

A Single Arm Phase II Pilot Study of Euthyroid Hypothyroxinemia in Metastatic Breast Carcinoma

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Sponsor: Aultman Health Foundation

Protocol ID: 2018.08.ST

ClinicalTrials.gov Identifier: NCT03787303

Version: 5.0 [April 8, 2020]

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1.0 Background and Rationale:

It is estimated that there are approximately 155,000 living with metastatic breast cancer in the US and the number is estimated to increase over the next years (SEER data). Although their median survival has improved over the last 2 decades from 17 months to approximately 24 months attributed to newer treatments, there is an ongoing need for additional strategies and research to improve survival and quality of life. (2,3,4)

Many studies have explored the connection between hypothyroidism and hyperthyroidism and breast cancer with varied results ranging up to one third prevalence. Low T3 and elevated TSH levels have been detected in newly diagnosed breast cancer patients. Other studies have suggested that some of the common symptoms reported by breast cancer survivors such as fatigue and depression can be attributed to subclinical hypothyroidism. (2,3,4)

L-thyroxine (T4) is the most commonly prescribed agent for the management of hypothyroidism in the US. However, there are data suggesting that T4 is a potent pro-oncogenic agent. Proposed mechanisms include stimulation of mitogenesis, angiogenesis and resistance to apoptosis, opposition of anti-PDL-1 and radiation effects. It has been postulated that the avbeta3integrin that is universally expressed on cancer cells harbors a thyroid hormone receptor and T4 interacts with it. (2,3,4)

Triiodothyronine (T3) on the other hand, is significantly less oncogenic and less mitogenic and is downstream of T4 which is a t3 pro-hormone. Therefore, exogenous supplementation of T3 would decrease the T4 levels creating the desired state of euthyroid hypothyroxinemia. (2,3,4)

Previous Data

Phase 2 clinical trial of recurrent GBM (Hercbergs et. al) demonstrated that this strategy was feasible and tolerable however due to small numbers and heavily pretreated population with high (expected) mortality, conclusive results are pending. (2,3)

Cross sectional retrospective compassionate use study inducing euthyroid hypothyroxinemia successfully reported improved progression free and overall survival in patients with high grade synovial sarcoma and brain stem glioma 8 and 7 years. (2,3)

Rationale and Hypothesis

The rationale of this study is to replace L-thyroxine (T4) with Triiodothyronine (T3) in hypothyroid patients with metastatic breast carcinoma while they continue to receive standard systemic therapy, titrating the dose to achieve a state of euthyroid hypothyroxinemia which in turn would result in a lower risk of disease progression and improved survival by lowering the concentration of T4.

2.0 Primary Objective

1. To prospectively evaluate the progression-free survival in hypothyroid patients with metastatic breast carcinoma who are rendered euthyroid and hypothyroxinemic.

Secondary Objectives

1. To quantitate the prevalence of hypothyroidism in metastatic breast cancer patients.
2. To monitor QOL at baseline, 3, 6, 9 and 12 months.
3. To prospectively study the feasibility and average time required to achieve the euthyroid hypothyroxinemia state in qualifying patients.

3.0 Investigational Plan / Schema

This is a single site Phase 2 interventional pilot study of euthyroid hypothyroxinemia in patients diagnosed with metastatic breast carcinoma. The study will enroll approximately 30 participants. It is anticipated that recruitment will take up to four (4) years. End of the study is the date of the last visit or last scheduled procedure for the last patient. An Intent-to Treat (ITT) population with a priori planned subgroup analysis will be used for analysis purposes.

Study Design: All enrolled participants will undergo baseline screening lab work (TSH, FreeT3, FreeT4, CBC, CMP), EKG and physical examination. Once it is determined that they meet eligibility criteria they will have their L-thyroxine (T4) discontinued and Triiodothyronine (T3) initiated. The Triiodothyronine (T3) will be titrated by the investigator to

maintain levels of free T4 < 50% normal range. Treatment duration will be 9 months. Disease status will be assessed at 3, 6, 9, and 12 months.

Eligibility Criteria

- Age greater than or equal to 18
- Male or female with diagnosis of metastatic breast carcinoma and documented history of hypothyroidism .
- TSH level within normal range at baseline
- Life expectancy estimated > 3 months
- Ability and willingness to provide informed consent

Exclusion Criteria

- Life expectancy estimated to be less than 3 months
- Is currently pregnant or intends to become pregnant during the duration of the study
- Active angina, NYHA advanced [Class III/IV] CHF, or uncontrolled cardiac arrhythmia within 6 months of enrollment
- History of thyrotoxicosis or adrenal insufficiency unless previously treated > 5 years ago and resolved without active replacement hormonal therapy as per Principal Investigator discretion.
- Hypersensitivity to any active or extraneous constituents in Cytomel/liothyronine sodium

4.0 Study Procedures

It is anticipated that 20% of the patients with metastatic breast cancer will qualify for participation in this study. Patients who screen fail after meeting initial eligibility will be asked to allow record follow-up so the data can be used for the initial endpoint of prevalence. Rescreening will not be permitted.

