

Phase 3, randomized, double-blind study of elesclomol and paclitaxel versus paclitaxel alone in Stage IV metastatic melanoma (MM): 1-year OS update

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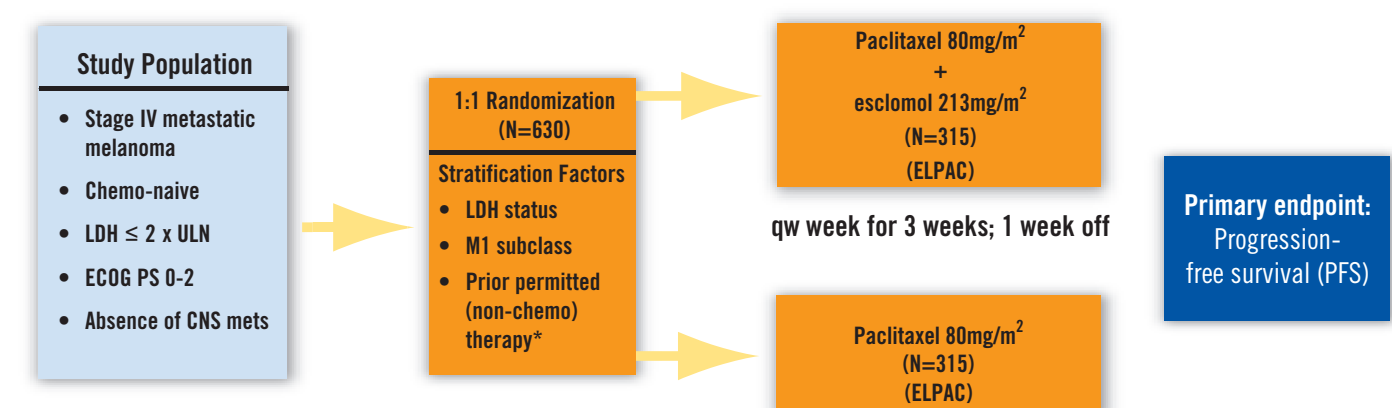
ELESCLOMOL BACKGROUND

- Investigational, first-in-class drug candidate that induces oxidative stress (reactive oxygen species, ROS), triggers apoptosis in cancer cells and enhances the activity of certain chemotherapies¹⁻⁴
- Preclinical *in vivo* studies demonstrated synergistic efficacy of paclitaxel and elesclomol in a variety of solid tumor models, including melanoma
- Elesclomol binds copper in plasma, facilitating its uptake into cells and enabling a transition between copper oxidation states. This reaction disrupts the metabolic properties of cancer cell mitochondria and generates the oxidative stress that triggers programmed cell death
- Elesclomol is more active in cells where energy production is primarily through mitochondrial respiration (normoxic conditions; normal LDH) and less active in cells where energy production occurs primarily through glycolysis (hypoxic conditions; high LDH)⁵
- In a blinded, randomized, Phase 2b study in patients with Stage IV metastatic melanoma, elesclomol plus paclitaxel demonstrated a statistically significant improvement in PFS compared to paclitaxel alone (N=81, p=0.035)⁶

METHODS

SYMMETRY STUDY DESIGN

- 160 centers in 15 countries
- Tumor assessment at baseline and every 8 weeks (RECIST)
- Patients were not allowed to cross-over between arms
- Same study drug dose and schedule as used in the Phase 2b trial



* Kinase inhibitor, immunotherapy, biologic therapy, vaccine, or investigational non-chemo

- On February 23, 2009, the DMC conducted an ad hoc interim analysis and recommended unblinding the SYMMETRY study based on the observation that while a trend towards improvement in the primary endpoint (PFS) was observed, there was an unexplained imbalance in deaths favoring the control arm (80 vs. 53) and the primary endpoint was unlikely to be achieved in the full population
- Sponsor decided to discontinue treatment in the SYMMETRY study pending further analysis. The last patient was enrolled in early February 2009; at the time of discontinuation, 242 patients remained on study (37% of ITT population)
- The data cutoff date for the analyses in this presentation is March 9, 2010

DEMOGRAPHICS - ITT POPULATION

		ELPAC (N=325)	PAC (N=326)
Age	Mean (SD)	59.4 (13.58)	59.5 (13.16)
	Median	60.0	60.0
	Min, Max	21.0, 87.0	21.0, 87.0
Gender	Male	196 (60.3%)	205 (62.9%)
	Female	129 (39.7%)	121 (37.1%)
Geographic Region	USA/Canada	100 (30.8%)	106 (32.5%)
	South America	19 (5.8%)	22 (6.7%)
	Western Europe/Australia	177 (54.5%)	164 (50.3%)
	Rest of World	29 (8.9%)	34 (10.4%)

