

**A Randomized, Double-blind, Phase 3 Trial of
STA-4783 (elesclomol) in Combination with
Paclitaxel versus Paclitaxel Alone for Treatment
of Patients with Stage IV Metastatic Melanoma
(SYMMETRY)
Review of Preliminary Data**

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On behalf of the SYMMETRY Trial Investigators

Disclosures

- A. Employment of Leadership Position:** Eric Jacobson
- B. Advisory Role:** Steven O'Day, Axel Hauschild, Alexander Eggermont
- C. Stock Ownership:** Eric Jacobson
- D. Honoraria:** Steven O'Day, Axel Hauschild, Alexander Eggermont
- E. Research Funding:** Steven O'Day, Axel Hauschild
- F. Expert Testimony:** None
- G. Other Remuneration:** None

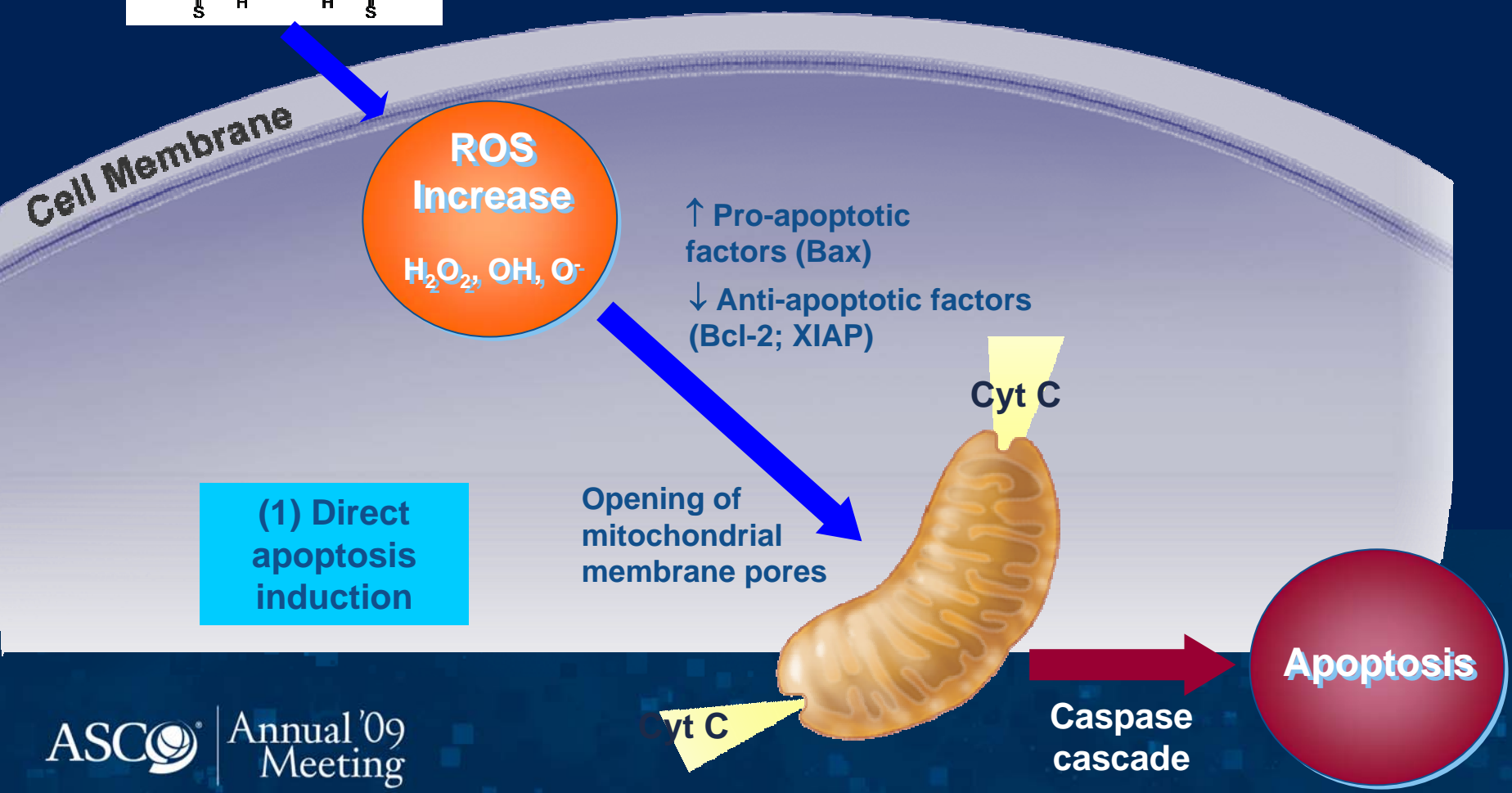
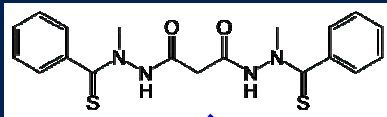
Elesclomol: Mechanism of Action

