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

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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-γ, 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/m2) 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- γ 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 ≥ 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 ≥ 3. Eight patients had ≥ 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-γ, RXR-α, 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

PPARγ is a DNA-binding nuclear hormone-receptor and controls cellular energy metabolism through transcriptional regulation. CS-7017 is a selective agonist of PPARγ and belongs to the thiazolidinedione (TZD) class of synthetic PPAR ligands. Several non-clinical studies suggest that PPARγ 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, PPARγ agonists have shown anti-tumor activity against variety of tumors.
In vitro, CS-7017 selectively activates PPARγ-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[i], 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 PPARγ-mediated antitumor activity include induction of cellular differentiation, promotion of cell cycle arrest, antiangiogenic effects, and induction of apoptosis. PPARγ agonists induce cell cycle arrest via a p53-independent pathway. In thyroid cancer, PPARγ may act as a tumor suppressor gene. PPARγ agonists are known to antagonize anti-apoptotic pathways such as survivin, which may account for synergy between PPARγ 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 PPARγ agonist that may antagonize survivin, and paclitaxel may enhance antitumor activity.
Paclitaxel is a potent suppressor of microtubule dynamics. By binding to the paclitaxel site on tubulin, it induces mitotic arrest through polymerization and stabilization of microtubules. Paclitaxel induces cell death by apoptosis. However, its effectiveness is limited because many tumors develop resistance. In *in vitro* studies, 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 2 agents in subjects with ATC.

RESULTS

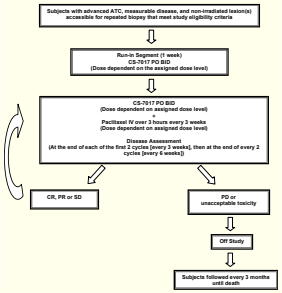
Methods

A.

Table 1: Dose Escalation Schedule

Dose Level	Minimum Number of Subjects	CS-7017 Dose[a]	Paclitaxel Dose
-1[a]	3	0.10 mg every 12 hours	135 mg/m² IV over 3 hours once every 3 weeks
1a[b]	3	0.15 mg every 12 hours	135 mg/m² IV over 3 hours once every 3 weeks
1b[b]		0.15 mg every 12 hours	175 mg/m² IV over 3 hours once every 3 weeks
2	3	0.30 mg every 12 hours	175 mg/m² IV over 3 hours once every 3 weeks
3	3	0.50 mg every 12 hours	175 mg/m² IV over 3 hours once every 3 weeks
4[c]	3	0.75 mg every 12 hours	175 mg/m² IV over 3 hours once every 3 weeks

B.



Safety

C.

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

Subject ID	Dose Level at Time of Event Onset: CS-7017 (mg BID)	Dose Level at Time of Event Onset: Paclitaxel (mg/m²)	Event (Preferred Term)	CTCAE Grade	Relationship (Y/N, specify)	Treatment Discontinued (Y/N)	Outcome
10011001	0.15	0	Carcinomal state	1	No	No	Resolved
	0.15	135	Septic shock	4	No	Yes, CS-7017	Resolved
	0.15	135	Disease progression	5	No	Yes, CS-7017	Fatal
10011002	0.15	135	Disease progression	5	No	Yes, CS-7017	Fatal
10031005	0.15	175	Dysphagia	3	No	Interrupted, CS-7017	Resolved
10071008	0.30	175	Clostridial infection	2	No	No	Resolved
10071015	0.30	175	Pneumonia	3	No	Interrupted, CS-7017	Resolved
10081012	0.30	175	Dyspnoea	4	No	No	Not resolved
	0.30	0	Anemia	4	Yes, CS-7017 and paclitaxel	No	Resolved
10071018	0.50	175	Loss of consciousness	3	No	No	Resolved
10071019	0.30	175	Anaphylactic reaction	4	Yes, paclitaxel	Paclitaxel discontinued permanently	Resolved

D.

