MADRID 2014 ESMO congress

A randomized phase 3 study (SYNERGY) of first-line docetaxel/prednisone (DP) vs. DP plus custirsen in metastatic castration-resistant prostate cancer

Abstract #5113

Kim N. Chi, Celestia S. Higano, James Reeves, Susan Feyerabend, Gwenaelle Gravis, Jean-Marc Ferrero, Cindy Jacobs, Ofra Barnett-Griness, Amitkumar Pande, Johann S. de Bono, for the SYNERGY study investigators

Disclosures

- K Chi – OncoGenex and TEVA (all uncompensated consultancy)
- CS Higano – Institutional clinical research funding during this trial
- C Jacobs – OncoGenex (employment/stock options), TEVA (travel support)
- O Barnett-Griness – TEVA (employment/stock options)
- A Pande – TEVA (employment/stock options)

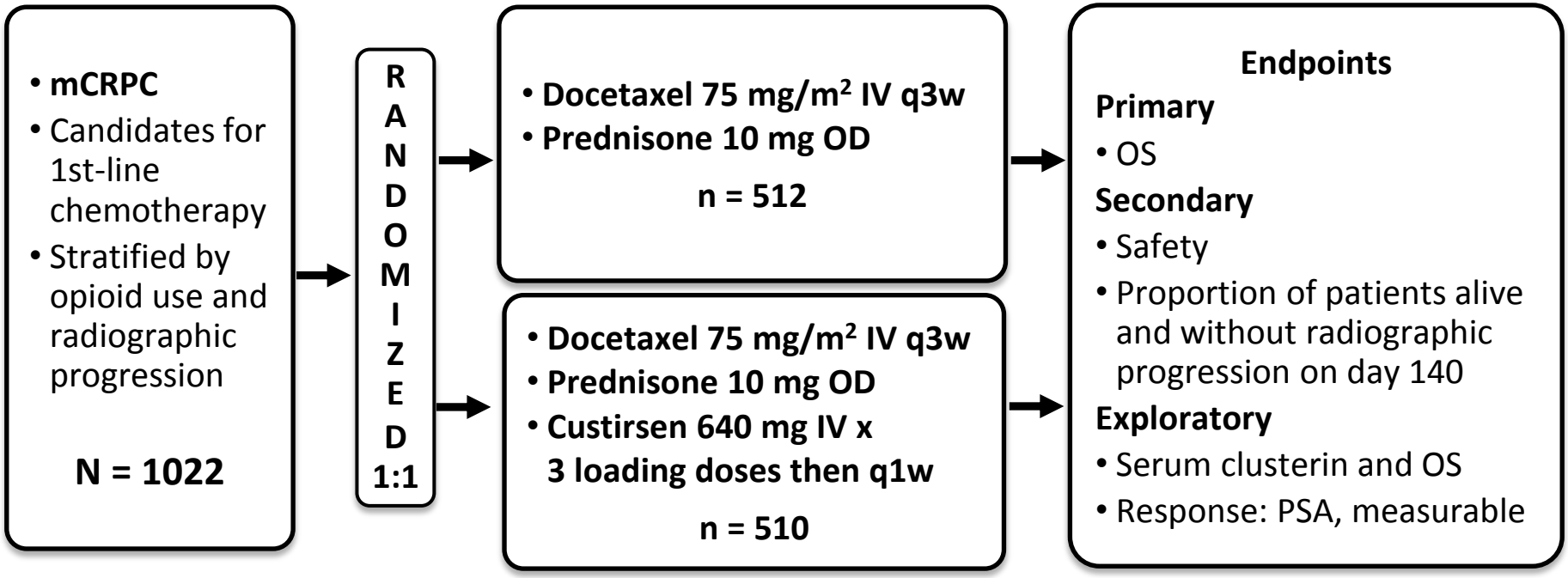
Background

- Clusterin is a pro-survival chaperone protein upregulated in prostate and other cancers in response to apoptotic stressors such as hormone therapy and chemotherapy[1]
- Custirsen is a second-generation antisense oligonucleotide that inhibits production of human clusterin and reverses resistance and enhances treatment efficacy in preclinical models[2,3]
- A phase 1 study determined that clusterin inhibition by custirsen in prostate cancer tissues was dose-dependent, with a biologically effective dose of 640 mg[4]
- A randomized phase 2 study in patients with mCRPC 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)[5]

