

Phase 2 Study of Pioglitazone in thyroid cancers that contain the PAX8-PPARgamma fusion gene

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SCHEMA

Patients with PAX8-PPARgamma – positive thyroid cancer that is either metastatic s/p thyroidectomy and radioiodine (if appropriate), or is locally advanced/recurrent not a candidate for further surgery, radioiodine or external beam radiotherapy

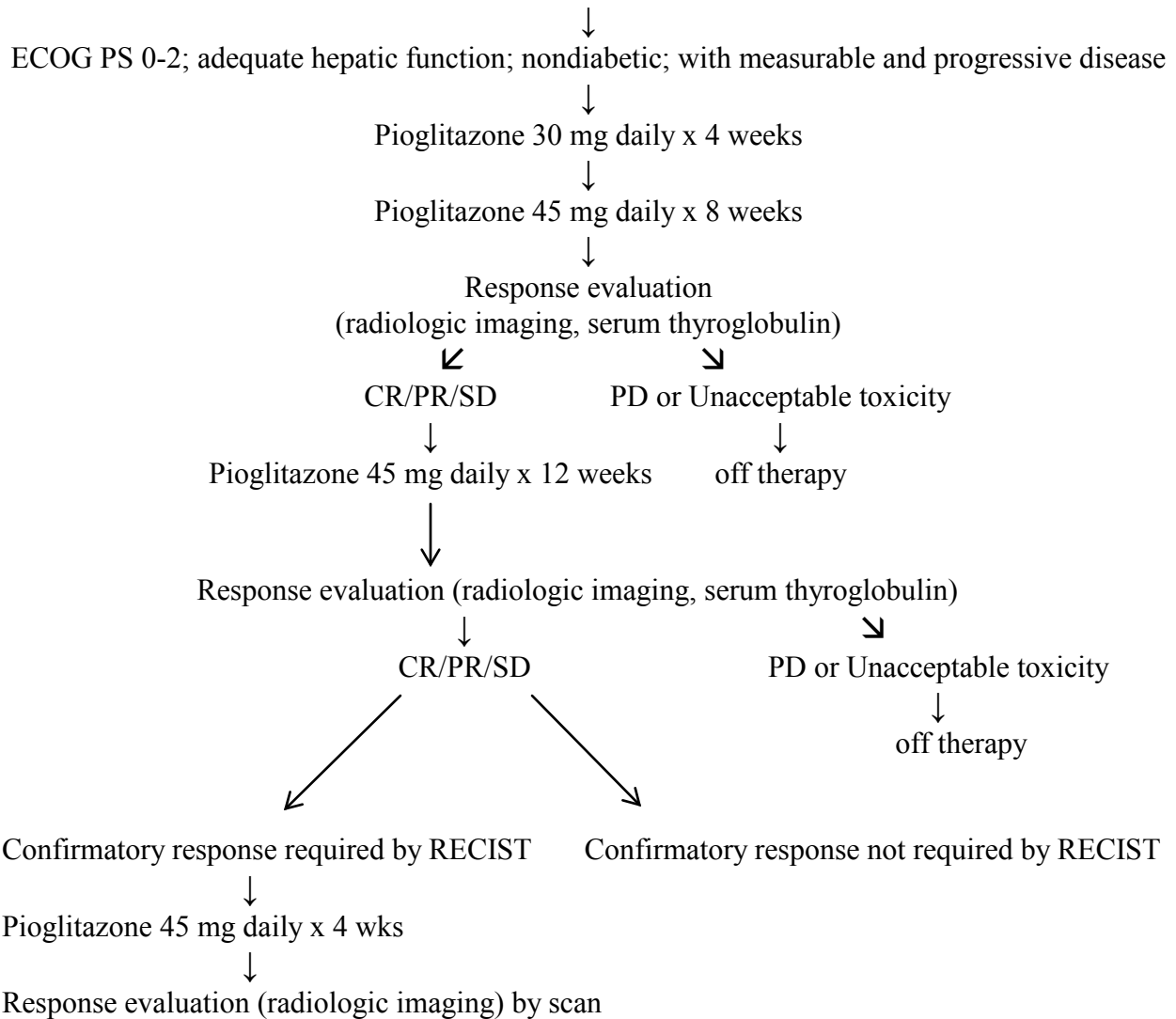


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1. OBJECTIVES

1.1 Primary Objectives

Determine the overall response (complete and partial response) rates of patients with PAX8-PPARgamma fusion gene-positive thyroid carcinomas treated with pioglitazone.