Table 3: Overall Summary of TEAEs: Number (%) of Subjects with at least 1 TEAEs in Each Category (Safety Analysis Set)

Category	All Subjects (N = 15)
TEAE	14
TEAE with CTCAE Grade ≥ 3	10
TEAE related to CS-7017	10
TEAE related to CS-7017 with CTCAE Grade ≥ 3	2
TEAE with fatal outcome	2
Treatment-emergent SAE	8
Treatment-emergent SAE related to CS-7017	1
Treatment-emergent SAE related to paclitaxel	2
TEAE leading to treatment discontinuation	3
TEAE leading to treatment discontinuation and related to CS-7017	0
TEAE leading to treatment discontinuation and related to paclitaxel	1

Patient Response Rates

Time to progression (median)	Dose 1 (0.15mg BID) (n=7)	Dose 2 (0.3mg BID)(n=6)
Days	49	70
Weeks	7	10 (↑ 43%)
Median survival (from trial start)		
Days	99	140
Weeks	14.1	20 (↑ 42%)
Peak PK (ng/ml) – median	8.6 (5.1 – 13.7)	22.0 (17.0 – 31.5)(↑155%)

Dose 3(0.5mg BID) Run-in only (n=2): Peak PK 32.7 & 39.5 ng/ml

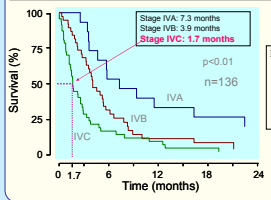


Figure 1. 50 year Mayo Clinic experience demonstrates that patients with metastatic ATC (stage IVC) have a median survival rate of 1.7 months (McIver et al. Surgery, 130:1028, 2001).

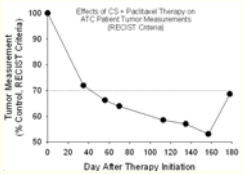


Figure 2. Partial Response (PR) in a 74 year old female with ATC and pulmonary metastases. Prior treatment included thyroidectomy and central compartment neck dissection.

IHC Biomarkers for Response to therapy

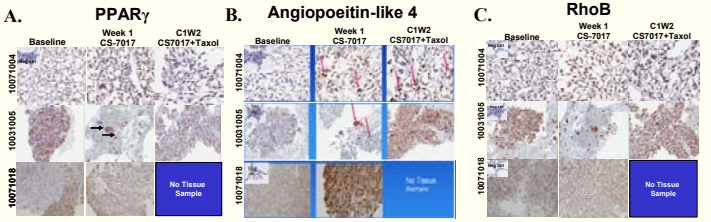


Figure 3. Immunohistochemistry of 3 ATC patient tumor biopsies at baseline, 1 week run in with CS-7017 and at cycle 1 week 2 with combinatorial CS-7017 plus paclitaxel demonstrates that PPARg is present in all biopsies B. that angiopoeitin-like 4 is upregulated in biopsies in response to CS-7017 treatment at week 1 and C1W2 and RhoB levels are elevated at baseline and not significantly elevated in response to CS-7017 treatment. Patient 10071004, and 10031005 and 10071018 were at dose level 1, 2 and 3 CS-7017 respectively.

SUMMARY

Safety:
- No dose-limiting toxicities were observed with CS-7017 dosages of up to 0.50 mg BID
- All deaths during study were due to disease progression
- Only two reported SAEs (Grade 4, anemia, anaphylaxis) was assessed by the investigator as possibly related to CS 7017 and/or paclitaxel
- Thirteen events of fluid retention and edema were reported in 8 subjects, but only 2 events had a CTCAE grade of 3.
- CS-7017 did not appear to affect vital signs or ECG findings

Efficacy:
- Median survival exceeds historical controls and single agent taxanes
- Median Time To Progression (TTP) exceeds docetaxel
- Dose level 2 increases TTP and survival by 42% vs. level 1
- One patient had Partial Response (PR); 8 had Stable Disease (SD)
- Tissue ANPTL-4 ↑ at 1 and 4 weeks in response to 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.