1. Miyake H, et al. *Cancer Res.* 2000;60:2547-2554. 2. Miyake H, et al. *Int J Urol.* 2005;12:785-794. 3. Chi KN, et al. *Expert Opin Investig Drugs.* 2008;17:1955-1962. 4. Chi KN, et al. *J Natl Cancer Inst.* 2005;97:1287-1296. 5. Chi KN, et al. *J Clin Oncol.* 2010;28:4247-4254.

SYNERGY Study Design

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



Final analysis following a target 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

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

Results: Baseline Characteristics (1)

	DP + Custirsen (n = 510)	DP (n = 512)
Age, median (range), years	69 (39-86)	69 (47-88)
Karnofsky Performance Status, n (%)[a]		
80-100%	470 (92)	473 (92)
≤ 70%	35 (7)	38 (7)
Gleason sum at diagnosis, n (%)[b]		
< 8	188 (37)	204 (40)
≥ 8	295 (58)	282 (55)
PSA, median (range), ng/mL	86 (0-5471)	78 (0-9966)
Sites of disease, n (%)		
Bone	439 (86)	447 (87)
Lymph nodes	323 (63)	300 (59)
Visceral	124 (24)	110 (21)

[a]Data missing: DP + custirsen, n = 5; DP, n = 1. [b]Data missing or unknown: DP + custirsen, n = 26; DP, n = 27.

Results: Baseline Characteristics (2)

n (%)	DP + Custirsen (n = 510)	DP (n = 512)
Alkaline phosphatase[a]		
≤ ULN	257 (50)	254 (50)
> ULN	252 (49)	256 (50)
LDH[b]		
≤ ULN	294 (58)	287 (56)
> ULN	208 (41)	220 (43)
Hemoglobin		
≤ 90 g/L	19 (4)	19 (4)
> 90 g/L	491 (96)	493 (96)
Opioid analgesic use		
No	336 (66)	341 (67)
Yes	174 (34)	171 (33)

[a]Data missing: DP + custirsen, n = 1; DP, n = 2. [b]Data missing: DP + custirsen, n = 8; DP, n = 5.
LDH, lactate dehydrogenase; ULN, upper limit of normal

MADRID 2014 ESMO congress

Study Treatment Exposure

	DP + Custirsen (n = 510)	DP (n = 512)
Number of cycles delivered, median (range)	8 (1-32)	9 (1-20)
Completed treatment phase (≥ 10 cycles), n (%)	150 (29)	210 (41)
Did not receive study treatment, n (%)	9 (2)	13 (3)
Reasons for discontinued study treatment, n (%)		
Adverse event	210 (41)	146 (29)
Disease progression	68 (13)	78 (15)
Withdrew consent	42 (8)	35 (7)
Symptomatic deterioration	25 (5)	17 (3)
Treatment delay > 3 weeks	0	1 (< 1)
Lost to follow-up	0	1 (< 1)
Death	1 (< 1)	3 (< 1)
Other[a]	5 (< 1)	8 (2)