BASELINE DISEASE CHARACTERISTICS

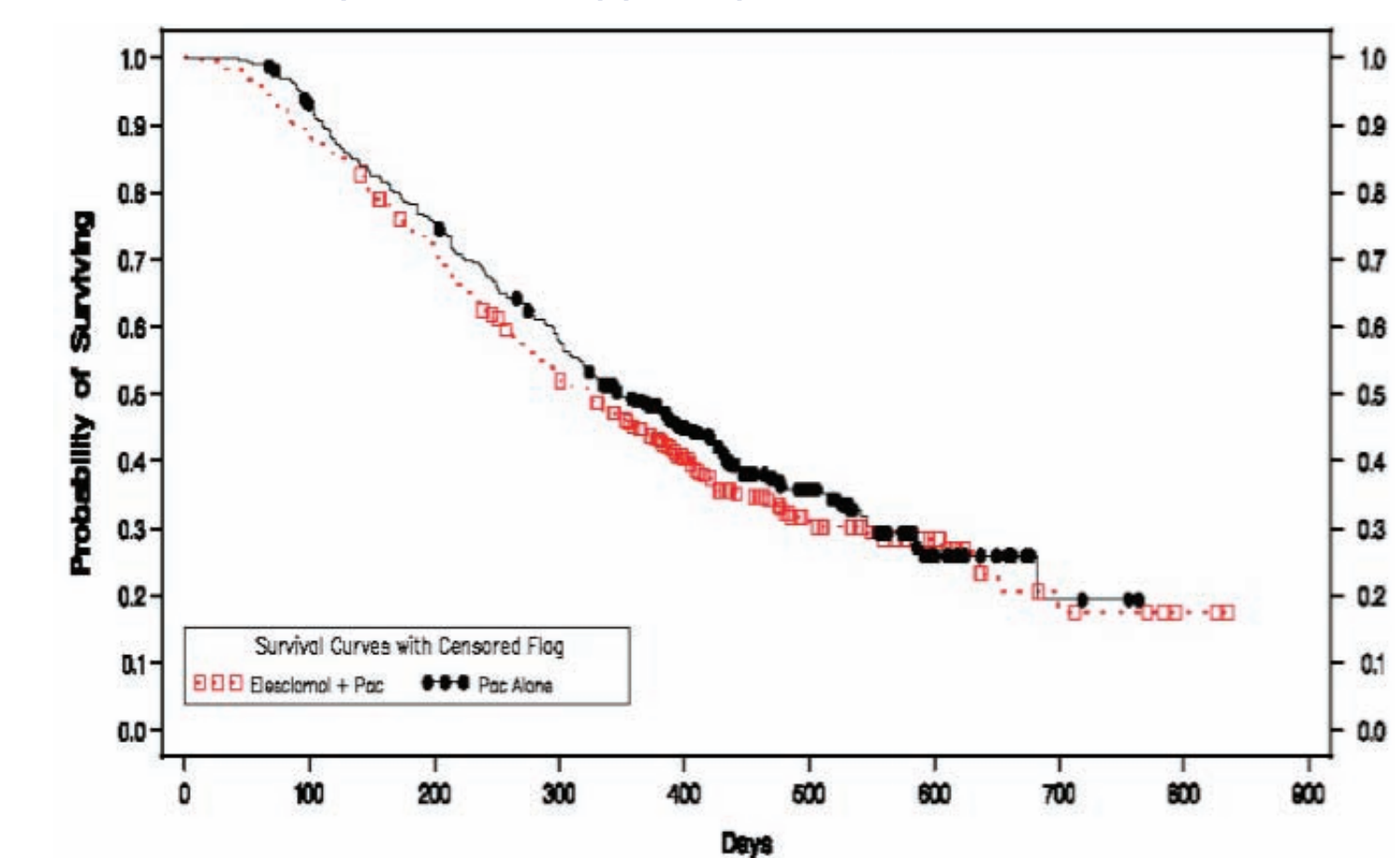
		ELPAC (N=325)	PAC (N=326)
M classification	M1a	27 (8.3%)	38 (11.7%)
	M1b	93 (28.6%)	75 (23.0%)
	M1c	205 (63.1%)	213 (65.3%)
LDH	Normal (<234 U/L)	213 (65.5%)	218 (66.9%)
	Elevated (≥ 234 U/L)	112 (34.5%)	108 (33.1%)
ECOG PS	0	233 (71.7%)	251 (77.0%)
	1	83 (25.5%)	68 (20.9%)
	2	9 (2.8%)	7 (2.1%)
Prior Treatment*	No Prior Treatment	228 (70.2%)	214 (65.6%)
	Prior D/C due to PD	50 (15.4%)	64 (19.6%)
	Prior D/C due to other reasons	47 (14.5%)	48 (14.7%)

