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Baseline Serum Clusterin Level in Patients with Poor Prognostic Features was Associated with Response to Custirsen Treatment: Results from the Phase 3 SYNERGY Trial of Docetaxel +/- Custirsen

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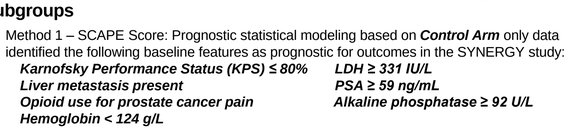
BACKGROUND

Clusterin

- Production of the protein clusterin (CLU) is a fundamental cellular repair mechanism that protects normal cells from programmed cell death.
- CLU is more highly expressed in aggressive cancers and upregulated in response to treatment such as chemotherapy, hormone ablation, and radiation therapy.
- CLU is overproduced in many malignancies including castration resistant prostate cancer (CRPC) and is associated with faster rates of cancer progression and shorter survival.
- Intracellular CLU within tumor cells helps those cells evade the destructive effects of anti-cancer therapies.
  - CLU is also secreted via the Golgi apparatus and can be measured in serum in µg/mL levels.

sCLU

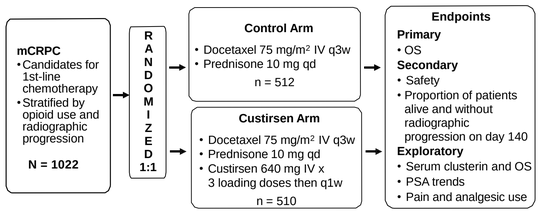


Custirsen

- Custirsen is a second-generation antisense oligonucleotide (ASO) designed to bind to CLU mRNA, blocking production of the clusterin protein. Preclinical studies demonstrate enhanced efficacy of chemotherapy when combined with custirsen and clusterin inhibition, including reversing taxane resistance.
- A phase 1 pre-surgery study determined that clusterin inhibition by custirsen in prostate cancer tissues was dose-dependent, with a biologically effective dose of 640 mg.[1]
- A randomized phase 2 study in patients with metastatic (m) CRPC showed that the addition of 640 mg custirsen to docetaxel plus prednisone (DP) reduced serum clusterin by 26% and prolonged overall survival (OS) vs. DP alone (23.8 vs. 16.9 mo; Cox regression hazard ratio [HR] 0.50; 95% confidence interval [CI] 0.29-0.87).[2]

SYNERGY: STUDY DESIGN AND RESULTS

Randomized, open-label, multinational phase 3 study conducted in 140 centers in 12 countries



Abbreviations: IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; qd, daily; q1w, weekly; q3w, every 3 weeks

- Final analysis at 509 deaths to assure 90% power for hypothesized HR 0.75, with one-sided type I error of 0.025 and type II error of 0.1.
- **Final results: Median OS was 23.4 months (m) vs. 22.2 m for the custirsen and control arms, respectively (HR 0.93; P = 0.42).**[3]

Exploratory Statistical Analyses Defining Poor and Good Prognostic Subgroups

- Method 1 – SCAPE Score: Prognostic statistical modeling based on ***Control Arm*** only data identified the following baseline features as prognostic for outcomes in the SYNERGY study:
  - ***Karnofsky Performance Status (KPS) ≤ 80%***
  - ***Liver metastasis present***
  - ***Opioid use for prostate cancer pain***
  - ***Hemoglobin < 124 g/L***
  - ***LDH ≥ 331 IU/L***
  - ***PSA ≥ 59 ng/mL***
  - ***Alkaline phosphatase ≥ 92 U/L***

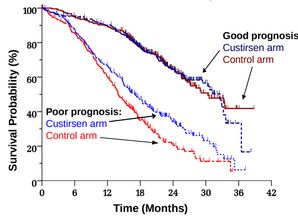
  Coefficients from above analysis were used to compute statistical model "SCAPE score" of patients in both arms; patients were defined as "poor" versus "good" prognosis by dichotomizing at overall median score.

- Method 2 – Feature Count: Findings from SCAPE score were used to develop a simplified 5-criteria prognostic index that classified patients as "poor" prognosis based on having 2 or more of the following 5 features:
  - ***Karnofsky Performance Status ≤ 80%***
  - ***Presence of liver metastasis***
  - ***Hemoglobin < 120 g/L***
  - ***LDH ≥ 360 IU/L***
  - ***PSA ≥ 150 ng/mL***

SURVIVAL RESULTS

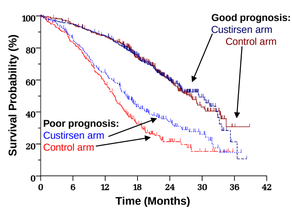
Similar Survival Results Obtained with Both Methods

Survival by SCAPE Score and Arm (N=984)



Good Prognosis Score Patients	Custirsen + Docetaxel (n = 240)	Docetaxel (control) (n = 252)
Median OS (Months)	32.6	30.4
HR (95% CI)	1.02 (0.76 to 1.37), *P = 0.901*	
Poor Prognosis Score Patients		
	Custirsen + Docetaxel (n = 250)	Docetaxel (control) (n = 242)
Median OS (Months)	17.0	14.0
HR (95% CI)	0.73 (0.59 to 0.90), *P = 0.004*	