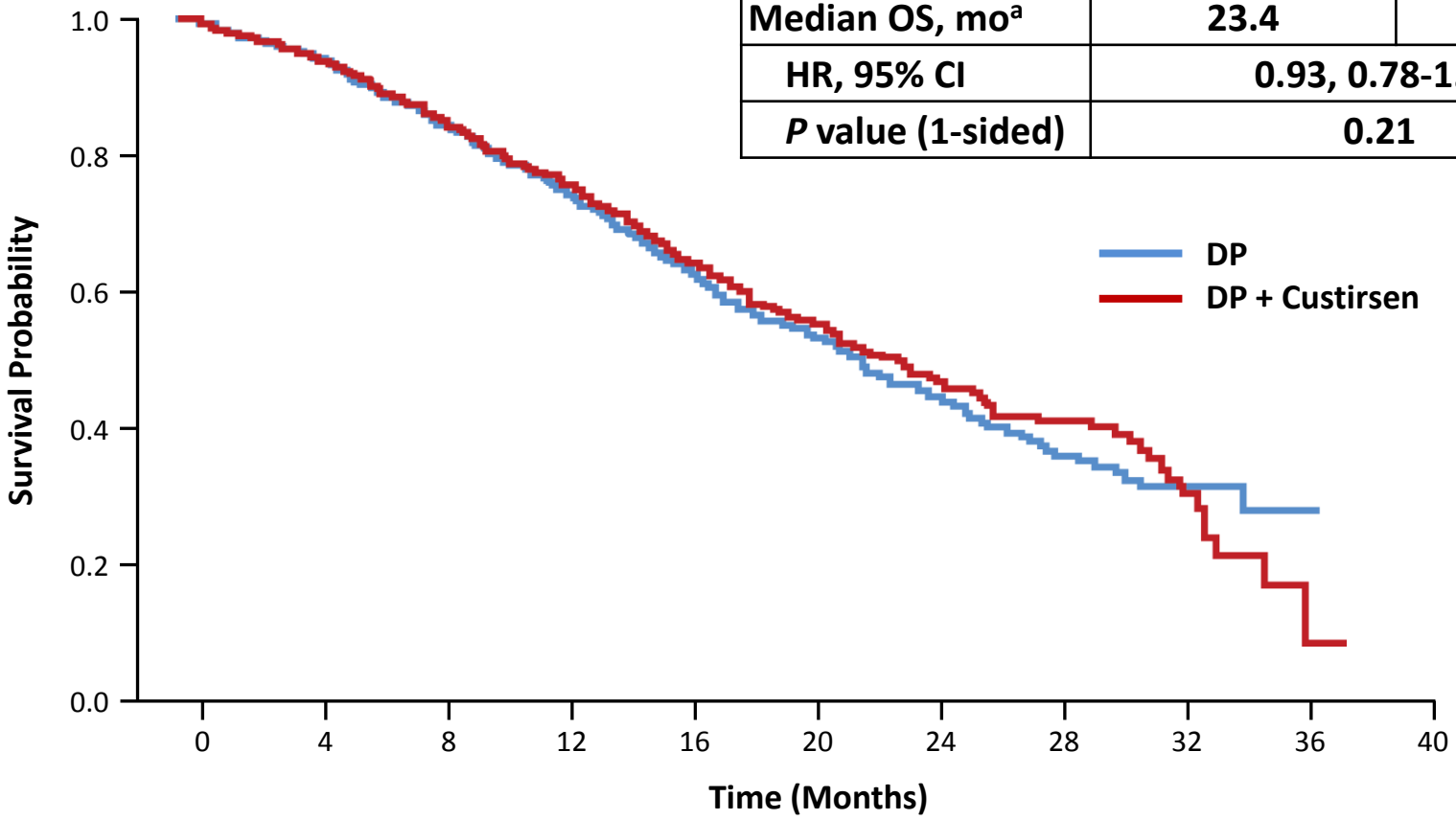
[a]Non-protocol-defined disease progression (DP, n = 3), investigator decision (DP + custirsen, n = 3; DP, n = 3), patient/investigator agreement (DP, n = 2), and error in assessment of disease progression (DP + custirsen, n = 2).

