Phase 1 Study of CS-7017, an Oral PPAR-gamma Agonist, in Combination with Paclitaxel in Subjects with Advanced Anaplastic Thyroid Cancer

R Smallridge, J Copland, M Brose, T Wadsworth, Y Houvras, M Menefee, K Bibble, M Shah, A Gramza, J Klopper, R Von Roemeling, Mayo Clinic, Jacksonville, FL; \*Univ Penn, Philadelphia, PA; \*EVA Medical Center, Norfolk, VA; \*Dana Farber Cancer Center, Boston, MA; \*Mayo Clinic, Rochester, MN; \*Ohio State Medical Center, Columbus, OH; \*Oregon Health and Science Center, Portland, OR; \*Univ Colorado, Denver, CO; \*Daiichi-Sankyo, Edison, NJ.

ABSTRACT

INTRODUCTION

Background: Anaplastic thyroid carcinoma (ATC) has a dire prognosis, with median overall survival (OS) of only 1.9 months for Stage IV disease. Paclitaxel, as single agent, has modest benefit. In preclinical studies, CS-7017 inhibits cell proliferation through a novel mechanism—activation of PPARs, followed by sequential upregulation of Rhod and pB1. In combination, CS-7017 augments the apoptotic effect of paclitaxel. Based on these results, a multicenter study was conducted to determine if this drug combination would provide benefit in patients with advanced ATC.

Design: A Phase 1 study was conducted to determine the Phase 2 dose. In Phase 1, patients received CS-7017 orally BID for one week (Run-in phase), followed by a 3-h infusion of paclitaxel (175 mg/m²) every 3 weeks in combination with paclitaxel. Safety and efficacy were assessed during the first 3 weeks of each cycle. 12 total patients were enrolled (5 M, 7 F; median age 59 years; range 43-81).

METHODS

A. Methods

1. Patient Eligibility

Inclusion criteria: 1. Histologically confirmed ATC. 2. Patients must have had progression of disease, refractory to prior therapies. 3. plasma thyroid stimulating hormone (TSH) levels > 10,000 mIU/ml. 4. ECOG performance status (PS) ≤ 2. 5. Adequate organ function, with the following exceptions: Creatinine clearance ≥ 30 ml/min, Serum bilirubin ≤ 256 ug/dl, ALT/AST ≤ 2.5 x upper limit of normal (ULN). 6. Able to provide informed consent.

B. Study Treatment Schedule

Week 1: Oral BID CS-7017 (4d/7d cycle)

Week 2: Paclitaxel 175 mg/m² IV over 3 hours every 3 weeks

C. Safety

No dose limiting toxicities were observed with CS-7017 dosages up to 0.5 mg BID. All deaths were due to disease progression. Two SAEs were drug related (one each with CS-7017 and paclitaxel). Median Time to Progression and Survival were increased by 42%, in Dose Level 2 vs. Level 1 patients, and one patient had a prolonged Rhod level duration partial regression. Tissue angiopoietin-6 was induced by CS-7017.

CONCLUSION

Combination therapy with CS-7017 and paclitaxel was tolerated and has biologic activity in patients with anaplastic thyroid carcinoma, with initial exploratory data suggesting a dose-dependent improvement in time to progression and survival in response to escalating CS-7017 dosage.