- Elesclomol is an investigational drug candidate that induces oxidative stress (reactive oxygen species, ROS)¹
- Oxidative stress induction represents a potential novel way of selectively targeting and killing cancer cells
- Cancer cells produce higher levels of reactive oxygen species (ROS) than normal cells, making them potentially more susceptible to further oxidative stress and ROS mediated apoptosis²
- Elevation of ROS may facilitate the ability of taxanes to induce apoptosis through the intrinsic mitochondrial pathway³
- Preclinical *in vivo* studies demonstrated synergistic efficacy of paclitaxel and elesclomol in a variety of solid tumor models, including melanoma

1. Kirshner *et al.* (2008) *Molecular Cancer Therapy* 7:2319-2327
2. Kong *et al.* (2000) *Medical Hypothesis* 55:29-35; Pelicano *et al.* (2004) *Drug Resistance Updates* 7:97-110
3. Ramanathan *et al.* (2005) *Cancer Research* 65:8455-8460

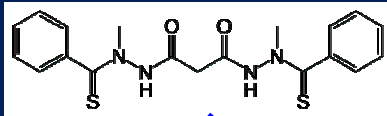
Elesclomol-ROS- apoptosis pathway

Elesclomol

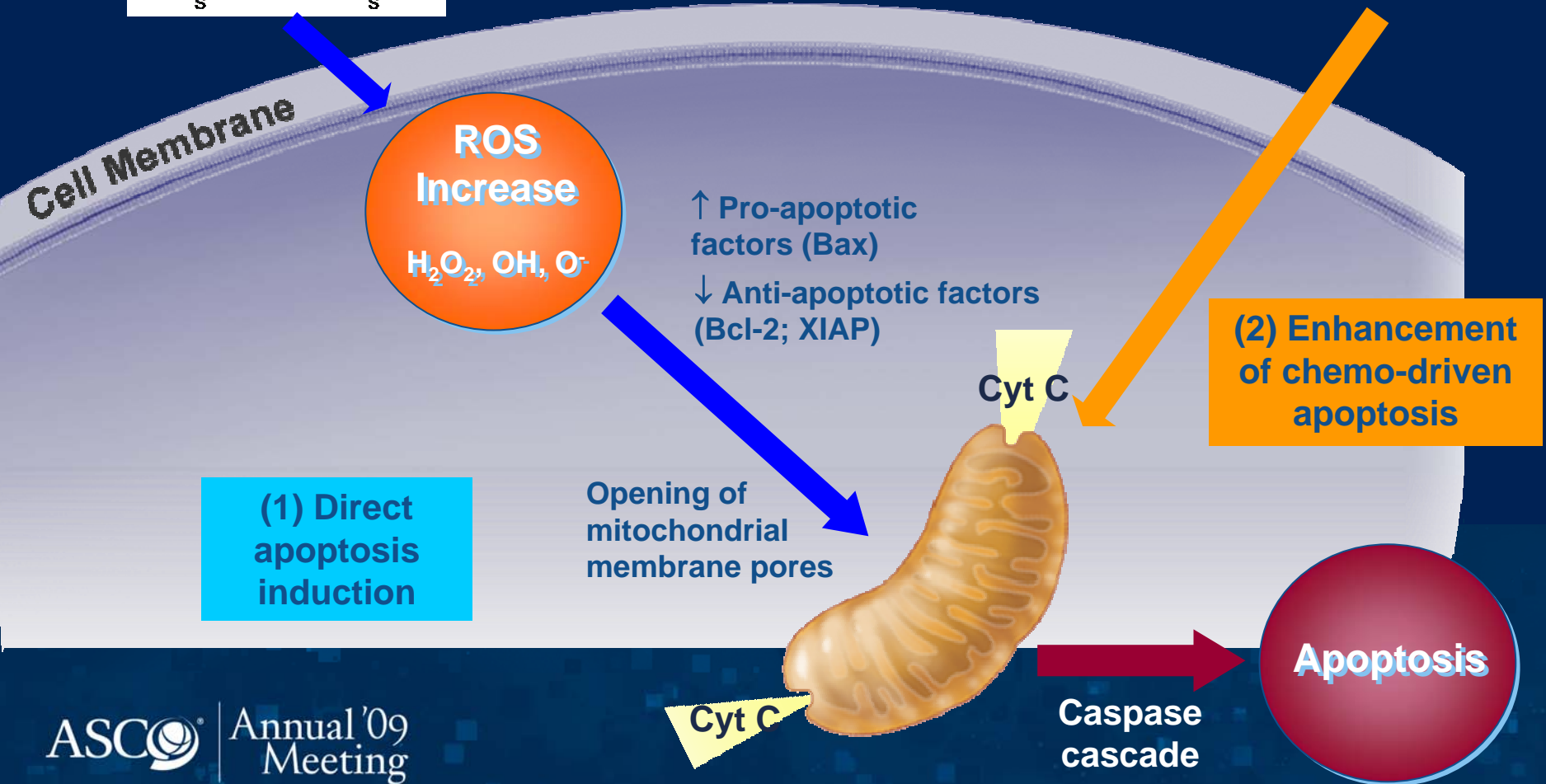


Elesclomol-ROS- apoptosis pathway

Elesclomol

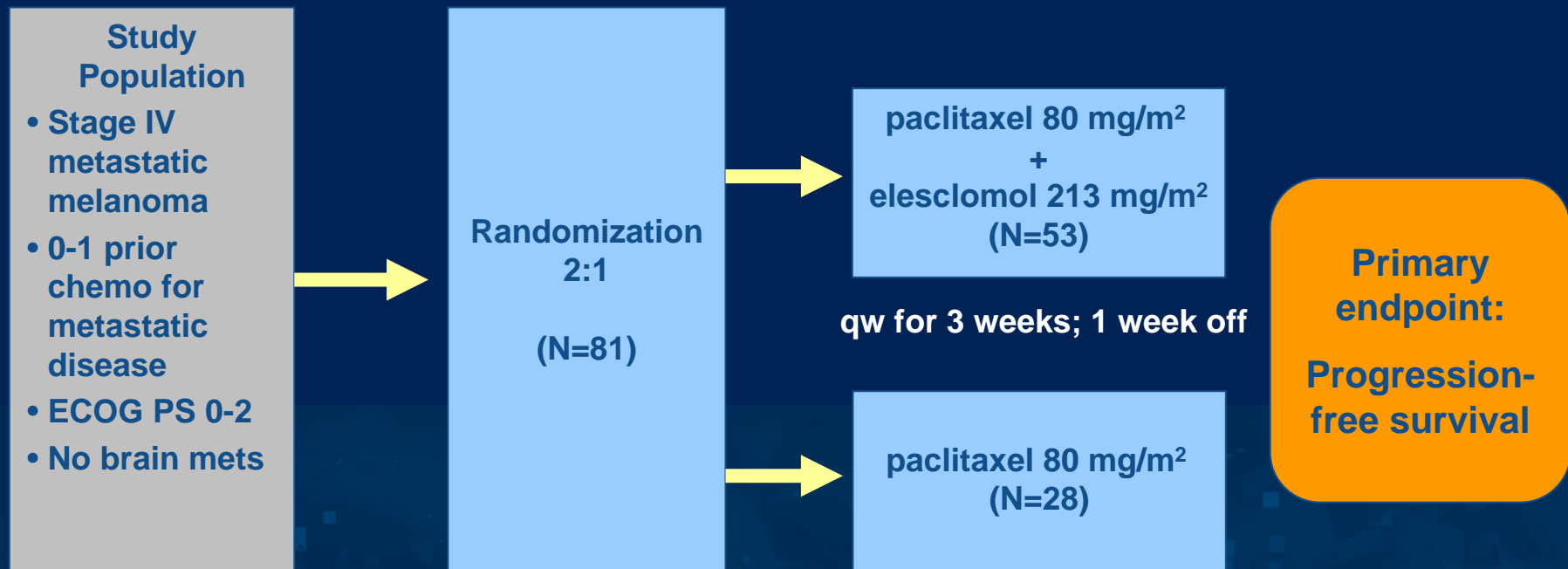


Chemotherapy agents acting through intrinsic mitochondria apoptosis pathway (taxanes)