Subsequent Treatments

	DP + Custirsen (n = 510)	DP (n = 512)
Time to initiation of subsequent therapy, median (range), days	285 (8-783)	279 (3-778)
Any anticancer therapy, % of patients	75	76
Abiraterone	53	54
Enzalutamide	19	20
Cabazitaxel	17	18
Docetaxel retreatment	12	11
Other chemotherapy	7	7
Radiation	26	24

Results: Overall Survival

	DP + Custirsen (n = 510)	DP (n = 512)
Median OS, mo[a]	23.4	22.2
HR, 95% CI	0.93, 0.78-1.11	
P value (1-sided)	0.21	



[a]Survival data were compared using a stratified log-rank test and included all randomized patients.

Results: Proportion of Patients Alive Without Event (AWE)[a] at Day 140

	DP + Custirsen (n = 510)	DP (n = 512)
AWE at Day 140[b]	57%	58%
Odds ratio (95% CI)	0.96 (0.75-1.24)	

[a]Event = radiographic disease progression or death.

[b]Cochran-Mantel-Haenszel test with 1-sided significance level = 0.025.

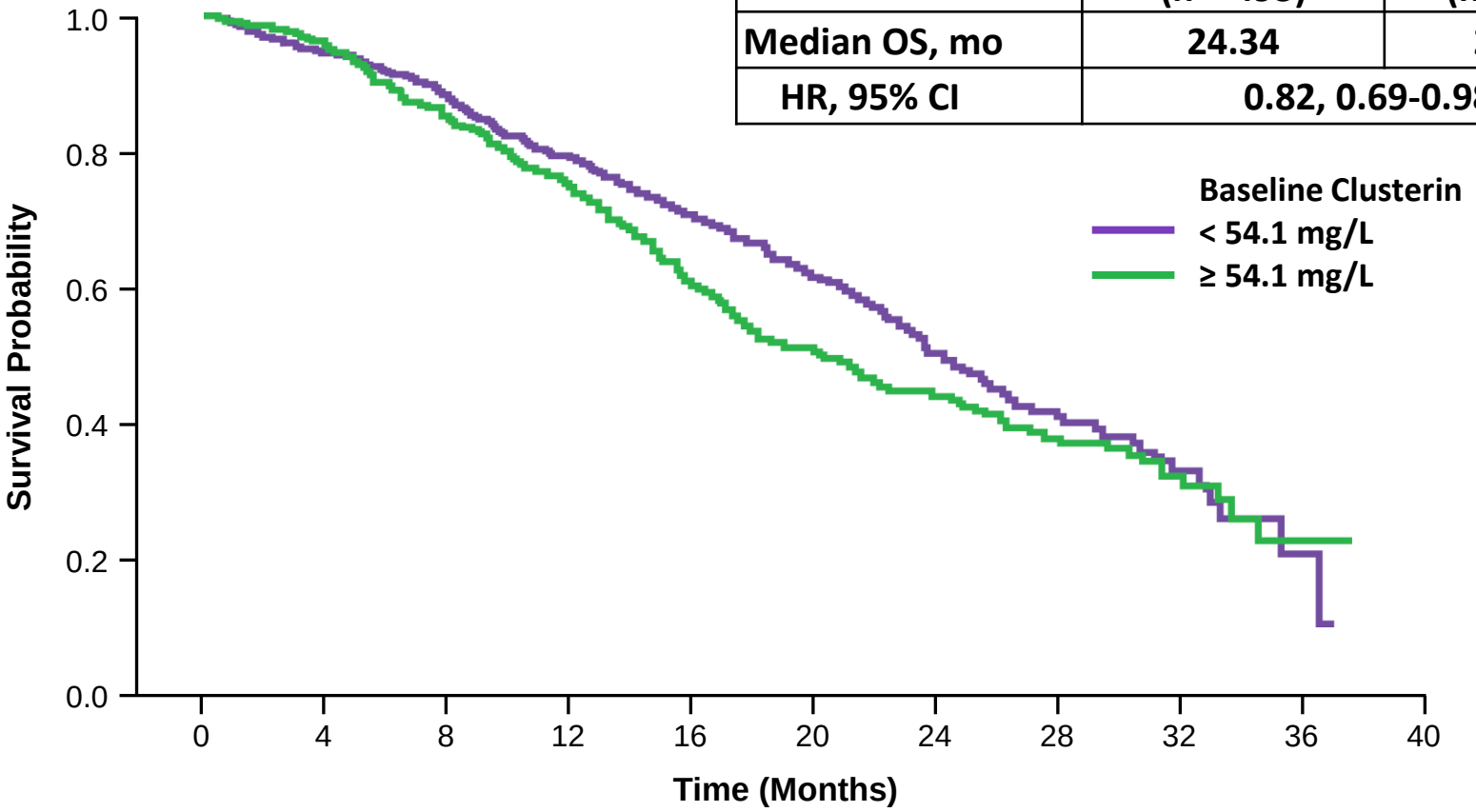
Results: Changes in Serum Clusterin

	DP + Custirsen (n = 510)	DP (n = 512)
Median baseline serum clusterin, µg/mL (range)	54.1 (15.6-164)	54.1 (22.6-228.6)
Median minimum serum clusterin, µg/mL (range)	34.9 (15.0-84.2)	43.8 (15.0-110.8)
Median maximal decrease from baseline serum clusterin, %	–35.6	–18.0
Any decrease in serum clusterin, n (%)	472 (93)	415 (81)