1.2 Secondary Objectives

Determine if pioglitazone decreases serum thyroglobulin in patients with thyroid carcinomas that contain the PAX8-PPARgamma fusion gene.

Measure toxicities experienced by patients with PAX8-PPARgamma fusion gene-positive thyroid carcinomas treated with pioglitazone.

1.3. Correlative Objectives (Optional)

Determine (by MRI) if pioglitazone induces lipid accumulation in thyroid carcinomas that contain the PAX8-PPARgamma fusion gene.

Define predictive markers of response or insensitivity to pioglitazone. Unstained tumor tissue slides from archival paraffin blocks, fresh biopsy specimens from measurable metastases, and blood samples (serum and peripheral blood cells) will be collected on enrolled patients who consented for the optional correlative studies. These will be used to identify factors that predict efficacy of pioglitazone. Analyses may include measures of expression of specific RNAs and proteins, and DNA sequence analysis.

Determine if pioglitazone induces a clinically significant level of radioiodine uptake in the residual thyroid carcinoma, and if so, whether there is a therapeutic response to radioiodine. This will be addressed in a separate follow-up protocol available to subjects completing this study.

2. BACKGROUND

2.1 Study Disease

Follicular carcinoma and follicular variant of papillary carcinoma (together called follicular-patterned thyroid carcinomas) constitute about 15% of thyroid carcinomas. Approximately one-third of follicular carcinomas (1, 2), as well as a subset of follicular variant of papillary carcinomas that has been reported to vary from 0 – 38% (3, 4), contain a chromosomal translocation that fuses the genes encoding PAX8 and PPARgamma, resulting in the production of a PAX8-PPARgamma fusion protein (PPFP).

In general the therapy of thyroid cancer is surgical thyroidectomy followed by radioactive iodine (5). These therapies are effective in the majority of cases, resulting in a 10 year survival of ~85% in follicular carcinoma (6). However, distant metastases occur, primarily in the lung and less commonly in organs such as liver and bone. Metastatic disease is not always responsive to radioiodine – in some cases the tumor concentrates radioiodine but not at sufficient levels to cause a response, and in other cases the metastases do not concentrate radioiodine. There is no accepted chemotherapy or other therapy for these patients, and for these reasons, the median survival of AJCC stage IV follicular carcinoma is only ~4 years (6).

2.2 Rationale

PPFP is a fusion protein between two transcription factors, PAX8 and PPARgamma (1). PAX8 is required for thyroid development, and in the mature thyroid, it drives the expression of thyroid specific genes. PPARgamma is expressed at very low levels in the normal thyroid and has no known function in that organ. PPARgamma is the master transcriptional regulator of adipogenesis, and in the mature adipocyte it drives the expression of adipocyte specific genes (7). PPARgamma is a nuclear hormone receptor. In clinical practice, it is best known because agonist ligands (thiazolidinediones) are insulin sensitizers (8). Thus, thiazolidinediones are commonly used to treat type 2 diabetes mellitus. One such drug, pioglitazone (trade name Actos® or generic equivalent), will be used in this study.

PPFP contains the entirety of PPARgamma, and hence thiazolidinediones also bind to PPFP. In cell culture transfection studies, we have shown that a PPARgamma-responsive promoter is induced by PPFP plus thiazolidinedione, similar to the action of PPARgamma plus thiazolidinedione (9). Furthermore, human PPFP thyroid cancers have increased expression of PPARgamma responsive genes, relative to PPFP-negative thyroid cancers (9).

