A Phase II Trial of the Rexinoid Bexarotene for Poorly Differentiated Thyroid Cancer

Joshua Klopper, Madeleine Kane, Antonio Jimeno and Bryan Haugen
Disclosures

- None

- Learning Objectives
  - Understand the efficacy of long-term bexarotene treatment for poorly differentiated thyroid cancer
  - Understand the efficacy of bexarotene to improve radioiodine uptake in poorly differentiated thyroid cancer
  - Appreciate the effects of bexarotene on thyrotropin and peripheral thyroid hormone metabolism
  - Understand the side effect profile of bexarotene
Advanced Thyroid Cancer

- Accounts for the majority of thyroid cancer deaths
- Is often unresponsive to TSH-suppression and $^{131}$I
- Approved chemotherapy has modest efficacy with potentially high side effects
Superfamily of nuclear hormone receptors

- ligand binding domain (LBD) which upon activation transduces transcriptional activation.

Retinoid Receptors

- Retinoic Acid Receptors - RAR (α, β, γ)
- Retinoid X Receptors - RXR (α, β, γ)
  - RXR selective agonists: rexinoids
    - LGD1069 (bexarotene, Targretin® – Eisai Pharmaceuticals)
      - Cutaneous T-Cell Lymphoma
Clinical studies of bexarotene in advanced thyroid cancer

Bexarotene increases uptake of radioiodide in metastases of differentiated thyroid carcinoma

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Radioiodine therapy after pretreatment with bexarotene for metastases of differentiated thyroid carcinoma

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## Clinical studies of bexarotene in advanced thyroid cancer

<table>
<thead>
<tr>
<th>LIU ET AL. EURO J ENDO 2006</th>
<th>LIU ET AL. CLIN ENDO 2008</th>
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<tbody>
<tr>
<td>12 patients</td>
<td>8 patients</td>
</tr>
<tr>
<td>300mg/day for 6 weeks</td>
<td>300mg/day for 6 weeks</td>
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<tr>
<td>“improvement“ in 131I uptake after low dose WBS</td>
<td>Change in measurable disease 6 months after 131I therapy</td>
</tr>
<tr>
<td>Subtle increased uptake in some lesions</td>
<td>7400 MBq (200 mCi)</td>
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<tr>
<td>Incomplete matching with known lesions on CT</td>
<td>No CR or PR</td>
</tr>
<tr>
<td>Only visible by SPECT imaging and could not be quantitated</td>
<td>4/8 SD</td>
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1μM LGD 1069 Inhibits RXRγ+ cancer cell proliferation

Klopper et al., Mol Cancer Ther 2004 3: 1011-1020
Rexinoid responsive xenografts – DRO (RXRg+, PPARg+)
Primary Objective
- To assess the tumor response of recurrent or metastatic radioiodine resistant thyroid cancer to bexarotene therapy.

Secondary Objectives
- To assess the ability of previously radioiodine resistant thyroid cancer to concentrate radioactive iodine after bexarotene therapy.
- To correlate tumor response with thyroid cancer expression of retinoid and peroxisome-proliferator activated receptor gamma (PPARγ) receptors
Study Design

- Open label
- Single Agent
  - Bexarotene 300mg/m^2/day initial dose
  - 1 year of therapy
  - 2 week run-in with high dose fish oils and continued use while on trial
    - Minimize hypertriglyceridemia
# Enrollment Criteria

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<th>Inclusion</th>
<th>Exclusion</th>
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<tr>
<td>Follicular cell derived thyroid cancer</td>
<td>Eligible for surgery</td>
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<tr>
<td>Progressive disease and/or PET+ measurable lesions</td>
<td>Pregnant or unwilling to take contraception during study period</td>
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<tr>
<td>Measurable disease by RECIST</td>
<td>Hyperlipidemia refractory to therapy</td>
</tr>
<tr>
<td>Cr &lt; 1.5x ULN; LFTs &lt; 2.5 ULN</td>
<td>Hypertriglyceridemia refractory to therapy</td>
</tr>
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<td>&gt;18 y.o.</td>
<td>Other malignancy within the last 3 years</td>
</tr>
<tr>
<td>Primary or other thyroid cancer tissue available for study</td>
<td>Unable/unwilling to comply with study procedures</td>
</tr>
<tr>
<td>Negative rhTSH $^{123}$I WBS</td>
<td>Positive rhTSH $^{123}$I WBS</td>
</tr>
<tr>
<td>ECOG 0-1</td>
<td>ECOG &gt; 1</td>
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Study Measurements