Achieved serum clusterin ≤ 45 mg/L[a], n (%)	415 (81)	278 (54)

[a]Blumenstein B, et al. *Cancer Med*. 2013;2:468-477.

Results: OS by Median Baseline Clusterin

	< 54.1 mg/L (n = 493)	≥ 54.1 mg/L (n = 494)
Median OS, mo	24.34	20.37
HR, 95% CI	0.82, 0.69-0.98	



Response to Treatment

	DP + Custirsen (n = 510)	DP (n = 512)
PSA response by 3 months, n (%)		
> 30% reduction	352 (69)	333 (65)
> 50% reduction	292 (57)	266 (52)
Best measurable disease response, n (%)[a]		
Patients evaluable[b], n	218	221
CR	18 (8)	18 (8)
PR	98 (45)	103 (47)
SD	95 (44)	91 (41)
PD	7 (3)	9 (4)

[a]Response categories assigned based on RECIST criteria; lesion measurements per clinical site (not central radiology vendor).
[b]Evaluable patients underwent a baseline assessment and at least one post-baseline assessment; 88 of 527 were excluded for no post-baseline assessment.

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

Common Grade ≥ 3 Adverse Events

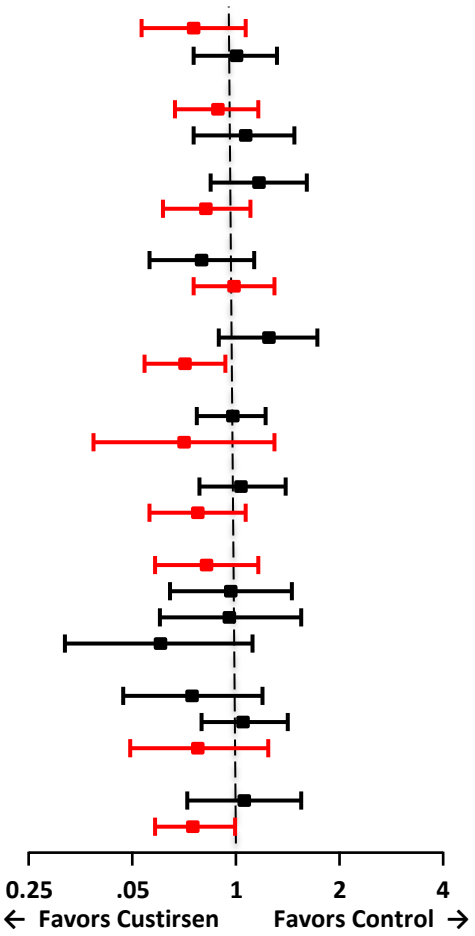
		DP + Custirsen (n = 501)	DP (n = 499)
Infusion	Pyrexia	1%	0
	Chills	< 1%	0
Non-heme	Fatigue	11%	8%
	Febrile neutropenia	11%	7%
	Asthenia	7%	3%
	Diarrhea	6%	3%
	Pulmonary embolism	5%	4%
	Pneumonia	4%	2%
Heme[a]	Neutropenia	43%	29%
	Lymphopenia	37%	24%
	Anemia	13%	5%

[a]Hematologic toxicities are based on laboratory assessments.