We have produced an animal model of follicular thyroid carcinomas by creating mice that have both thyroid-specific expression of PPFP and thyroid-specific deletion of the tumor suppressor Pten (hereafter denoted PPFP;Pten Δ mice) (10). PPFP expression alone causes mild benign hyperplasia, and Pten Δ alone causes a much greater degree of benign hyperplasia but no tumors. In contrast, the combined PPFP;Pten Δ mice develop thyroid cancer with local invasion into soft tissues, vascular invasion, and distant metastases. The reason we combined PPFP expression with Pten Δ is that we previously found that human PPFP cancers have high expression of phosphorylated AKT, which is not replicated in mice by PPFP expression alone. Pten is a negative regulator of AKT phosphorylation, so Pten deletion is known to increase phosphorylated AKT levels. We treated PPFP;Pten Δ mice with pioglitazone or control diet beginning at 2 months of age for 10 weeks. Ten mice received pioglitazone and 12 mice served as controls. Ultrasound measurements showed that, over the 10 week treatment period, the control mouse thyroids grew 3-fold in size and the pioglitazone-exposed thyroids decreased to less than half their starting size. At the end of the study, the control mouse thyroids were 7 fold larger

(by weight) than the pioglitazone mouse thyroids. Seven of the 12 control mice had distant metastases, whereas none of the pioglitazone mice had metastases ($P<.005$).

Perhaps the most striking result pertained to the histology of the thyroid glands in the pioglitazone treated mice. The thyroid cells were laden with lipid droplets, suggesting that pioglitazone caused a trans-differentiation of the thyroid cells into adipocyte-like cells. These cells express PPFP and the thyroid specific markers TTF-1 and thyroglobulin, indicating they are thyroid in origin. However, we also examined the expression of 17 adipocyte PPARgamma target genes, and all 17 were induced in the pioglitazone-treated thyroids.

To test whether this adipogenic response is dependent on PPFP, we also studied Pten Δ mice that do not have PPFP. Eleven Pten Δ mice received pioglitazone and 15 served as controls. Pioglitazone had no effect on either thyroid size or histology.

We conclude that pioglitazone has a remarkable therapeutic effect in this PPFP;Pten Δ mouse model of thyroid cancer, and that the effect requires the expression of PPFP. The effect involves the trans-differentiation of PPFP expressing thyroid cells into adipocyte-like cells, which reflects the PPARgamma-like action of PPFP in the presence of pioglitazone, a PPARgamma ligand. If similar activity is seen in human PPFP thyroid cancers, pioglitazone should have a powerful salutary effect on this disease. Furthermore, pioglitazone is commonly used to treat type 2 diabetes, and it has a well established safety profile in that setting in chronic use. Therefore, dosing in this study will adhere to the levels for the approved indication.

The duration of therapy in the proposed clinical trial is 24 weeks. The rationale for this duration is as follows. In the mouse model of PPFP thyroid cancer, 10 weeks of pioglitazone decreased thyroid diameter to less than half that of untreated mice, and completely eliminated metastatic disease. Therefore, we believe that a response in patients should be measurable by 24 weeks of therapy, if a response is to occur.

2.3 Correlative Studies Background

Serum thyroglobulin levels will be measured. Thyroglobulin is a well established tumor marker in thyroid cancer. Serial serum thyroglobulin measurements are part of the accepted standard of care for thyroid cancer management (5).

Optional for enrolled patients who consent: MRI will be used to assess fat content of the cancer metastases. MRI is an accepted non-invasive method to assess tissue fat content. Our mouse tumor model data indicate that pioglitazone causes a lipogenic response (i.e. the mouse tumors accumulate lipid droplets), which reflects the PPAR γ -like action of PPFP. To assess feasibility, we performed thyroid MRIs on two PPFP;Pten Δ mice that were treated with pioglitazone and two that were not. Thyroid fat content was 13% in the two control diet mice, and 25 to 26% in the pioglitazone-treated mice. This optional MRI consent will allow us to assess whether a similar effect occurs in patients, and will provide another index of a response to pioglitazone.

Optional for enrolled patients who consent: Unstained tumor tissue slides from archival paraffin blocks, and/or fresh biopsy of tumor metastases, and/or peripheral blood (sera and/or DNA) will be collected and stored for potential analyses of tumor markers that may predict response or insensitivity to pioglitazone.

Optional radioiodine scan, and potentially radioiodine therapy, at the end of pioglitazone therapy. In non-PPFP thyroid carcinomas, thiazolidinediones have been shown to induce radioiodine uptake in some patients with otherwise non-iodine avid metastases, although in general the level of uptake has been clinically insignificant (11, 12), with rare exception (13, 14). It seems unlikely that pioglitazone would induce clinically useful radioiodine uptake in PPFP carcinomas, since in the mouse model the thyroid cells differentiate toward adipocytes, not thyrocytes. However, radioiodine uptake in patients should be determined to formally address this question. Patients with clinically significant uptake would be considered for radioiodine therapy, if clinically appropriate. This will be addressed in a separate follow-up protocol available to subjects completing this study.

