Pain Palliation as an Oncology Label Indication: Lessons Learned in Custirsen Phase 3 Development

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INTRODUCTION

- Docetaxel plus prednisone q3 wks is standard 1st-line chemotherapy in metastatic castration-resistant prostate cancer (mCRPC).
- Depending on response to 1st-line docetaxel, 2nd-line cabazitaxel treatment or docetaxel retreatment have shown clinical benefits.
- Pain is a common and disabling symptom of advanced mCRPC. Durable pain palliation in mCRPC is a measure of clinical benefit suitable for a label indication.
- Custirsen is an ASO-based agent designed to decrease chemotherapy resistance.
- When docetaxel retreatment was given in combination with custirsen as 2nd-line chemotherapy, the proportion of patients having a pain response was 59%, with median duration of pain response estimated at 6.9 months.[1]
- This randomized, double-blind, placebo-controlled, Phase 3 study was designed to evaluate whether custirsen plus taxane 2nd-line chemotherapy could improve pain palliation compared to placebo plus taxane 2nd-line chemotherapy for patients with mCRPC and disease progression.

OBJECTIVES

PRIMARY

- Proportion of patients with durable pain palliation compared to control arm

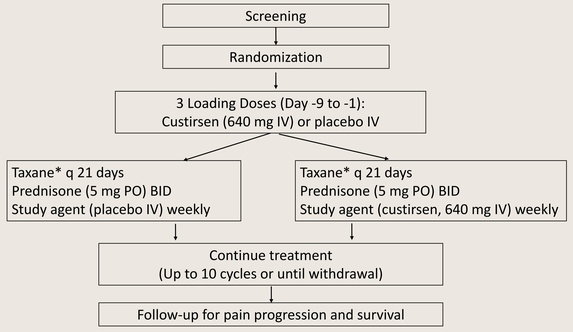
SECONDARY

- Time to pain progression compared to the control arm
- Incidence of serious adverse events and ≥Grade 3 adverse events

EXPLORATORY

- Overall survival, including relationship between serum clusterin and other efficacy measures

STUDY DESIGN AND TIMELINE



*The selection of type of taxane therapy (docetaxel 75 mg/m² IV or cabazitaxel 25 mg/m² IV) was at the discretion of the Investigator. Patients selected to receive docetaxel retreatment had to comply with additional inclusion and exclusion criteria to receive docetaxel retreatment.
Note: cabazitaxel could only be used in countries where it was available on the basis of regulatory approval.

METHODS

- Double-blind, placebo-controlled, randomized Phase 3 study (N=292 planned)
- Patients treated with taxane (docetaxel retreatment or cabazitaxel) plus prednisone and study agent (placebo or custirsen 640 mg) for up to 10 cycles (3 wks each cycle)
- Type I error probability of one-sided 0.025; power of 90%. Proportion of durable pain palliation in control arm assumed to be 10% due to required duration of ≥12 wks

KEY ELIGIBILITY CRITERIA

- Metastatic CRPC with prostate cancer-related pain and progression of disease during/after at least 4 cycles of prior 1st-line docetaxel therapy
- Concurrent pain and analgesic use related to prostate cancer
- Must have been on opioids for pain control, with stable baseline pain and analgesic use:
  - Mean baseline worst pain score at least 3 and ≤7 points
  - Stable pain over 7 daily baseline assessments (min 5) prior to randomization
  - Stable analgesic use in each analgesic category (long-acting opioid, short-acting opioid, or non-opioid) over 7 daily baseline assessments (min 5) prior to randomization
- For docetaxel retreatment: No disease progression while on or within 6 wks of receiving the last dose of 1st-line docetaxel therapy
- Acceptable baseline liver, kidney, and bone marrow function
- Karnofsky score ≥ 70% at screening
- Willing to provide written informed consent

DEFINITIONS

- **Durable pain palliation (dPP):** Reduction in pain for a minimum of 12 wks duration. dPP measured on the basis of responses to the Brief Pain Inventory, which asked subjects to describe their worst pain in the last 24 hrs. A pain palliation period started when a subject's mean worst-pain scores had decreased from baseline by ≥2 points during 2 consecutive assessment periods, and ended when a subject's mean worst-pain scores were ≥baseline values during 2 consecutive assessment periods, or when pain progression occurred.
- **Pain progression:** Receipt of any radiation therapy for pain palliation, or meeting one of the following criteria during 2 consecutive assessment periods after Cycle 3 Day 1: 1) mean worst-pain scores had increased ≥2 points from baseline, or 2) specified increases in analgesic use, regardless of pain status. Pain progression was the major determinant for when subjects were removed from study treatment.

BASELINE

Baseline Characteristics, Pain, and Analgesic Use

- Age, median (range): control arm, 65 yrs (63-73), vs. custirsen arm, 59 yrs (53-69)
- Karnofsky Performance Status: control arm, 90-100%, 2/7 patients (29%); 70-80%: 5/7 patients (71%), vs. custirsen arm, 90-100%, 4/7 patients (57%); 70-80%: 3/7 patients (43%)
- Worse Pain Scores: median 5 (both arms); range: control arm, 4-6, vs. custirsen arm, 4-7
- Analgesic Use: All patients on short-acting opioids; most patients on long-acting opioids

Prior Docetaxel Use

	Placebo (N=7)	Custirsen (N=7)	All Subjects (N=14)
Number of cycles, median (range)	7 (6-15)	10 (4-30)	10 (4-30)
Positive response to 1st-line, n (%)	7 (100)	6 (86)	13 (93)
Time (months) from end of 1st-line to progression, median (range)	1 (-8 – 5)	2 (1 – 44)	1 (-8 – 44)
Reason for ending 1st-line, n (%)			
Planned course completed	3 (43)	4 (57)	7 (50)
Disease progression	1 (14)	2 (29)	3 (21)
Physician decision	2 (29)	0 (0)	2 (14)
Adverse event	1 (14)	0 (0)	1 (7)
Other	0 (0)	1 (14)	1 (7)
Basis of progression, n (%)			
Bone scan	5 (71)	5 (71)	10 (71)
Increased PSA	2 (29)	2 (29)	4 (29)

