University of Colorado Cancer Center

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

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Anschutz Medical Campus

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

Retinoid Receptors

- 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

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CLINICAL STUDY

Bexarotene increases uptake of radioiodide in metastases of differentiated thyroid carcinoma

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ORIGINAL ARTICLE

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

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Clinical studies of bexarotene in advanced thyroid cancer

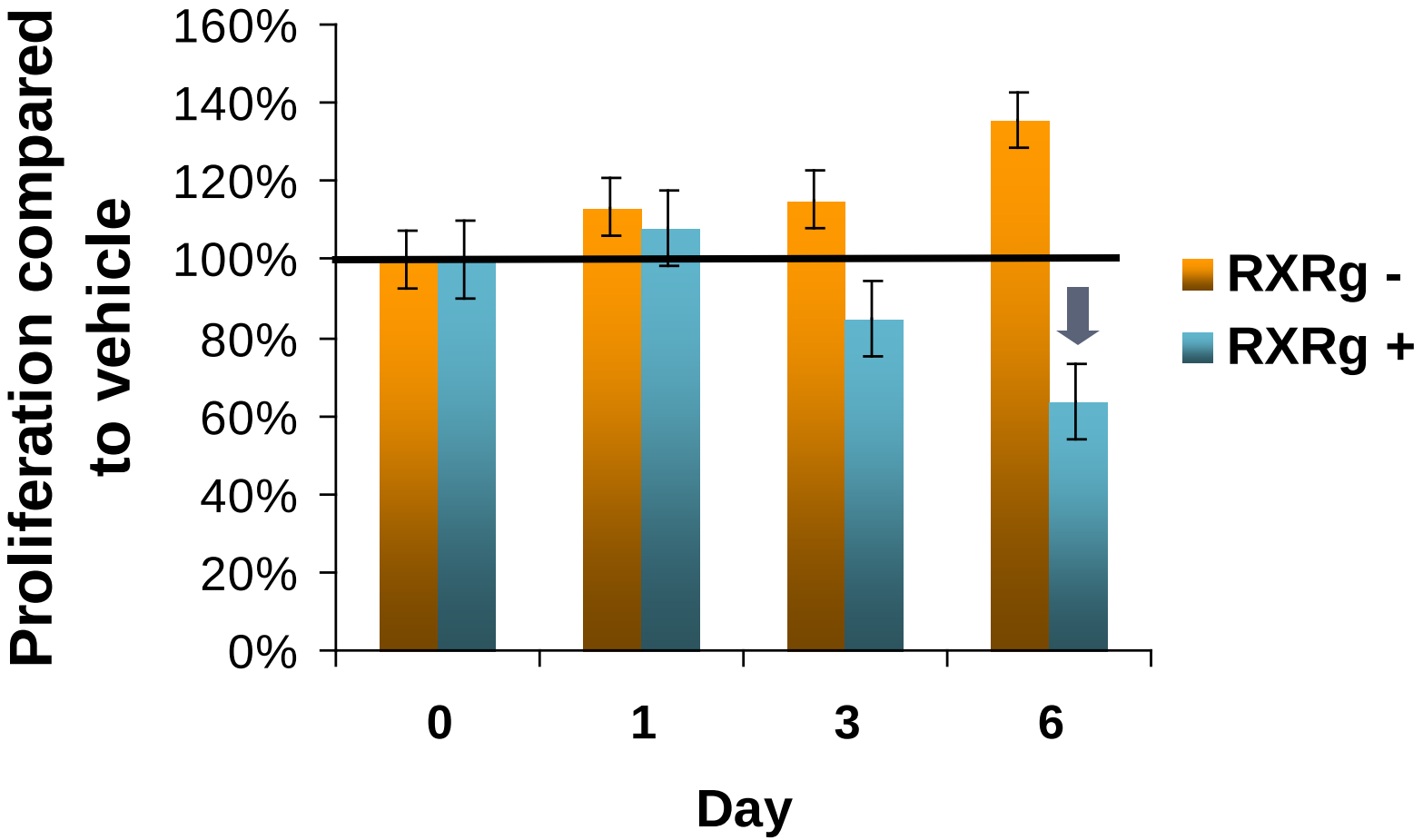
LIU ET AL. EURO J ENDO 2006

- 12 patients
- 300mg/day for 6 weeks
- "improvement" in 131I uptake after low dose WBS
- Subtle increased uptake in some lesions
  - Incomplete matching with known lesions on CT
  - Only visible by SPECT imaging and could not be quantitated