* Kinase inhibitor, immunotherapy, biologic therapy, vaccine, or investigational non-chemo

PFS OUTCOMES BY LDH SUBGROUP: ITT POPULATION

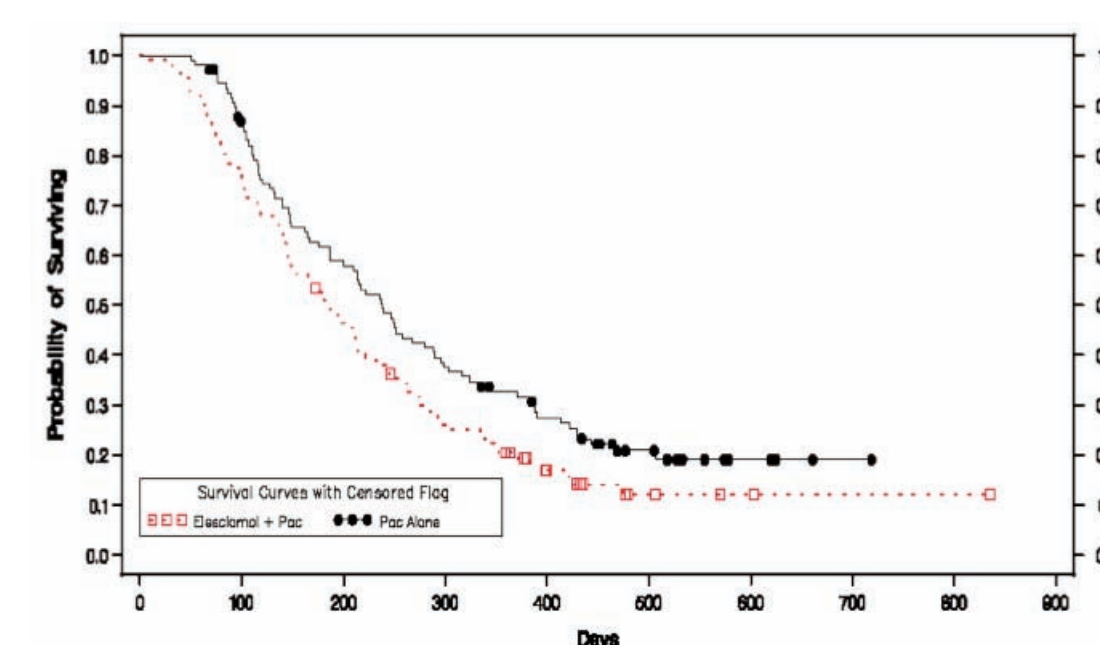
	All patients (N=651)	High LDH (≥1x ULN) (N=220)	Normal LDH (<1x ULN) (N=431)
Median PFS (months)	ELPAC: 3.4 PAC: 1.9	ELPAC: 1.8 PAC: 1.9	ELPAC: 3.7 PAC: 2.1
HR (95% CI)	0.89 (0.73 - 1.07)	1.13 (0.84 - 1.53)	0.76 (0.59 - 0.97)
P-value	0.2076	0.4229	0.0264

OVERALL SURVIVAL (ITT POPULATION) (N=651)