MADRID 2014 ESMO congress

Post Hoc Effect Modifier Analysis

Subgroup	# Pts (Median OS, days) Control	Custirsen	HR (95% CI)	*P* Value
Performance Status				0.1339
<90	146 (421)	168 (481)	0.79 (0.60-1.04)	
≥90	365(778)	337(795)	0.99 (0.79-1.24)	
Hemoglobin (g/L)				0.396
<125 (median)	259 (513)	249 (539)	0.90 (0.72-1.12)	
≥125 (median)	253 (829)	261 (841)	1.04 (0.79-1.37)	
LDH (u/L)				0.1298
<271 (median)	235 (801)	268 (802)	1.12 (0.86-1.47)	
≥271 (median)	272 (530)	234 (606)	0.85 (0.68-1.08)	
Alkaline Phosphatase (u/L)				0.3496
<139 (median)	257 (845)	251 (951)	0.83 (0.62-1.10)	
≥139 (median)	253 (512)	258 (498)	0.98 (0.79-1.22)	
PSA (ng/mL)				0.0122
<82 805 (median)	260 (845)	246 (785)	1.18 (0.91-1.55)	
≥82 805 (median)	247 (531)	259 (639)	0.76 (0.61-0.95)	
Liver Involvement				0.3438
No	465 (681)	462 (726)	0.98 (0.81-1.18)	
Yes	47 (379)	48 (542)	0.75 (0.46-1.22)	
Use of Opioids for Prostate Cancer Pain				0.1289
No	341 (795)	336 (791)	1.03 (0.82-1.30)	
Yes	171 (453)	174 (481)	0.81 (0.62-1.05)	
Halabi et al Nomogram (months, quartile)				0.5959
1st quartile	123 (316)	125 (409)	0.85 (0.64-1.12)	
2nd quartile	123 (609)	134 (632)	0.97 (0.70-1.35)	
3rd quartile	131 (756)	128 (924)	0.96 (0.66-1.41)	
4th quartile	135 (NR)	123 (1002)	0.66 (0.40-1.10)	
Chi et al Prognostic Model				0.3062
0-1 (Good)	164 (853)	164 (1002)	0.79 (0.54-1.14)	
2-3 (Intermediate)	283 (659)	273 (660)	1.04 (0.83-1.31)	
4-6 (Poor)	65 (341)	73 (373)	0.82 (0.56-1.19)	
SYNERGY prognostic risk score				0.129
Below median	248 (926)	248 (970)	1.04 (0.77-1.41)	
Above median	252 (426)	244 (492)	0.79 (0.64-0.98)	



Note: subgroups with poorer prognosis are in red.

LDH, lactate dehydrogenase; NR, not reached; PSA, prostate-specific antigen; Halabi et al Nomogram, per Halabi S, et al. *J Clin Oncol.* 2014;32:7671-7677; Chi et al Prognostic Model, per Chi KN, et al. *J Clin Oncol.* 2013;31:abstr 5013.

Conclusions

- Custirsen was biologically active and reasonably well tolerated in combination with docetaxel, although numerically there was some increased toxicity
- The addition of custirsen to first-line docetaxel did not significantly improve OS in patients with mCRPC
- Certain post-hoc effect modifier analyses suggested a possible effect from custirsen in patients with poor prognosis features
- The AFFINITY[a] study of second-line cabazitaxel +/- custirsen for mCRPC previously treated with docetaxel and abiraterone acetate or enzalutamide is ongoing

[a]ClinicalTrials.gov identifier: NCT01578655.