3. PATIENT SELECTION

3.1 Inclusion Criteria

- 3.1.1 Patients must have histologically confirmed thyroid carcinoma with the PAX8-PPARgamma translocation.

Refractory to radioactive iodine (RAI) as defined by: the tumor does not concentrate RAI; or the patient has had RAI within the last 16 months and has had progression despite that RAI; or the last RAI treatment was >16 months ago and the patient progressed after at least two RAI treatments; or the patient has received RAI treatments with a cumulative RAI dose of ≥ 22.2 GBq (600 mCi)

Not a candidate for surgery or RAI therapy with curative intent.

Lesions that would be treated by external beam radiation therapy (EBRT) based on standard of care can be so treated, but then cannot be used as target lesions unless there has been progression of the lesion since treatment (see criteria 3.1.7).

- 3.1.2 Measurable disease by RECIST 1.1 criteria.
- 3.1.3 Disease progression in the past 14 months.
- 3.1.4 Availability of histological material (primary tumor or metastases) for review of the diagnosis and demonstration of PAX8-PPARgamma fusion gene.

- 3.1.5 Adequate TSH suppression (<0.5 mIU/L)
- 3.1.6 Prior chemotherapy or surgery must have been completed at least 28 days prior to registration, and all toxicities must have resolved.
- 3.1.7 Prior radioactive iodine must have been completed at least 6 months prior to registration, or there must be documented disease progression since such therapy if it was within 6 months. Sites that have received EBRT must have disease progression post-EBRT to be used as sites of measurable disease.
- 3.1.8 Age ≥ 18 years.
- 3.1.9 Life expectancy of greater than 6 months.
- 3.1.10 ECOG performance status 2 or less.
- 3.1.11 Patients must have normal organ function as defined below:

$AST(SGOT)/ALT(SGPT) \leq 2.5 \times$ institutional upper limit of normal
(within 1 month of study Day 1)
- 3.1.12 Patients must be able to consume oral medications.
- 3.1.13 Women of childbearing potential must have a negative pregnancy test at baseline prior to receiving any study drug and must practice effective contraception while on study. (Pregnant or lactating patients are excluded).
- 3.1.14 All patients must sign an informed consent prior to enrollment.

3.2 Exclusion Criteria

- 3.2.1 Patients may not be receiving any other investigational agents.
- 3.2.2 Patients with known untreated brain metastases.
- 3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to pioglitazone.
- 3.2.4 Diagnosis of diabetes mellitus or current therapy with any drugs used to treat diabetes mellitus, including but not limited to insulin, sulfonylureas, metformin, rosiglitazone (Avandia), and pioglitazone (Actos) within 14 days of study Day 1
- 3.2.5 Therapy with rosiglitazone (Avandia) or pioglitazone (Actos) at any time since the diagnosis of thyroid cancer.

- 3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, congestive heart failure, unstable angina pectoris, or cardiac arrhythmias.
- 3.2.7 Pregnant women are excluded from this study because pioglitazone is a U.S. Food and Drug Administration Pregnancy Category C drug. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with pioglitazone, breastfeeding should be discontinued if the mother is treated with pioglitazone.
- 3.2.8 No concurrent radiotherapy or chemotherapy may be given to the patient during the administration of the study drug.
- 3.2.9 Patients with uncontrolled malabsorption syndromes.
- 3.2.10 Patients with a history of congestive heart failure of any New York Heart Association class.
- 3.2.11 Any medical or psychiatric illness which, in the opinion of the principal investigator, would compromise the patient's ability to tolerate this treatment regimen.
- 3.2.12 Use of rifampin (strong CYP2C8 inducer) within 14 days of study Day 1.
- 3.2.13 Other current malignancy than the disease under study.
- 3.2.14 Grade 2 or worse edema within 14 days prior to study Day 1, per CTCAE v4.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4. TREATMENT PLAN

4.1 Pioglitazone Administration

This study will be conducted under an exemption of IND (# 113,492) granted by the FDA. Pioglitazone will be obtained from an outpatient pharmacy using a prescription issued by a study investigator.

Drug information is available in the drug package insert (See link in Appendix D).