Following consent and confirmation of eligibility participants will have their L-thyroxine (T4) discontinued and Triiodothyronine (T3)/liothyronine sodium initiated at 3: 1 mcg respectively. Study will allow use of Triiodothyronine (cytomel/liothyronine) and all available generic liothyronine sodium compounds. Triiodothyronine dosing will be rounded up to the closest commercial dose available. For patients on L-thyroxine there will be a washout period of four (4) days between discontinuation and the initiation of triiodothyroinine. Day 0 will be the day of enrollment. Day 1, or day 5 (if washout required) will be the day of the first dose of Triiodothyronine treatment. Triiodothyronine tablets are administered orally as a once a day dosing, or split dosing at the Investigators discretion. Usual maintenance dose is 25 to 75mcg daily. It will be recommended that the drug be taken at the same time each day, but this is not mandatory.

Drug titration will be in accordance with thyroid function testing to maintain levels of free T4 at <50% normal range. The treatment period will continue for 9 months (270 days). In the event of loco/regional recurrence or progression there is no need to discontinue study treatment because this is not one of the endpoints.

During the treatment period participants will have lab testing every 4 weeks for the first 12 weeks and then every 12 weeks until study drug is discontinued. Participants will be scheduled for a clinic visit every 12 weeks. Compliance with Triiodothyronine (T3) and adverse events will be assessed at each clinic visit. Disease state will be assessed at 3, 6, 9, and 12 months via clinical examination, laboratory results and radiographic findings performed as part of routine care. Participants will also be asked to complete a Quality of Life survey (FACT-B) at each clinic visit.

Unscheduled visits and management for metastatic breast cancer are at the discretion of the investigator. Unscheduled visits may include physical examinations, vital signs, ECOG performance status, concomitant medication, adverse event collection, disease symptoms assessment, laboratory testing, Triiodothyronine (T3) dose adjustments, or to resumed dosing, if previously interrupted.

Discontinuation of Study Treatment: At the end of the treatment period, the investigator will have the discretion to resume thyroxine or continue Triiodothyronine (T3); however, if it is not covered by insurance the patient will be responsible.

If subjects discontinue study treatment prematurely for any reason they will be asked to continue follow-up until study completion.

All patients will be scheduled for a 12-month safety follow-up visit.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	Screening	Study Visits			Follow Up Visit
Visit		3mo (+/- 14 days)	6mo (+/- 14 days)	9mo (+/- 14 days)	12mo (+/- 14 days)
ECOG PS	X	X	X	X	X
Informed Consent	X				
Review Inclusion/Exclusion Criteria	X				
Demographics/Medical History	X				
Physical Examination	X	X	X	X	X
Vital Signs: BP, HR, RR	X	X	X	X	X
EKG	X				
Disease assessment	X	X	X	X	X
FACT-B QOL questionnaire	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X
Clinical Laboratory Evaluation*	X	X	X	X	X
Pregnancy Test (women of childbearing potential only)	X				
Adverse Event Assessment	X	X	X	X	X

- *TSH, FreeT3, FreeT4, CBC, CMP every 4 weeks for the first 12 weeks and then every 12 weeks until end of study.
- Additional lab work at physician's discretion.

Study Drug

Cytomel (liothyronine sodium) is a commercially available compound which is a synthetic formulation of triiodothyronine. Study drug may be obtained from the Aultman Hospital Retail Pharmacy or the pharmacy of the participant's choice. The cost will be charged to the participant/insurance company unless they meet the hospital's indigent policy, in which case study drug will be provided free of charge.

Cytomel capsules should not be opened, crushed, or chewed. Patients should store the Cytomel capsules in the original package provided and be instructed to keep all medication out of reach of children. Further details obtained from accessdata.fda.gov can be found in appendix D.

HOW SUPPLIED

Cytomel (liothyronine sodium) Tablets: 5 mcg in bottles of 100;

25 mcg in bottles of 100; and 50 mcg in bottles of 100.

5 mcg 100's: NDC 52604-3414-1

25 mcg 100's: NDC 52604-3416-1

50 mcg 100's: NDC 52604-3417-1

Store between 15° and 30°C (59° and 86°F).

The Investigator is submitting this study as IND exempt. Cytomel or liothyronine sodium are being used in this study in accordance with approved indications.

