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## ABSTRACT

**Background:** Anaplastic thyroid cancer (ATC) has a dire prognosis, with median overall survival (OS) of only 1.9 months for Stage IVC disease. Paclitaxel, as single agent, has modest benefits. In pre-clinical studies, CS-7017 inhibits cell proliferation through a novel mechanism—activation of PPAR- $\gamma$ , followed by sequential upregulation of RhoB and p21. 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 benefits 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 iv infusion of paclitaxel (175 mg/m<sup>2</sup>) every 3 weeks in combination with BID CS-7017. CS-7017 doses were 0.15, 0.3, or 0.5 mg. Tissue biopsies were obtained at baseline, one week, and after cycle 1 for immunohistochemistry of PPAR- $\gamma$  responsive proteins, and serum PK studies were performed.

**Results:** Nineteen patients were enrolled, but 4 were not dosed (3 due to progression, 1 ineligible). Seven participated in CS-7017 dose levels 1a/1b (0.15 mg BID), six in dose level 2 (0.3 mg BID), and two in dose level 3 (run-in phase only—0.5 mg BID). **Demographics—**Of the 15 treated patients, 10 (67%) were women. Median age was 59 years (range: 43-82).

**Efficacy:** Of 15 patients receiving drug, one had a confirmed partial response (PR) lasting from Day 69 to Day 175. Eight patients had stable disease (SD) as their best response. Median Time to Progression in 7 patients at Dose Level 1 was 49 days, and was 70 days (43% prolongation) in Dose Level 2. Median survival from start of trial was 99 (0.15 mg BID) vs. 140 days (0.3 mg BID) (42% increase). Median peak CS-7017 blood level was 8.6 ng/mL (range: 5.1 to 13.7) at Level 1 and 22.0 ng/mL (17.0 to 31.5) in Dose Level 2.

**Safety:** No dose limiting toxicity was observed. CS-7017 did not appear to affect vital signs or ECG findings. **Adverse Events:** Ten patients had AEs  $\geq$  Grade 3, with two (anemia and localized edema) related to CS-7017. Thirteen events of fluid retention and edema were reported in 8 patients, but only 2 events had a CTCAE grade of  $\geq$  3. Eight patients had  $\geq$  one SAE, with one (anemia) due to CS-7017. One SAE (anaphylactic reaction) was related to paclitaxel.

**Immunohistochemistry:** Biopsies were available on 7 patients. PPAR- $\gamma$ , RXR- $\alpha$ , RhoB were present in all, while Angiopoietin-like 4 was induced by CS-7017.

**Summary:** 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 RECIST documented partial regression. Tissue angiopoietin-like 4 was induced by one week, documenting biologic activity.

**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.

## INTRODUCTION

PPAR $\gamma$  is a DNA-binding nuclear hormone-receptor and controls cellular energy metabolism through transcriptional regulation. CS-7017 is a selective agonist of PPAR $\gamma$  and belongs to the thiazolidinedione (TZD) class of synthetic PPAR ligands. Several non-clinical studies suggest that PPAR $\gamma$  agonists may inhibit tumor cell growth through the induction of terminal differentiation, cell cycle arrest and/or apoptosis induction, as well as inhibition of angiogenesis. In the *in vitro* and/or in animal models, PPAR $\gamma$  agonists have shown anti-tumor activity against variety of tumors.

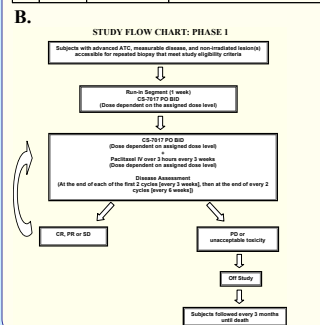
*In vitro*, CS-7017 selectively activates PPAR $\gamma$ -mediated transcription, with little effect on other PPAR subtypes. The compound inhibits proliferation of human pancreatic and anaplastic thyroid tumor-cell cultures as well as growth of human colorectal tumor xenografts in nude mice, significantly improving survival of tumor-bearing animals. Additional data suggest the anti-tumor activity of CS-7017 *in vivo* may be enhanced in combination with cytotoxic agents. While thyroid cancer is the most common endocrine malignancy, anaplastic thyroid cancer (ATC) is extremely rare. In 2007, the estimated incidence rate for thyroid cancer in the United States (US) is about 33,500 newly diagnosed cases<sup>[1]</sup>, of which ATC comprises less than 2%. ATC is a poorly differentiated, highly aggressive tumor with a median survival of 4 months from diagnosis and a 1 year survival of no more than 10%. Mechanisms of PPAR $\gamma$ -mediated anti-tumor activity include induction of cellular differentiation, promotion of cell cycle arrest, antiangiogenic effects, and induction of apoptosis. PPAR $\gamma$  agonists induce cell cycle arrest via a p53-independent pathway. In thyroid cancer, PPAR $\gamma$  may act as a tumor suppressor gene. PPAR $\gamma$  agonists are known to antagonize anti-apoptotic pathways such as survivin, which may account for synergy between PPAR $\gamma$  agonists and taxanes, since taxanes upregulate survivin. Since survivin is highly expressed in poorly differentiated cancers including ATC, it is hypothesized that the combination of CS-7017, a PPAR $\gamma$  agonist that may antagonize survivin, and paclitaxel may enhance anti-tumor activity.