Acknowledgements

- All study patients and their families
- SYNERGY Study Investigators from participating countries:

Belgium
Canada
France
Germany
Hungary
Israel
Italy
Netherlands
Republic of Korea
Spain
United Kingdom
United States

MADRID 2014 ESMO congress

- ***Belgium***. Thierry Gil; Wim Wynendaele; Sylvie Rottey; Jan Brande
- ***Canada***. Kim Chi; Daniel Heng; Roanne Segal-Nadler; Urban Emmenegger; Conrad Oja; Eric Winquist; Scott North; Piotr Czaykowski; Som Mukherjee; Frederick Saad; Michael Pollak; Arik Drucker; Heidi Martins; Ian Tannock; Pawel Zalewski; Christopher Booth; Muhammad Zulfiqar
- ***France***. Karim Fizazi; Remy Delva; Werner Hilgers; Laura Dupuy-Brousseau; Jean-Francois Berdah; Frank Priou; Gwenaelle Gravis; Jean-Marc Ferrerro; Stephane Oudard; Philippe Beuzeboc; Emmanuelle Bompas; Aline Guillot; Loic Mourey; Ivan Krakowski; Anne-Claire Hardy-Bessard
- ***Germany***. Axel S. Merseburger; Martin Boegemann; Susan Feyerabend; Rolf Gillitzer; Jochen Gleissner; Boris Hadaschik; Axel Heidenreich; Maren Schwickardi; Ursula Steiner; Arnulf Stenzl; Michael Stoeckle; Manfred Wirth; Goetz Geiges; Patrick Bastian; Thomas Kretz; Gabriel Steiner; Jan Marin; Uwe Zimmermann
- ***Hungary***. Istvan Bodrogi; Janos Szanto; Laszlo Thurzo; Imre Romics; Lajos Hornyak; Tamas Pinter; Judit Toth; Tibor Solymosi; Jozsef Erfan
- ***Israel***. Svetlana Kovel; Raanan Berger; Eliahu Gez; Eli Rosenbaum; Hovav Nechushtan
- ***Italy***. Cora Nanette Sternberg; Francesco Boccardo; Sergio Bracarda; Giacomo Carteni; Giorgio Cruciani; Sabino De Placido; Luigi Dogliotti; Pierosandro Tagliaferri; Dino Amadori; Marina Faedi; Alberto Ravaioli; Paolo Marchetti; Giuseppe Procopio; Armando Santoro; Giampaolo Tortora
- ***Netherlands***. André Bergman; Ronald de Wit; Franciscus Peters
- ***Republic of Korea***. Byung Ha Chung; Kang Hyun Lee; Choung Soo Kim; Sae Woong Kim; Wun-Jae Kim; Moon Kee Chung; Sung Joon Hong
- ***Spain***. José Luis González-Larriba; José Angel Arranz; Miguel Angel Climent; Cristina Martín Lorente; Enrique Gallardo; Jose Luis Pérez Gracia; Jesús García Donás; Javier Cassinello Espinosa; Joan Carles Galcerán; Begoña Mellado; Marta Zafra; Arantxa González del Alba; Pilar López Criado; José Luis Alonso Romero; Montserrat Domenech; Eva María Fernández Parra
- ***United Kingdom***. Johann de Bono; Danish Mazhar; Tony Elliott; Angus Robinson; Hardev Pandha; Andrew Stockdale; Zafar Malik
- ***USA***. Celestia Higano; Manish Kohli; Allen Yeilding; Guy Tillinghast; Gary Gross; Robert Droder; Bradley Somer; Merrill Shum; James Moore; Mark Scholz; Michael Wertheim; Vasileios Assikis; Charles Redfern; David Smith; Katisha Vance; John Hainsworth; Neal Shore; David Hanson; Mark Fleming; William Butler; James Reeves; David Waterhouse; Sheela Tejwani; Naveen Kella; Nicholas Vogelzang; Fairooz Kabbinavar; Peter Rubin