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 6. Appropriate dose modifications for

pioglitazone are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Pioglitazone will be administered once daily without regard to meals. The initial dosage will be 30 mg daily, increased to 45 mg after 4 weeks unless side effects require otherwise.

4.2 General Concomitant Medication and Supportive Care Guidelines

Pioglitazone may decrease the efficacy of oral contraceptive pills. Women taking OCPs also should use barrier contraception.

Levothyroxine should be administered to the same target TSH as would be done if the patient were not enrolled in this clinical trial.

4.3 Duration of Therapy

Subjects will continue treatment for 28 weeks unless one of the following applies;

- Progressive Disease per RECIST criteria at any time
- Stable Disease per RECIST at 24 weeks
- Best Response per RECIST at 12 weeks and confirmed at 24 weeks
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.4 Duration of Follow Up

Patients will be followed for 6 months after removal from study or until death, whichever occurs first. In addition, patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 4.3 applies. The reason for study removal and the date the patient was removed will be documented in the Case Report Form.

4.6 Continued treatment of responding patients after completion of the study

Patients who complete the study and are responding without significant adverse effects will be allowed to continue on pioglitazone provided that they are under the care of a study investigator or another appropriately qualified licensed clinician who is willing to use this product "off-label" and can provide them with a prescription.

Patients would be able to use this prescription to obtain the product at any pharmacy. Continued treatment in the “off-label” setting will not be conducted under the auspices of this trial, and continued follow up will not be conducted for study. There are no plans to continue to provide pioglitazone for long-term follow up studies at this time.

4.7 Study Calendar

	Pre-Study	Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 24/ EOT	Wk 28	Post treatment
Pioglitazone ^a		X	Daily from study day 1 through week 24-28												
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds	X														
Physical exam	X							X					X		
Vital signs	X							X					X		
Height	X														
Weight ^b		Pre-study and once/week through week 28													
Performance status	X							X					X		
Serum chemistry ^{cd}	X	X ^e				X				X			X		
CBC ^d	X	X ^e				X				X			X		
Thyroid blood tests ^{de}	X	X ^e						X					X		
β-hCG ^{df}	X														
Adverse event evaluation ^h	X		X	X				X			X		X		X
Tumor related imaging ⁱ	X							X					X	X	
Other correlative studies ^j	X												X		

- a: Dose per protocol; orally administered once daily for 24-28 weeks..
- b: Weight obtained at each study site visit and once/week on each subject's same home scale.
- c: Pre-Study and Day 1 chemistries: bicarbonate, BUN, chloride, creatinine, glucose, potassium, SGOT[AST], sodium. At weeks 8, 16, 24: glucose, AST.
- d: Blood tests can be performed locally.
- e: TSH, Free T4, thyroglobulin, thyroglobulin antibodies. All thyroglobulin measurements are to be performed in the same laboratory. Serum thyroglobulin will not be used as a response parameter if endogenous antibodies invalidate the measurement.
- f: Pregnancy test in women of childbearing potential only.
- g: Within 1 month prior to administration of protocol therapy. Pre-Study assessments if within 1 month will suffice.
- h: Adverse events evaluations at weeks 2, 4, 18 and post treatment (within 4 weeks and at 6 months) will be by telephone.
- i: Baseline CT or MRI scans must be done within 4 weeks prior to the start of therapy. Baseline CT includes neck, chest and abdomen. Follow-up imaging for disease response is at sites of disease detected at baseline and must include abdomen in cases of elevated AST to evaluate for liver metastases. Week 28 confirmatory CT for patients who need such for RECIST criteria confirmation. Baseline MRI includes: areas with lesions on CT for which there is reasonable diagnostic uncertainty that may be clarified by MRI; and/or brain if clinically indicated.
- j: Optional correlative studies at Pre-Study and within 1 day of final dose of pioglitazone. Baseline optional tumor lipid MRI includes areas of measurable disease. Follow-up tumor lipid MRI to be at sites of quantifiable tumor lipid at baseline, and is done at week 24 or end of treatment, whichever comes first.
- k: All visits beyond day 1 shall occur at their designated timepoint \pm 5 days.

