A Phase II Trial of Bexarotene for Advanced Differentiated Thyroid Cancer

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Dear Editor:

Approximately 5–10% of patients have an aggressive form of differentiated thyroid cancer that does not respond to conventional therapy, chemotherapy, or radiation therapy. We have shown that ~20% of human thyroid cancers express retinoid X receptor (RXR) protein, making it a potential target for treatment of advanced thyroid cancers with bexarotene (TargretinTM), an FDA-approved, orally administered treatment for T-cell lymphoma (1). Preclinical studies demonstrate decreased cell growth *in vitro* and decreased tumor growth *in vivo* in response to bexarotene that correlates with the presence of the RXR isotype RXR γ (2,3). Therefore, we conducted an open label, single agent, phase II clinical trial to assess the tumor response by RECIST criteria of metastatic radioiodine-resistant thyroid cancer to bexarotene therapy. Secondary objectives included assessment of the ability of previously radioiodine-resistant thyroid cancer to concentrate radioactive iodine after bexarotene therapy and to correlate tumor response with thyroid cancer expression of RXR γ receptors. We planned a two-part study with 19 enrollees and subsequent enrollment of 12 more if we had responders. Due to slow recruitment and high toxicity/low efficacy, the trial was stopped after enrollment of 10 patients.

Adult patients with papillary (PTC), follicular (FTC), or anaplastic thyroid cancer with radioiodine-resistant RECIST measureable disease were eligible if their disease was progressive (within the previous 12 months) or PET-positive on ¹⁸F-FDG PET-CT fusion studies. This study was approved by the Colorado Multiple Institutional Review Board (COMIRB# 07-0727).

Nineteen patients signed consent, but there were nine screen failures due to leukopenia, unavailability of primary tumor samples, clinical deterioration, or unwillingness to follow study protocol. Patients received bexarotene at a dose of 300 mg/m²/day after a two-week run-in of high-dose fish oils (omega-3 fatty acids targeted to 2 g three times a day with meals to mitigate hypertriglyceridemia that affects most patients on bexarotene). Bexarotene was provided by Eisai Pharmaceuticals. Primary tumor specimens were assessed for RXR γ protein expression by immunohistochemistry. We

enrolled seven women and three men with an average age of 61.4 $\pm$ 8.1 years. Nine patients had PTC, and one had FTC (Table 1a). All had received ¹³¹I therapy, and three had received other therapy, including combination Adriamycin/taxol therapy, external beam radiation therapy, axitinib, or sorafenib. Nine out of 10 patients had progressive disease by RECIST criteria at enrollment (one patient was PET-positive only).

Two out of 10 patients had stable disease (SD), and completed one year of treatment (one did not have progressive disease [PD] at study entry—PET-positive only). Four patients had PD (two within three months and two at six months). Four patients went off study due to toxicity, despite dose reductions within three months (one for neutropenia and three for hypertriglyceridemia). There were no severe adverse events, and all toxicities were reversible upon bexarotene cessation. The average time on the study drug was 128.8 days for all participants (69.8 days if excluding the patients completing one year).

Four patients were on study until the six-month rhTSH-stimulated ¹²³I whole body scans, and none had visible radioactive iodine (RAI) uptake. This is in contrast to the study by Liu *et al.* that demonstrated RAI uptake in two out of five patients with previously RAI-resistant disease after eight weeks of bexarotene treatment (4).

All patients had baseline thyroid function tests and thyroglobulin testing and eight-week repeat testing. All patients were thyroglobulin antibody negative. Average baseline thyrotropin was 0.076 mIU/L and was 0.05 mIU/L at eight weeks (p =n.s.). Free thyroxine decreased from 1.72 to 0.91 ng/L (p <0.01), total thyroxine decreased from 11.9 to 7.83 μ g/dL (p <0.05), and total triiodothyronine decreased from 104.8 to 90.5 ng/dL (p =n.s.; Table 1b). Only one treatment patient complained of fatigue. A dose change of levothyroxine from 150 μ g to 175 μ g was made and was stable throughout the rest of the trial. Average serum thyroglobulin was 1676.39 ng/mL at baseline (median 97 ng/mL; range 7–15,486 ng/mL) and 2484.77 ng/mL at eight weeks (median 128 ng/mL; range 2.4–16,879 ng/mL; p =ns). Only one patient had 1+ staining for RXR γ protein scattered sparsely in some cells. This was the patient who had PD upon study

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TABLE 1A. PATIENT DEMOGRAPHICS

Characteristic	Value
Female, <i>n</i> (%)	7 (70%)
Age at trial enrollment (years $\pm$ avg)	61.4 $\pm$ 8.1
Primary histopathology, <i>n</i> (%)	
Papillary thyroid cancer (PTC)	9 (90%)
Follicular thyroid cancer (FTC)	1 (10%)
Disease localization for RECIST assessment	Lungs (100%)
Baseline disease	
RECIST Progressive $\pm$ PET-positive	9 (90%)
PET-Positive only	1 (10%)

TABLE 1B. RESULTS

Laboratory test	Baseline	Week 8	p-value
TSH	0.076 $\pm$ 0.095	0.05 $\pm$ 0.07	n.s.
ftT4	1.72 $\pm$ 0.35	0.91 $\pm$ 0.43	<0.01
TT4	11.9 $\pm$ 2.2	7.83 $\pm$ 3.6	<0.05
TT3	104.8 $\pm$ 49.0	90.5 $\pm$ 37.5	n.s.
Tg median (all pts Ab neg)	138	97.9	

TSH, thyrotropin; ftT4, free thyroxine; TT4, total thyroxine; TT3, total triiodothyronine; Tg, thyroglobulin.

entry and completed one year of therapy (SD on study drug). All other tumor samples were negative for RXR γ .

Whether targeted therapy with bexarotene for patients with thyroid cancers that strongly expresses RXR γ protein is a reasonable strategy remains unclear. However, in the era of TKI therapy for advanced thyroid cancer, it is unlikely based on our data that bexarotene will be a viable therapy for the majority of patients with advanced thyroid cancer.

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Author Disclosure Statement

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