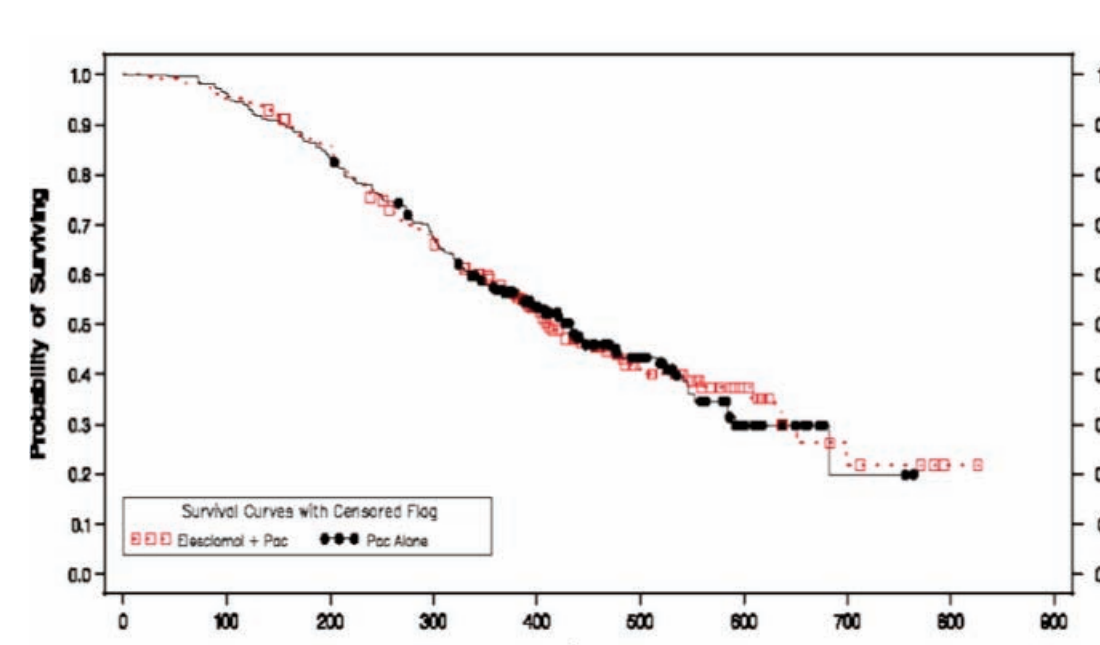
RESULTS

OVERALL SURVIVAL (ITT POPULATION): HIGH LDH PATIENTS* (N=220)



* High LDH: ≥234 U/L (≥ 1x ULN); pre-specified exploratory analysis

OVERALL SURVIVAL (ITT POPULATION): NORMAL LDH PATIENTS* (N=431)



* Normal LDH: <234 U/L (<1x ULN); pre-specified exploratory analysis

OS OUTCOMES BY LDH SUBGROUP: ITT POPULATION

	All patients (N=651)	High LDH (≥1x ULN) (N=220)	Normal LDH (<1x ULN) (N=431)
Median OS (months)	ELPAC: 10.6 PAC: 11.5	ELPAC: 6.0 PAC: 7.8	ELPAC: 13.5 PAC: 14.2
% OS events censored	35%	20%	43%
HR (95% C.I.)	1.13 (0.93 - 1.37)	1.35 (0.99 - 1.84)	1.02 (0.79 - 1.31)
P-value	0.2196	0.0596	0.8786

N.B.: OS data still evolving, not yet mature in normal LDH group

SUMMARY OF ADVERSE EVENTS: SAFETY POPULATION

	ELPAC (N=323)	PAC (N=325)
Patients with at least one:	N (%)	N (%)
AE	318 (98.5)	310 (95.4)
NCI CTC Grade ≥3 AE	133 (41.2)	109 (33.5)
SAE	79 (24.5)	64 (19.7)
AE leading to treatment discontinuation	41 (12.7)	31 (9.5)
AE leading to death*	16 (5.0)	7 (2.2)

* Events include reports of progression of disease, development of new metastases, and symptoms secondary to disease progression as well as reports of potential toxicity