5. DOSING DELAYS/DOSE MODIFICATIONS

Dose Level	Pioglitazone Dose
-1	15 mg, daily (1 tablet, 15 mg)
0	30 mg, daily (1 tablet, 30 mg)
+1	45 mg, daily (1 tablet, 45 mg)

Initial therapy is 30 mg po once daily. After 4 weeks, the dose is increased to 45 mg PO once daily and is maintained at that dose unless a dosage reduction is indicated, as described below. Excursions to this plan may be permitted based on medical need after consultation with the PI.

Weight gain of more than 5 pounds in the first week, or more than 15 pounds during therapy, prompts evaluation for fluid retention. If there is significant edema, the dose is reduced one level (45 mg to 30 mg; 30 mg to 15 mg; 15 mg to discontinue drug).

Serum ALT is measured every two months. Dosage reduction by one level is indicated if ALT exceeds 2.5x ULN.

Congestive heart failure of New York Heart Association Class II (slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea), dosage reduction by one level. NYHA Class III (marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea), dosage reduction by two levels. NYHA Class IV (unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency

at rest. If any physical activity is undertaken, discomfort is increased) discontinue pioglitazone.

The principal investigator may consider rechallenging with the prior dose should the toxicity resolve.

6. ADVERSE EVENTS:

6.1 Known Adverse Events and Mitigation Strategy

Adapted from Micromedex

- * Cardiovascular: Congestive heart failure, Edema
- * Dermatologic: Angioedema
- * Endocrine metabolic: Diabetes mellitus exacerbation, weight gain
- * GI: Abdominal discomfort, tooth disorder
- * Hematologic: Anemia, decreased hemoglobin
- * Hepatic: Hepatotoxicity, liver failure
- * Musculoskeletal: Fracture of bone, myalgia, osteopenia
- * Neurologic: Headache, paresthesia
- * Ophthalmic: Diabetic macular edema, retinopathy
- * Renal: Malignant tumor of urinary bladder
- * Reproductive: Ovulation in premenopausal anovulatory women
- * Respiratory: Dyspnea, pharyngitis, sinusitis, upper respiratory infection

The ACTOS (pioglitazone hydrochloride) prescribing information contains the following information. The same side effect profile is expected in all generic equivalents.

In monotherapy studies, edema was reported for 4.8% (with doses from 7.5 mg to 45 mg) of patients treated with pioglitazone versus 1.2% of placebo-treated patients.

Placebo-Controlled Clinical Studies of pioglitazone Monotherapy: Adverse Events Reported at a Frequency >5% of Patients Treated with pioglitazone(% of Patients) the following:

	Placebo N=259	pioglitazone N=606
Upper Resp. Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Tooth Disorder	2.3	5.3
Diabetes Mellitus Aggravated	8.1	5.1
Pharyngitis	0.8	5.1

These known risks are the basis for several inclusion exclusion criteria.

Per the current Black Box Warning, patients will be strictly monitored for signs and

symptoms of heart failure. They will report weight gain, new edema, and new dyspnea immediately to the study site.

All subjects will be given the ACTOS(pioglitazone) Medication Guide as recommended in the 9/2009 REMS. Please see Appendix E.

6.2 Adverse Event Reporting

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting, available for download from the CTEP web site (<http://ctep.cancer.gov>).
- **“Expectedness”:** All AEs will be designated as ‘Unexpected’ or ‘Expected’
- **Attribution** of the AE will be designated in this manner:
 - Definite – The AE *is clearly related* to the study treatment.
 - Probable – The AE *is likely related* to the study treatment.
 - Possible – The AE *may be related* to the study treatment.
 - Unlikely – The AE *is doubtfully related* to the study treatment.
 - Unrelated – The AE *is clearly NOT related* to the study treatment.

6.3 Data and Safety Monitoring

- 6.3.1 Scheduled meetings by the study specific Data and Safety Monitoring Committee (DSMC) will occur quarterly or more frequently depending on the activity of the protocol. This committee will include the protocol investigators, data manager or designee, and other members of the study team involved with the conduct of the trial.
- 6.3.2 During these regular meetings, the DSMC will discuss matters related to:
 1. safety of study participants (SAE/UaP reporting)
 2. validity and integrity of the data
 3. enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol deviations)
 5. data completeness
- 6.3.3 DSMC meetings will be documented by the Protocol Specific Data and Safety Monitoring Report (DSMR). The data manager or designee assigned to the trial will be responsible for completing the report. DSMRs will be signed by the Principal Investigator or by one of the co-investigators and will be kept on file in the study record.
- 6.3.4 The University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Board (UMCCC DSMB) will provide independent oversight of the safety and data integrity for this trial. DSMRs and any other pertinent documents will be submitted to the UMCCC DSMB for review on a quarterly basis unless specified more frequently by a DSMB ruling.