RESULTS

DISPOSITION

- Trial activated at 62 sites, stopped after 20 months; 35 subjects screened at 19 sites
- 14 subjects assigned to treatment with study agent (placebo, n=7; custirsen, n=7)

EXTENT OF EXPOSURE

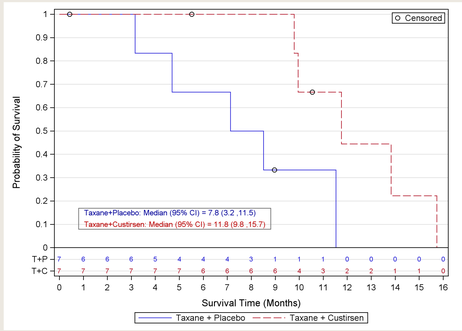
- 14 subjects received 3 loading doses of study agent; 13 subjects began Cycle 1 + received treatment (docetaxel/pred/study agent [n=3]; cabazitaxel/pred/study agent [n=10])
- Time on study treatment was a median 4 cycles taxane/9 wks placebo (taxane + placebo arm) and a median 6 cycles taxane/18 wks custirsen (taxane + custirsen arm)
- No subject completed all 10 treatment cycles; adverse event was the most common reason for treatment discontinuation (n=9/14)

EFFICACY

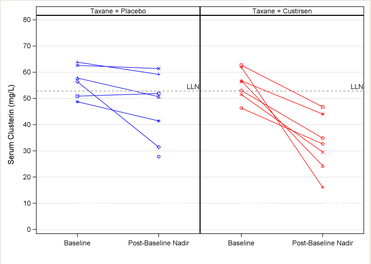
- **Durable Pain Palliation ≥ 12 weeks duration:** 3/14 subjects
  - Placebo arm, n=1 (14%)
  - Custirsen arm, n=2 (29%)
- **Time To Pain Progression:** Median (95% confidence interval [CI]) by Kaplan-Meier analyses
  - Placebo (n=7): not estimable [NE] (2.7 months, NE); range: 0plus - 6.4plus months
  - Custirsen (n=7): 6.4 months (2.9, 6.8); range: 2.9 - 6.8 months

  plus = time of censoring for subjects without pain progression at analysis
- **Overall Survival:** Median (95% CI) by Kaplan-Meier analyses
  - Placebo (n=7): 7.8 months (3.2, 11.5); range: 0.4plus - 11.5 months
  - Custirsen (n=7): 11.8 months (9.8, 15.7); range: 5.5plus - 15.7 months

  plus = time of censoring for living subjects at analysis



- **Serum Clusterin:**
  - Change from baseline to minimum observed level greater in custirsen vs. placebo arm



RESULTS (CON'T)

ADVERSE EVENTS

AEs ≥ Grade 3 reported for ≥2 patients included: back pain (n=0, placebo arm; n=2, custirsen arm), hyperesthesia (n=0, n=2), and asthenia (n=2, n=1).

SERIOUS ADVERSE EVENTS

Chemo-therapy	Study Agent	MedDRA Preferred Term	Severity Grade	Relationship* to: Study Drug	Relationship* to: Chemotherapy
Cabazitaxel	Placebo	Muscular weakness	3	Possible	None
Cabazitaxel	Placebo	Bile duct obstruction	3	None	None
		Cholangitis	3	None	None
Cabazitaxel	Placebo	Diplopia	2	None	None
Cabazitaxel	Placebo	Esophageal hemorrhage	2	None	Possible
		Thrombocytopenia	4	None	None
		Disseminated intravascular coagulation	5	None	None
		Fibrinolysis	5	None	None
Docetaxel	Custirsen	Idiopathic thrombocytopenic purpura	3	Definite	None
		Thrombocytopenia	3	Possible	Possible
Cabazitaxel	Custirsen	Pyrexia	3	Probable	None
		Hyperaesthesia	3	None	None
Cabazitaxel	Custirsen	Hypersensitivity	3	Possible	None
Cabazitaxel	Custirsen	Hyperaesthesia	3	None	None
Cabazitaxel	Custirsen	Dysuria	2	None	None

* As determined by the Investigator

CONCLUSIONS

- Restrictive protocol-specified criteria of stable baseline pain and consistent analgesic use prevented the ability to complete study enrollment. **Pragmatic criteria for oncology pain studies are needed.**
- Durable pain palliation was 1 of 7 (14%) in placebo arm, vs. 2 of 7 (29%) in custirsen arm, which appears to be in line with statistical assumptions; unable to draw conclusions due to small sample size.
- Custirsen was generally well tolerated when administered in combination with a taxane (docetaxel or cabazitaxel) and prednisone.
- Median number of chemotherapy cycles was 4 (placebo arm) vs. 6 (custirsen arm). Median duration of study agent treatment was 9 weeks (placebo arm) and 18 weeks (custirsen arm).
- Median survival was 7.8 months (placebo arm) and 11.8 months (custirsen arm). Further clinical development of custirsen in a larger **Phase 3 study in 2nd-line cabazitaxel treatment for mCRPC (AFFINITY) is underway, evaluating survival as the primary endpoint** while monitoring for pain/analgesic use.

REFERENCE

[1] Data on file, OncoGenex Pharmaceuticals, Inc., 2013.

ACKNOWLEDGEMENTS

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