5.0 STUDY ADMINISTRATION

Data Collection and Management

- Data collection for this study will be recorded on paper case report forms. A compilation of the data will be stored in password-protected excel files and follow HIPPA guidelines
- Access to study data will limited to investigator and delegates who have an active role in the study.
- The identifiers will be destroyed after publication. The other data will be retained for three years.
- Data sources (if applicable, for existing records) include office and hospital records.

Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

No identifiable data will be used for future studies without first obtaining IRB approval. The investigator will obtain a data use agreement between provider (the PI) and any recipient researchers (before sharing a limited dataset (dates and zip codes)).

Risk Assessment

Per Cytomel/liothyronine sodium product labeling adverse reactions, other than those indicative of hyperthyroidism because of therapeutic overdose are rare. In rare instances, allergic skin reactions have been reported.

Signs and symptoms of overdose include: Headache, irritability, nervousness, sweating, arrhythmia (including tachycardia), increased bowel motility and menstrual irregularities. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may also develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

Dosage should be reduced or therapy temporarily discontinued if signs and symptoms of overdosage appear. Treatment may be reinstated at a lower dosage. In normal individuals, normal hypothalamic-pituitary-thyroidaxis function is restored in 6 to 8 weeks after thyroid suppression.

Thyroid hormones do not readily cross the placental barrier. The clinical experience to date does not indicate any adverse effect on fetuses when thyroid hormones are administered to pregnant women.

Precautions: Thyroid hormones should be used with great caution in a number of circumstances where the integrity of the cardiovascular system, particularly the coronary arteries, is suspected. These include patients with angina pectoris or the elderly, in whom there is a greater likelihood of occult cardiac disease. In these patients, liothyronine sodium therapy should be initiated with low doses, with due consideration for its relatively rapid onset of action.

Thyroid hormone therapy in patients with concomitant diabetes mellitus or insipidus or adrenal cortical insufficiency aggravates the intensity of their symptoms. Appropriate adjustments of the various therapeutic measures directed at these concomitant endocrine diseases are required. Hypothyroidism decreases, and hyperthyroidism increases the sensitivity to oral anticoagulants. Prothrombin time should be closely monitored in thyroid-treated patients on oral anticoagulants and dosage of the latter agents adjusted on the basis of frequent prothrombin time determinations.

In cases of concomitant diabetes mellitus, the daily dosage of antidiabetic medication may need readjustment as thyroid hormone replacement is achieved. If thyroid medication is stopped, a downward readjustment of the dosage of insulin or oral hypoglycemic agent may be necessary to avoid hypoglycemia. At all times, close monitoring of urinary glucose levels is mandatory in such patients.

Potential Benefits of Study Participation

Direct benefits are unknown, but intervention may improve quality of life and prolong progression free survival.

Indirect benefits for the greater good of society and science.

Recruitment Strategy

Patients with the diagnosis of metastatic breast cancer and estimated life expectancy of greater than 3 months will be identified either by the investigators from within their practice or referred by other oncologists in the community.

Potential and eligible participants will be screened by collection of data (via medical record review, direct query or other procedures), and this screening will take place before subjects' consent to participation in the study.

Investigator will notify and coordinate care with all physicians involved in the patients care, specifically primary care physician (PCP), endocrinologist and cardiologist.

Informed Consent/Assent and HIPAA Authorization

In order to protect human rights this study will be conducted in full conformance with principles of "Declaration of Helsinki" and Good Clinical Practice. The investigator, or delegate, will obtain informed consent/ HIPAA Authorization. Patient privacy will be assured as per HIPPA. Potential

participants will be permitted ample time to make a decision regarding participation. Every effort will be made to ensure that the patient comprehends the nature of the study and to avoid coercion and facilitate an informed consent process. This study will comply with all policies/procedures set forth for research at Aultman Health Foundation under the guidance of the Human Research Review Board (HRRB).

6.0 Safety Management

Data Monitoring

The investigator will ask the HRRB/Compliance Office to assign a data monitor to review each case for eligibility, adherence to the protocol, occurrence of adverse events, and accuracy of data. The first review will be conducted after enrolling the first 5 patients. Regular reviews will be scheduled at increments of 10 randomized patients until enrollment goals are met. Unscheduled random chart audits may be performed to ensure data integrity. Any deficiencies found during these reviews will be addressed and reported to the PI, HRRB and federal agencies as appropriate.

Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study by the Principal Investigator.

Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

Definition of a Serious Adverse Event (SAE)

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death,
- a life-threatening event (at risk of death at the time of the event),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity, or

- a congenital anomaly/birth defect in the offspring of a subject.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms: definitely, probably, possibly, unlikely or unrelated.

Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the HRRB. The Investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

Adverse Event Reporting

The Investigator is responsible for recording and reporting unanticipated problems related to research that occur during and after study treatment. Given the safety profile of the investigational product Serious Adverse Events (SAEs) are not expected. All local SAEs will be reported to the Aultman Health Foundation Human Research Review Board (HRRB) in accordance with policies. AEs that are not serious will be summarized in narrative, or other format, and submitted to the HRRB at the time of continuing review.

If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) these will be reported to the HRRB in accordance with Aultman Health Foundation policy: Unanticipated Problems Involving Risks to Subjects.

7.0 Statistical Methods

Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g., means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

Analysis of Primary Outcome of Interest

The primary analysis will include all subjects meeting all inclusion and exclusion criteria and completing Visit 1.

The primary endpoint will be the progression free survival at 12 months

Secondary endpoints will include:

- the prevalence of hypothyroidism in successive metastatic breast cancer patients,
- the change in QOL measures between baseline, 3, 6, 9 and 12 months and
- the duration of time to achieve the euthyroid hypothyroxiemic state

Sample Size and Power

The sample size is estimated to be approximately 30 patients.

Given the many uncertainties to calculate power precisely, this is an estimate made, based on clinical experience.

8.0 Publication

Investigator intends to publish.

9.0 References

1. Chiappa, C.; Rovera, F.; Rausei, S.; DelFerraro, S.; Fachinetti, A.; Lavazza, M.; Marchionini, V.; Arlant, V.; Tanda, M. L.; Piantanida, E.; Kim, H. Y.; Anuwong, A.; & Dionigi, G. (2017, February). Breast cancer and thyroid diseases: analysis of 867 consecutive cases. *J. Endo Invest*, 40(2), 179-184.
2. Hercbergs, A.; Davis, P. J.; Lin H. Y.; & Mousa S. A. (2016, December). Possible contributions of thyroid hormone replacement to specific behaviors of cancer. *Biomed Pharm*, 84, 655-659.
3. Hercbergs, A.; Johnson, R. E.; Ashur-Fabian, O.; Garfield, D. H.; & Davis, P. J. (2015, Jan). Medically Induced Euthyroid Hypothyroxinemia May Extend Survival in Compassionate Need Cancer Patients: An Observational Study. *Oncologist*, 20, 72-76.
4. Hercbergs, A.; Mousa, S. A.; Leinung, M. Lin, H. Y.; & Davis P. J. (2018, June). Thyroid Hormone in the Clinic and Breast Cancer. *Horm Cancer*, 9 (3), 139-143.
5. Weng, C. H.; Chen, Y. H.; Lin C. H.; Luo, X.; & Lin T. H. (2018, Mar 30). Thyroid disorders and breast cancer risk in Asian population: a nationwide population-based case-control study in Taiwan. *BMJ Open*, 8(3), e20194.

10.0 Appendixes

- A. ECOG Performance Status
- B. FACT-B Questionnaire (<http://www.facit.org/FACITOrg/Questionnaires>)
- C. Package Insert Cytomel (liothyronine sodium) (accessdata.fda.gov)
Package Insert Generic Liothyronine Sodium (Sigma, Mayne, Mylan)

Summary of Changes Amendment Version 4.0 [1/6/2020]

- Primary objective updated to match clinicaltrials.gov recommendation. Now reads “To prospectively evaluate the progression-free survival in hypothyroid patients with metastatic breast carcinoma who are rendered euthyroid and hypothyroxinemic.
- Anticipated recruitment period updated to four (4) years.
- Exclusion criteria edited to allow history of thyroxicosis or adrenal insufficiency as long as previously treated \geq 5 years ago and resolved without active replacement hormonal therapy as per Principal Investigator discretion.
- Corrected treatment period day calculation error to read 9 months (270 days).
- Edited frequency of labs to every 4 weeks for the first 12 weeks and then every 12 weeks until the end of study. This was amended to match the clinic visit frequency. Additional labs can be drawn at the physician’s discretion.
- Clarified that data collection will be recorded on paper case report forms and that a compilation of data will be stored in a password-protected excel file.
- Clarified that the Data Monitoring Committee will monitor data integrity, however the Principal Investigator will be responsible for monitoring safety and adverse events.
- Updated Analysis of Primary Outcome section to read “The primary endpoint will be the progression free survival at 12 months” to match clinicaltrials.gov approved record.
- Minor grammatical corrections throughout.

Summary of Changes Amendment Version 5.0 [4.8.20]

- Corrected page 4 making frequency of labs “every 12 weeks after first 12 weeks until study drug is discontinued” to align with amendment version 4.0.
- Minor spelling corrections throughout.