- Weeks: 8, 18, 24, 30, 38, 46 and 52
  - TSH, FT₄, TT₄, TT₃, Tg, Tg Abs
- Weeks 24 and 52
  - PET-CT fusion
  - Neck US
  - rhTSH ¹²³I WBS
Response Evaluation Criteria in Solid Tumors (RECIST)

- Target lesions > 2cm in maximal dimension
- Tumor response (as measured by the sum of the longest dimension of target lesions)
  - CR – no measureable disease
  - PR – >30% reduction in target lesions
  - SD - < 30% reduction and < 20% progression of target lesions
  - PD - > 20% of target lesions or appearance of new lesions
Safety and Monitoring

- For Grade 2 or greater AEs
  - Hold bexarotene for 1 week
  - Confirm AE resolved
    - 25% reduction from initial dose
- Future AEs
  - Further 25% decrease
  - 3 total decreases allowed (75%, 50%, 25% of initial dose)
Patient Characteristics

- 19 patients signed consent
- 9 screen failed
  - Leukopenia
  - Inability to obtain archived thyroid cancer tissue
  - Clinical deterioration
  - Unwilling to follow study requirements
Patient Characteristics

- 10 patients enrolled
- Avg age – 61.4 ± 8.1 yrs
- Gender
  - 7 female
  - 3 male
- Tumor type
  - 9 PTC
  - 1 FTC

- All had previously received $^{131}$I therapy
- 3 with other therapy
  - Adriamycin/taxol
  - XRT
  - Axitinib
  - Sorafenib
- Baseline disease
  - 9/10 with Progressive/PET+ disease
  - 1/10 with PET+ disease only
2/10 patients completed 1 year of therapy
  ▪ 1/10 only PET+ (no documented progression)
Average time on study: 128.8 days
  ▪ Average time if early cessation: 69.8 days
Average starting dose: 585 ± 85.1 mg
4/10 patients off study for PD
  ▪ 3/4 had no dose reduction prior to discovery of PD
4/10 patients off study for drug related toxicity
  ▪ 1 Neutropenia
  ▪ 3 Hypertriglyceridemia
Radioiodine uptake
rhTSH $^{123}$I WBS

- 0/4 patients with visible uptake at 6 mos
- 0/2 patients with visible uptake at 12 mos
Bexarotene effect on thyroid hormone levels

Central Hypothyroidism Associated with Retinoid X Receptor-Selective Ligands

Single-Dose Rexinoid Rapidly and Specifically Suppressed Serum Thymotropin in Normal Subjects

Bexarotene-Induced Hypothyroidism: Bexarotene Stimulates the Peripheral Metabolism of Thyroid Hormones

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## Results

<table>
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<th>Lab test</th>
<th>Baseline</th>
<th>Week 8</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>TSH</td>
<td>0.076 ± 0.095</td>
<td>0.05 ± 0.07</td>
<td>ns</td>
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<tr>
<td>FT4</td>
<td>1.72 ± 0.35</td>
<td>0.91 ± 0.43</td>
<td>&lt; 0.01</td>
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<tr>
<td>TT4</td>
<td>11.9 ± 2.2</td>
<td>7.83 ± 3.6</td>
<td>&lt; 0.05</td>
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<tr>
<td>TT3</td>
<td>104.8 ± 49.0</td>
<td>90.5 ± 37.5</td>
<td>ns</td>
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<tr>
<td>Tg (all pts Ab neg)</td>
<td>1676.39 ± 4853.99</td>
<td>2484.77 ± 5942.18</td>
<td>ns</td>
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</table>
Bexarotene therapy in poorly advanced thyroid cancer resulted in SD in 2/10 patients
- 1/10 with documented progression prior to therapy
- 4/10 had progressive disease on maximum tolerable dose

Toxicity was common resulting in dose reductions or removal from trial
- Symptomatically well tolerated

No appreciable increase in radioiodine uptake was observed up to one year on therapy

Bexarotene therapy caused a significant decrease in FT\textsubscript{4} and TT\textsubscript{4} serum concentrations
- Thyrotropin decreased but not significantly
**Conclusions**

- Bexarotene is unlikely to have a role as a single agent for advanced thyroid cancer therapy
  - or for redifferentiation for improved radioiodine uptake
- Potential for adjuvant therapy with a role at decreasing thyrotropin/thyroid hormone levels
- IHC for nuclear hormone receptors is currently underway
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