6.3.5 The Principal Investigator or designee will forward all correspondence and recommendations generated by the UMCCC DSMB to the Institutional Review Board.

6.4 Pregnancy

Any pregnancy must be reported to the Principal Investigator at the Coordinating Center in the same manner as a Serious Adverse Event. A subject who becomes pregnant shall be removed from study treatment. All pregnancies will be followed until outcome can be reported.

7. CORRELATIVE/SPECIAL STUDIES

7.1 Laboratory Correlative Studies

Detection of the PAX8-PPARgamma fusion gene.

Eligibility requires that the tumor contain the PAX8-PPARgamma fusion gene. This will be assessed in specimens of the resected primary tumor or metastases obtained from all participating patients. Please see supplemental Lab Manual for procedures.

Optional MRI evaluation of tumor lipid.

Since pioglitazone induces lipid accumulation in the thyroids of the mouse model, we predict that pioglitazone will induce lipid accumulation in the metastases of patients. For patients who consent, tumor lipid content will be evaluated by MRI at baseline (any time after informed consent and before the first dose of pioglitazone), and at 24±1 weeks or the end of treatment, whichever comes first.

Optional fresh biopsy of metastasis.

For patients with biopsy-accessible metastases that meet RECIST criteria for measurable disease, optional fresh biopsies of the metastases may be obtained. Institutional procedures for procurement of fresh tumor biopsies will be followed. Biopsies should be obtained pretreatment (anytime after informed consent and before the first dose of pioglitazone) and also may be obtained within 1 day of the last treatment. The biopsy specimens will be analyzed for the PAX8-PPARgamma fusion gene per above, and will be stored for potential future analyses of biomarkers that may correlate with response to or lack of response to pioglitazone. For example, the expression of PPARgamma target genes may be analyzed.

Optional collection of sera.

For patients who consent, serum (up to 21 mL) may be collected pretreatment (anytime after informed consent and before the first dose of pioglitazone) and also may be collected within one day of the last treatment. Sera will be stored at -80C for potential future analysis of biomarkers that may correlate with response to or lack of response to pioglitazone.

Optional collection of peripheral blood DNA

For patients who consent, peripheral venous blood (up to 7 mL) will be collected for the isolation of DNA and the determination of DNA sequence. This may be compared to DNA extracted from the primary tumor or metastases to identify gene mutations or polymorphisms that may correlate with the development of the cancer and its response or lack thereof to pioglitazone.

Optional radioiodine scan and potential radioiodine therapy at the end of pioglitazone therapy.

This will be addressed in a separate follow-up protocol available to subjects completing this study.

8. MEASUREMENT OF EFFECT

8.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 \pm 1 weeks, with a confirmatory CT 4 or more weeks after the 24 week imaging if required by RECIST criteria.

Response and progression will be evaluated in this study using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

8.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with pioglitazone.

Evaluable for objective response. Only those patients who have measurable disease present at baseline (an eligibility criterion), have received at least 11 weeks of therapy and have had their disease re-evaluated; or who come off therapy due to progressive disease or unacceptable adverse events at any time, will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

8.2 Response Criteria (using tumor related imaging CT)

8.2.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the

smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

8.2.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and serum tumor marker (thyroglobulin) level ≤ 0.5 ng/mL

Incomplete Response/
Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or serum tumor marker (thyroglobulin) level > 0.5 ng/mL

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

8.2.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	>4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	>4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once >4 wks. from baseline

PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	
* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.				
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “ <i>symptomatic deterioration</i> ”. Every effort should be made to document the objective progression even after discontinuation of treatment.				

8.3 Other Response Parameters

Serum thyroglobulin will be reviewed for the 12 months prior to enrollment, and will be obtained at enrollment and at 12±1 and 24±1 weeks of therapy. The changes in thyroglobulin before pioglitazone treatment and after treatment will be summarized overall and by response. Serum thyroglobulin will not be used as a response parameter if endogenous antibodies invalidate the measurement.