ADVERSE EVENTS OCCURRING IN ≥10% OF ELPAC PATIENTS

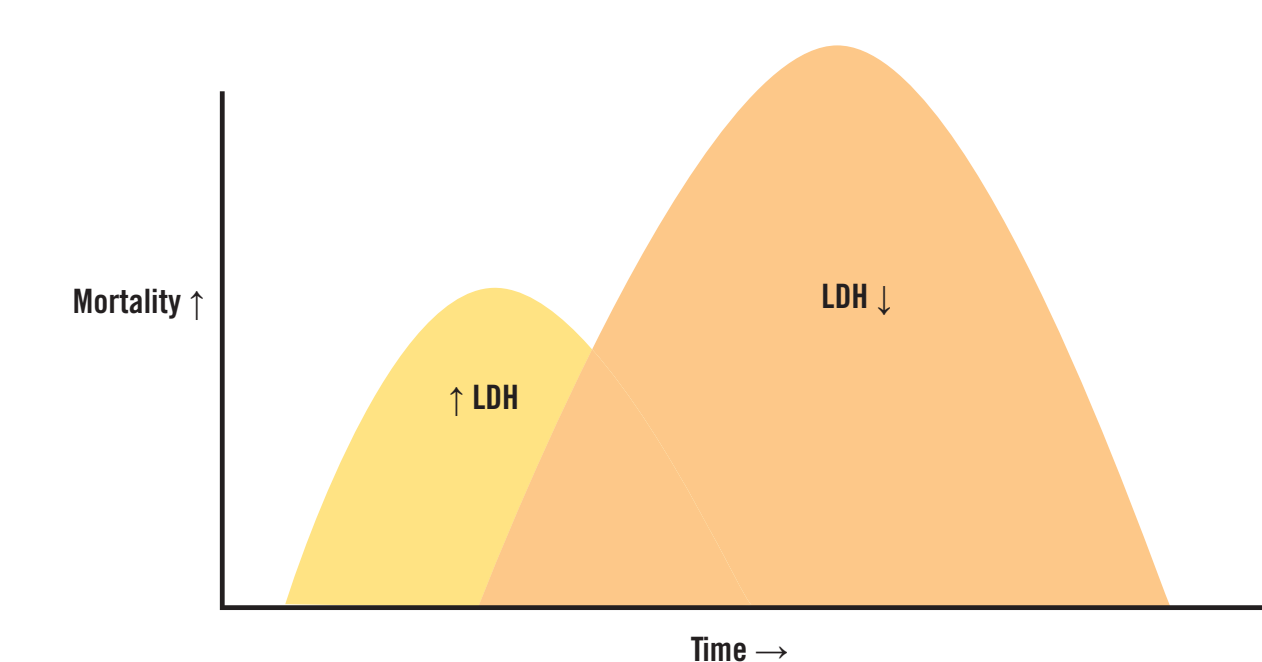
	ELPAC (N=323) N (%)	PAC (N=325) N (%)
Alopecia	156 (48.3)	163 (50.2)
Fatigue	135 (41.8)	142 (43.7)
Nausea	113 (35.0)	107 (32.9)
Diarrhea	91 (28.2)	82 (25.2)
Constipation	74 (22.9)	64 (19.7)
Cough	55 (17.0)	53 (16.3)
Asthenia	52 (16.1)	32 (9.8)
Rash	52 (16.1)	54 (16.6)
Headache	46 (14.2)	48 (14.8)
Peripheral Neuropathy	46 (14.2)	46 (14.2)
Peripheral Edema	46 (14.2)	39 (12.0)
Vomiting	44 (13.6)	33 (10.2)

MOST FREQUENT ≥ GRADE 3 ADVERSE EVENTS

	ELPAC (N=323) N (%)	PAC (N=325) N (%)
Neutropenia	22 (6.8)	8 (2.5)
Fatigue	13 (4.0)	4 (1.2)
Anemia	7 (2.2)	6 (1.8)
Dyspnea	7 (2.2)	6 (1.8)
Alopecia	6 (1.9)	9 (2.8)
Peripheral Neuropathy	6 (1.9)	4 (1.2)
Vomiting	6 (1.9)	5 (1.5)
Infusion related reaction	6 (1.9)	7 (2.2)

- Review of the safety profile indicates that ELPAC was well-tolerated in this clinical study
- Analysis of the safety results from this trial and prior trials with elesclomol showed no acute toxicity or safety issues which could explain the early interim observation of an imbalance in the number of deaths

MORTALITY IN LDH PATIENT SUBGROUPS



This schematic diagram demonstrates what appears to have occurred in the study; at the time of the earlier interim data analyses, more mortality events were seen in patients with high baseline LDH. In later data analyses, more events are seen in patients with low baseline LDH.

CONCLUSIONS

- SYMMETRY data continues to mature; time from last patient enrolled to follow-up data is less than the normal LDH median OS.
- LDH continues to be an important predictor of both PFS and OS outcomes for treatment with elesclomol in combination with paclitaxel in metastatic melanoma
- Clinical results are consistent with preclinical observations that elesclomol is more active in cells where energy production is primarily through mitochondrial respiration (normoxic conditions; normal LDH) and less active in cells where energy production occurs primarily through glycolysis (hypoxic conditions; high LDH)⁵
- Adverse event profile between ELPAC and PAC alone was comparable indicating treatment with elesclomol was well tolerated

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