Survival by Feature Count (Index Score) and Arm (N=984)



Good Prognosis (<2 of 5 Negative Prognostic Factors*)	Custirsen + Docetaxel (n = 283)	Docetaxel (control) (n = 295)
Median OS (Months)	29.4	27.7
HR (95% CI)	1.00 (0.78 to 1.29), *P = 0.979*	
Poor Prognosis (≥2 of 5 Negative Prognostic Factors*)		
	Custirsen + Docetaxel (n = 208)	Docetaxel (control) (n = 201)
Median OS (Months)	16.0	13.7
HR (95% CI)	0.73 (0.58-0.92), *P = 0.008*	

*Negative Prognostic Factors: KPS ≤80%; presence of liver metastasis; hemoglobin <120 g/L; LDH ≥ 360 IU/L; PSA ≥ 150 ng/mL

GOALS OF THIS ANALYSIS

To evaluate the effect of custirsen treatment on serum CLU (sCLU) levels in patients with mCRPC, and to assess the correlation between sCLU levels and survival benefits

- Assess sCLU levels in serum collected at baseline and throughout the first 140 days of treatment to evaluate effect of custirsen on sCLU levels.
- Assess relationship between survival outcome and lower sCLU levels in patients treated with custirsen, using baseline and change in sCLU levels for each patient as a normalized Area Under the Curve (AUC) calculation
  - Evaluation of 2-year survival status
  - Landmark evaluation for survival status
- Null hypothesis: Low sCLU levels at baseline or lowered sCLU levels following custirsen treatment do not correlate to a beneficial survival outcome.

METHODS

Measurement of Serum CLU (sCLU) Levels

- sCLU levels were assessed in serum samples collected at baseline, Day 1 of each cycle, end of study treatment, and every 4 weeks until disease progression for all study patients.
- Samples were analyzed utilizing solid-phase ELISA in microplate format (BioVendor clusterin ELISA kit; Laboratorni medicina a.s., Czech Republic) designed for quantitative measurement of human CLU.
- Baseline sCLU levels were evaluated in all subgroups.
  - Analyses included any study treatment or prognostic subgroup differences in survival outcomes for lower vs higher baseline sCLU levels
- Day 140 study interval was included in sCLU analyses since a milestone Day 140 disease assessment following randomization had been prospectively defined in the phase 3 protocol.
  - Analyses evaluating sCLU levels included normalized AUC calculations for sCLU levels from baseline to Day 140

Evaluation of 2-Year Survival Status by Day 140 AUC Levels for sCLU

- Survival outcome was assessed as alive at two years (yes or no).
- sCLU change for each patient was calculated as a normalized Area Under the Curve (AUC).
  - AUC of sCLU by time through all assessments ≤ Day 140
  - Divided by AUC assuming no change through ≤ Day 140 and then multiplied by 100
    - 100 → no material change in sCLU levels
    - < 100 → general reduction in sCLU levels
    - > 100 → general increase in sCLU levels
  - Results showed a high correlation between AUC and minimum percent sCLU change
- Waterfall graphs of AUC for poor and good prognosis and arms (4 graphs)
- Color used to distinguish patients alive or dead at two years

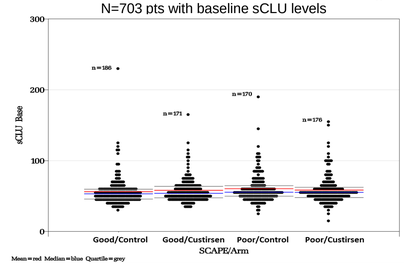
Landmark Evaluation for Survival Status with Day 140 AUC Levels for sCLU

- Survival outcome landmark analysis: Survival time among patients living beyond Day 140
- Survival arm effect: estimated hazard ratio (custirsen arm over control arm) and associated 95% confidence interval (CIs)
- sCLU change for each patient: Normalized Area Under Curve (AUC) as previously defined
- Patients grouped either by AUC values above or below median, or by tertiles
- For patients meeting the landmark criterion, a forest graph was used to display HR estimates and CIs for:
  - All poor prognostic patients
  - 2 groups identified by median AUC
  - 3 groups identified by tertile AUC

RESULTS

sCLU Levels at Baseline: Similar Across Subgroups

N=703 pts with baseline sCLU levels



Effect of Baseline sCLU Levels on Survival Outcomes

Poor Prognostic (by SCAPE)
Median sCLU level: 55.3 µg/mL

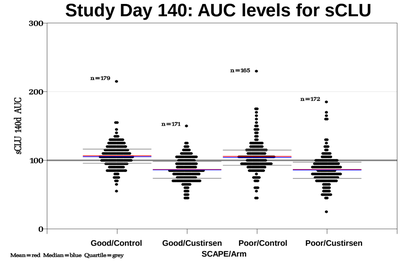
Baseline median sCLU level	Median Survival: Custirsen Arm n=176	Median Survival: Control Arm n=170
Lower	18.4 mo	14.4 mo
	HR = 0.689 (95%CI: 0.483-0.983)	
Higher	15.0 mo	13.9 mo
	HR = 0.863 (95%CI: 0.608-1.22)	