Optional correlative study. MRI will be used to assess lipid content of target lesions pre-study, and at 24±1 weeks or the end of treatment, whichever comes first. The changes in lipid content after treatment will be summarized overall and by response.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design

This is a phase II study with a primary endpoint of response (CR or PR per RECIST criteria) to pioglitazone therapy. Best response during the 24 weeks on Pioglitazone therapy will be assessed in thyroid cancer patients with metastatic disease who have CT evidence of disease progression in the prior 14 months. It is expected that without treatment there would be no improvement in the disease in these patients. This drug will be of interest to pursue alone or in combination with other therapies with a 40% best response rate. Accrual of 14 evaluable patients at a 95% two-sided significance level will provide 87% power to detect a 40% response rate compared to the expected 5% or less. A patient will be evaluable if they remain on treatment for 11 weeks or they are removed from study due to progression or toxicity.

Secondary endpoints include toxicity, serial measurements of serum thyroglobulin, lipid content of metastases determined by MRI, and radioiodine uptake. Since this drug is well known and used in humans we do not expect toxicity to be a problem. However, toxicity will be observed and reported throughout the trial as this is the first trial with Pioglitazone in this patient population.

9.2 Analysis Plan

All CT and MRI scans will be reviewed centrally through the University of Michigan Department of Radiology. The primary endpoint analysis will report the best response percent and corresponding 95% binomial confidence interval. Only those patients who have measurable disease present at baseline (an eligibility criterion), have received at least 11 weeks of therapy and have had their disease re-evaluated; or who come off therapy due to progressive disease or unacceptable adverse events at any time, will be considered evaluable for response. Each evaluable patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data). All of the patients who met the evaluability criteria will be included in the analysis of the primary endpoint. Patients in response categories 1-2 while on treatment will be considered responders to treatment. Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All patients enrolled and who receive any drug will be assessable for toxicity from the time of their first treatment with study drug. Toxicity will be described by grade and type using frequencies and percentages.

Serum thyroglobulin will be reviewed for the 12 months prior to enrollment, and will be obtained at enrollment and at 12 ± 1 and 24 ± 1 weeks of therapy. The changes in thyroglobulin before pioglitazone treatment and after treatment will be summarized overall and by response. Patient profile plots will be created to descriptively show the serum thyroglobulin values over time. Means and standard deviations or medians and minimum and maximums will be used to summarize all patients at each time and changes from baseline at the later times. Similarly, statistical descriptions of the response group and the non-response groups will be reported.

The changes in target lesion lipid content at 24 ± 1 weeks (or the end of treatment, whichever comes first), compared to pre-study, will be summarized overall and by response. Means and standard deviations or medians and minimum and maximums will be used to summarize the overall patient population at each time. Similarly, statistical descriptions of the response group and the non-response groups will be reported. A paired t-test (or paired Wilcoxon rank test if the data distribution requires it) will be used to compare the changes in target lesion lipid content after treatment to the baseline lipid content in the overall study population with both measurements. In an exploratory analysis, a logistic model will be used with the outcome being response and the independent predictor will be the lipid content change from baseline. The changes in target lesion radioiodine uptake will be summarized overall and by response in a follow-up protocol available to subjects completing this study.

9.3 Sample Size/Accrual Rate

We will accrue 15 evaluable patients, which allows for one drop out while still achieving the target enrollment of 14 patients. We expect to accrue ~4-5 patients per

year, for a total study accrual period of ~4 years.

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APPENDIX A Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B RECIST Version 1.1

Available for download from

http://ctep.cancer.gov/protocoldevelopment/docs/recist_guideline.pdf

APPENDIX C CTCAE Version 4.0

Available for download from

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX D ACTOS (pioglitazone) Package Insert v Jan 2011

Available for download from

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021073s043s044lbl.pdf

APPENDIX E ACTOS (pioglitazone) Medication Guide

Available for download from

<http://www.actos.com/actospro/patientprofile.aspx>

APPENDIX F ACTOS (pioglitazone) FDA approved generic equivalents

Available for download from

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&ApplNo=021073&DrugName=ACTOS&ActiveIngred=PIOGLITAZONE%20HYDROCHLORIDE&SponsorApplicant=TAKEDA%20PHARMS%20USA&ProductMktStatus=1&goto=Search.Generics