervention***

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| Week 3: | Phone interview for assessment of toxicities |
| Week 6: | Phone interview for assessment of toxicities; if indicated, increase dose to two 5mg tablets of donepezil daily or two placebo tablets starting at week 7 |
| Week 12: | Clinic visit for study assessment, Neurocognitive test battery, Patient Reported Outcomes, Toxicity assessment, Verify dosage and continued compliance with study medication |
| Week 24: | End of drug administration; beginning of wash-out. Clinic visit for study assessment, Neurocognitive test battery, Patient Reported Outcomes, Toxicity assessment |
| Week 36: | End of wash-out. Clinic visit for study assessment, Neurocognitive test battery, Patient Reported Outcomes, Toxicity assessment |

*Select patients will have an ECG or heart rate taken 3-7 days post start of intervention, at the 3 Week study time point, and 3-7 days post study agent dose increase.

**Endpoints**

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| Primary: | Memory: HVLT-R Immediate Recall score |
| Secondary: | Other cognitive domains: Executive function, working memory, processing speed, verbal fluency, global cognitive function,<br>Patient-reported outcomes: cognitive problems<br>Other: toxicities, adverse events. |

***Stratification:*** **Age (<50, 50-59, 60-69, ≥70)**
***Study Sample*: N=276 (138 per group)**
***Study Duration*: Approximately 40 months**
***Brief Eligibility Criteria:*** ≥18 years old, female, history of invasive breast cancer, completed adjuvant/neo-adjuvant chemotherapy between 1-5 years prior to enrollment, received ≥ 4 cycles of cytotoxic chemotherapy, self-reported cognitive complaint, documented memory deficit.