Good Prognostic (by SCAPE)
Median sCLU level: 53.2 µg/mL

Baseline median sCLU level	Median Survival: Custirsen Arm n=171	Median Survival: Control Arm n=186
Lower	31.2 mo	27.2 mo
	HR = 0.823 (95%CI: 0.505-1.34)	
Higher	33.2 mo	NR
	HR = 1.057 (95%CI: 0.660-1.69)	

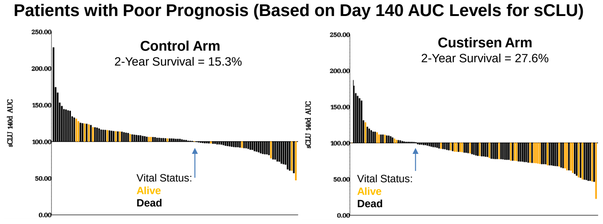
Trend for greater custirsen treatment effect in patients with baseline sCLU levels lower than median, especially in poor prognostic subgroups

Study Day 140: AUC levels for sCLU



In both prognostic subgroups, patients on Custirsen Arm had significantly lower Day 140 AUC levels for sCLU compared to patients on Control Arm.

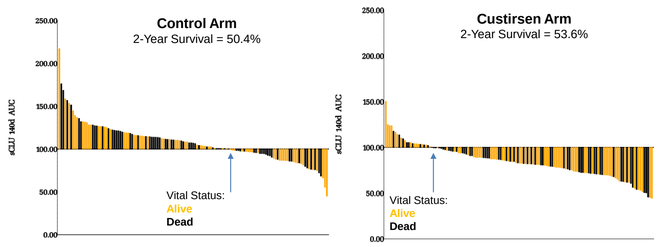
Trend Toward Improved 2-Year Survival Status in Custirsen Arm Among Patients with Poor Prognosis (Based on Day 140 AUC Levels for sCLU)



Poor prognosis by Feature Count method: 2-year survival trend is in favor of Custirsen Arm
Note: Waterfall graphs also show that more poor prognostic patients in the Custirsen Arm have a reduction in Day 140 AUC for sCLU levels (AUC < 100) as compared to Control Arm (inflection point more to the left).

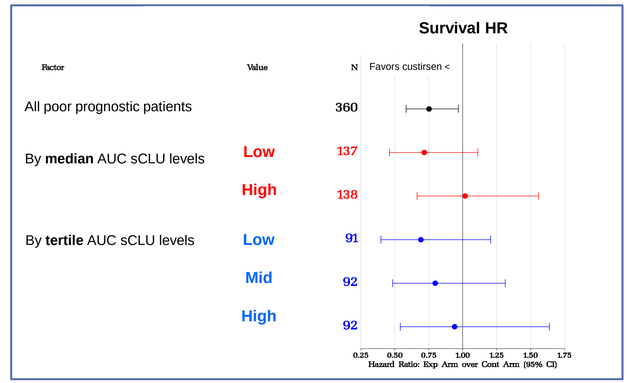
RESULTS

No Trend In 2-Year Survival Status in Custirsen Arm Among Patients with Good Prognosis (Based on Day 140 AUC Levels for sCLU)



Good prognosis by Feature Count method: 2-year survival trend is similar in both arms
Note: Custirsen Arm continues to show more good prognostic patients with a reduction in Day 140 AUC for sCLU levels (AUC < 100) as compared to Control Arm (inflection point more to the left).

Greater Treatment Effect with Lower Day 140 AUC sCLU Levels in Poor Prognostic Subgroup (Landmark Analysis)



CONCLUSIONS

- **Custirsen treatment was associated with a survival benefit in patients with poor prognostic features.**
  - **Effect was similar using both SCAPE and Feature Count (Index) scores**
- **Custirsen treatment significantly lowered sCLU levels in both poor and good prognostic patients.**
- **There was a trend for greater custirsen effect on survival if baseline sCLU levels were lower than median, especially in patients with poor prognostic features.**
- **Patients in the poor prognostic subgroup treated with custirsen and with reduced Day 140 AUC sCLU levels had a trend for higher 2-year survival status.**
- **Survival benefit for the Custirsen Arm appeared greater in poor prognostic patients who achieved lower Day 140 AUC sCLU levels (Landmark Analysis).**
- **For patients in the poor prognostic subgroup treated with custirsen, the greater the sCLU decrease (baseline to Day 140 post-treatment), the more survival benefit observed.**
  - **Monitoring for lower sCLU levels may be worthwhile; however CLU levels within tumor cells may be more important for evaluating a potential survival benefit due to custirsen treatment.**
- **Further evaluation of custirsen in patients with poor prognosis disease is warranted and is on-going in the AFFINITY trial (NCT01578655).**

ACKNOWLEDGEMENTS

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[2]Chi KN, et al. *J Clin Oncol* 2010;28(27):4247-54.
[3]Chi KN, et al. *Ann Oncol* 2014;25(suppl 4):iv256