Paclitaxel is a potent suppressor of microtubule dynamics. By binding to the paclitaxel site on tubulin, it induces microtubule arrest through polymerization and stabilization of microtubules. Paclitaxel induces cell death by apoptosis. However, its effectiveness against solid tumors develops resistance. CS-7017 has no direct effect on apoptosis in ATC cells, but synergistically enhances the apoptotic effect of paclitaxel. When CS-7017 and paclitaxel were used as single agents in an ATC xenograft model, they inhibited tumor growth by 63% and 73%, respectively. However, in combination they reduced tumor size by 96%. These studies, in aggregate, have provided preclinical data to support a clinical study using these two agents in subjects with ATC.

## A. Methods

**Table 1: Dose Escalation Schedule**

Dose Level	Minimum Number of Subjects	CS-7017 Dose <sup>a</sup>	Paclitaxel Dose
1a	3	0.10 mg every 12 hours	175 mg/m <sup>2</sup> IV over 3 hours every 3 weeks
1b	3	0.15 mg every 12 hours	175 mg/m <sup>2</sup> IV over 3 hours every 3 weeks
1b <sup>b</sup>	3	0.15 mg every 12 hours	175 mg/m <sup>2</sup> IV over 3 hours every 3 weeks
2	3	0.30 mg every 12 hours	175 mg/m <sup>2</sup> IV over 3 hours every 3 weeks
3	3	0.50 mg every 12 hours	175 mg/m <sup>2</sup> IV over 3 hours every 3 weeks
4 <sup>c</sup>	3	0.75 mg every 12 hours	175 mg/m <sup>2</sup> IV over 3 hours every 3 weeks



## C. Safety

**Table 2: Subjects with Serious Adverse Events (Enrolled Analysis Set)**

Subject ID	CS-7017 (mg BID)	Paclitaxel (mg/m <sup>2</sup> )	Event (Preferred Term)	CTCAE Grade	Relationship (Y/N, unspecified)	Treatment Discontinued (Y/N)	Outcome
10071001	0.15	175	Conjunctivitis	1	No	Yes (CS-7017)	Resolved
10071002	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071003	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071004	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071005	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071006	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071007	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071008	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071009	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071010	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071011	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071012	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071013	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071014	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071015	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071016	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071017	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071018	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071019	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071020	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071021	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071022	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071023	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071024	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071025	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071026	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071027	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071028	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071029	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071030	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071031	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071032	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071033	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071034	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071035	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071036	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071037	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071038	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071039	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071040	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071041	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071042	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071043	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071044	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071045	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071046	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071047	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071048	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071049	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071050	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071051	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071052	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071053	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071054	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071055	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071056	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071057	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071058	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071059	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071060	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071061	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071062	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071063	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071064	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071065	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071066	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071067	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071068	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071069	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071070	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071071	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071072	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071073	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071074	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071075	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071076	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071077	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071078	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071079	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071080	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071081	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071082	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071083	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071084	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071085	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071086	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071087	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071088	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071089	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071090	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071091	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071092	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071093	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071094	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071095	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071096	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071097	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071098	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071099	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved
10071100	0.15	175	Diarrhea	1	No	Yes (CS-7017)	Resolved

**D. Overall Summary of TEAEs: Number (%) of Subjects with at least 1 TEAEs in Each Category (Safety Analysis Set)**

Category	All Subjects (n = 19)
TEAE	14
TEAE with CTCAE Grade $\geq$ 3	10
TEAE related to CS-7017	10
TEAE related to CS-7017 with CTCAE Grade $\geq$ 3	2
TEAE with fatal outcome	2