LIU ET AL. CLIN ENDO 2008

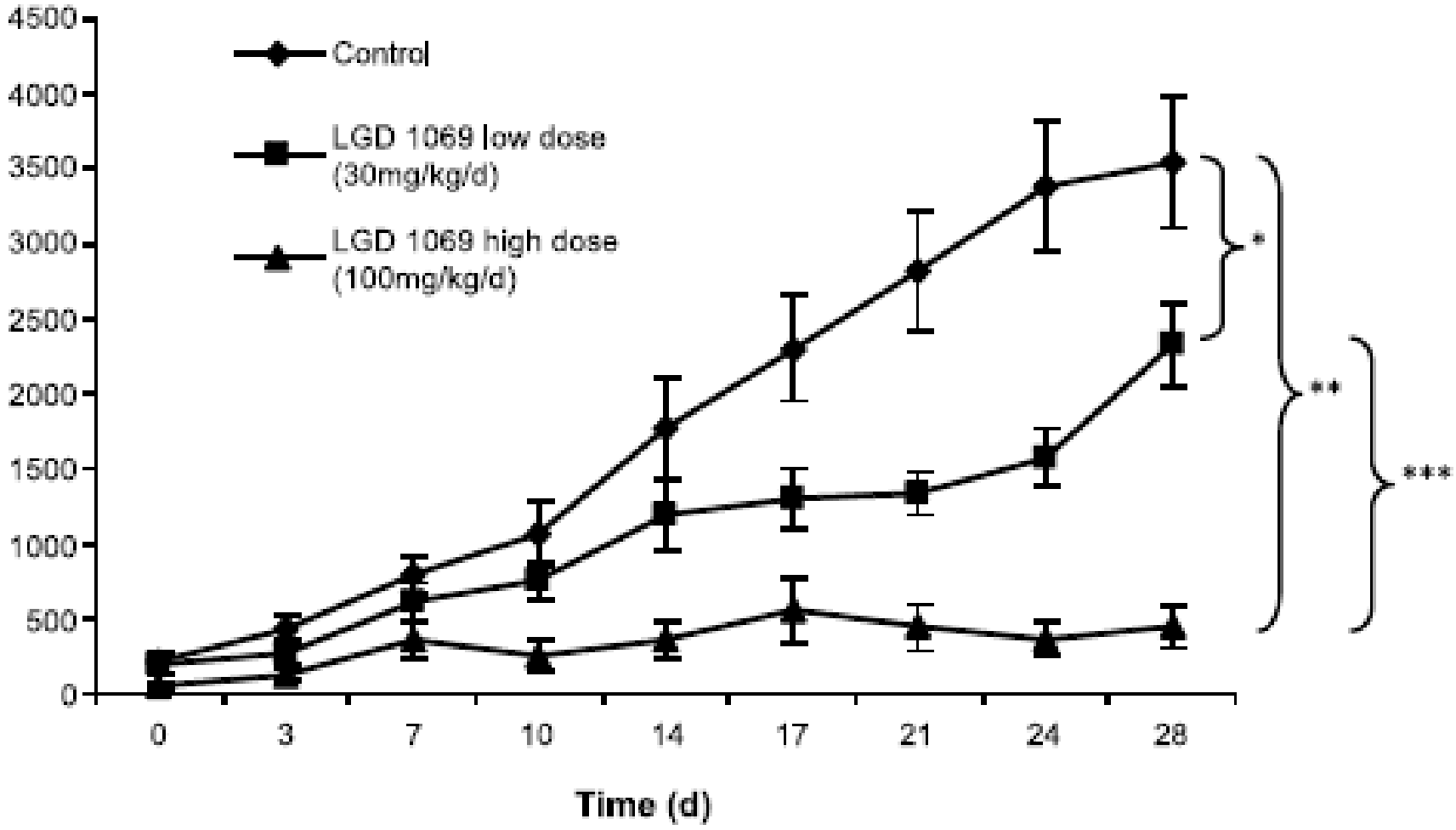
- 8 patients
- 300mg/day for 6 weeks
- Change in measurable disease 6 months after 131I therapy
- 7400 MBq (200 mCi)
- No CR or PR
  - 4/8 SD
    - No clear documentation of PD prior to intervention
  - 4/8 PD/new lesions
- IHC for RAR and RXR receptors from primary tissue
  - No + RXRg

1μM LGD 1069 Inhibits RXRγ+ cancer cell proliferation



Klopper et al., Mol Cancer Ther 2004 3: 1011-1020

Rexinoid responsive xenografts – DRO (RXRg+, PPARg+)



Klopper J. et al., Clin Cancer Res. 2008 Jan 15; 14(2):589-596

Study objectives

- **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

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

Study Measurements

- Weeks: 8, 18, 24, 30, 38, 46 and 52
  - TSH, FT_4, TT_4, TT_3, Tg, Tg Abs
- Weeks 24 and 52
  - PET-CT fusion
  - Neck US
  - rhTSH ^{123}I 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

Results

- 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

0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(1):124–130

doi: 10.1210/jc.2006-0696

Single-Dose Rexinoid Rapidly and Specifically Suppresses Serum Thyrotropin in Normal Subjects

0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(7):2496–2499

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

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Results

Lab test	Baseline	Week 8	p value
TSH	**0.076** ± 0.095	**0.05** ± 0.07	ns
FT_4	**1.72** ± 0.35	**0.91** ± 0.43	< 0.01
TT_4	**11.9** ± 2.2	**7.83** ± 3.6	< 0.05
TT_3	**104.8** ± 49.0	**90.5** ± 37.5	ns
Tg (all pts Ab neg)	**1676.39** ± 4853.99	**2484.77** ± 5942.18	ns

Summary

- 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_4 and TT_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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