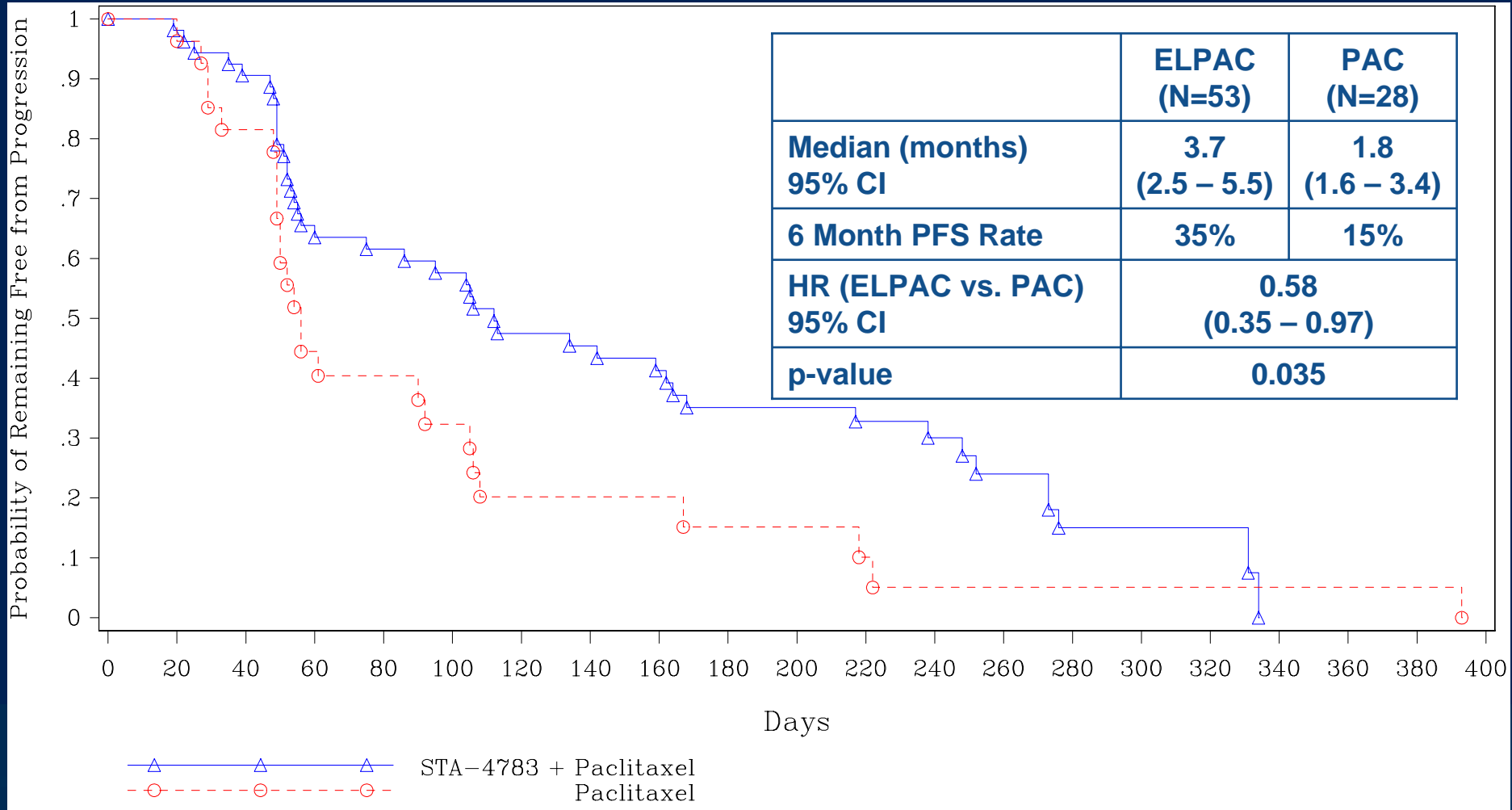


A multi-center, randomized Phase 2 trial of elesclomol in combination with paclitaxel for the treatment of patients with metastatic melanoma

- Double-blind, randomized, controlled; 21 centers in U.S.
- Cross-over for paclitaxel alone arm after PD



Kaplan-Meier Plot of Progression-Free Survival ITT population



Ref: O'Day, et al. JCO in press

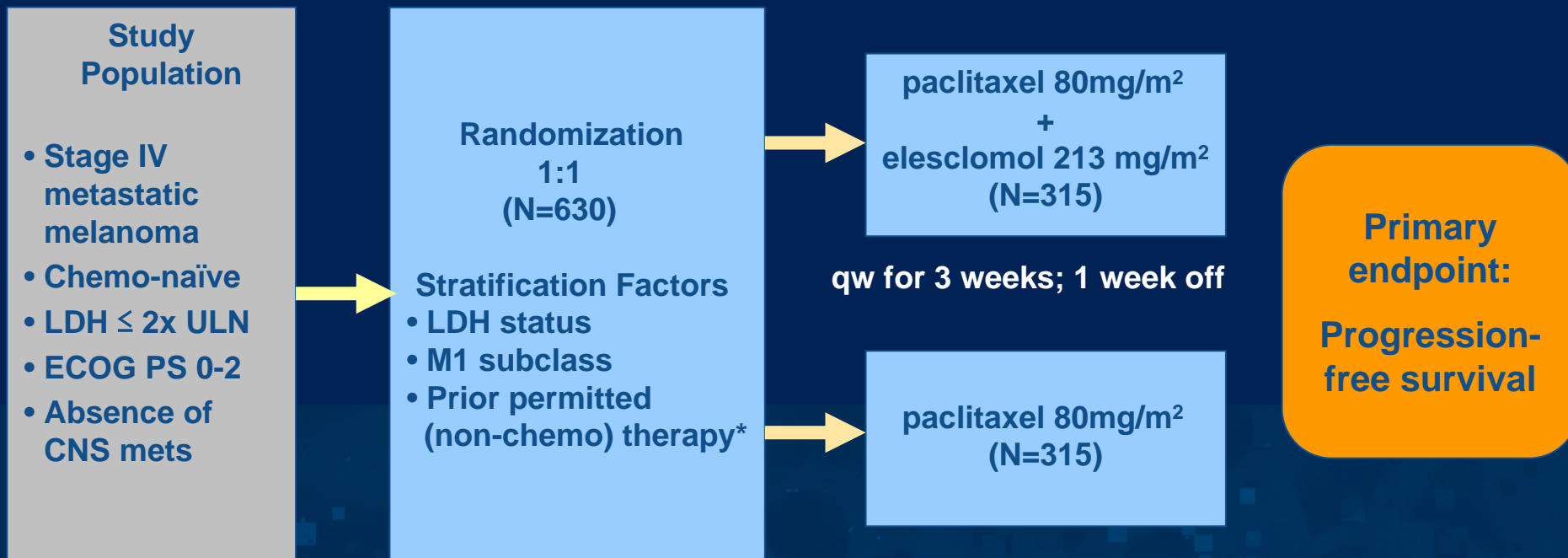
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***Chemo-Naïve subgroup had a significantly higher median PFS which led to the chemo-naïve patient population for the SYMMETRY study**

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SYMMETRY Study design

- 160 centers in 15 countries
- Tumor Assessment: at baseline and every 8 weeks from time of randomization (RECIST)
- No patient cross-over



Subject Accrual, Randomization, and Treatment

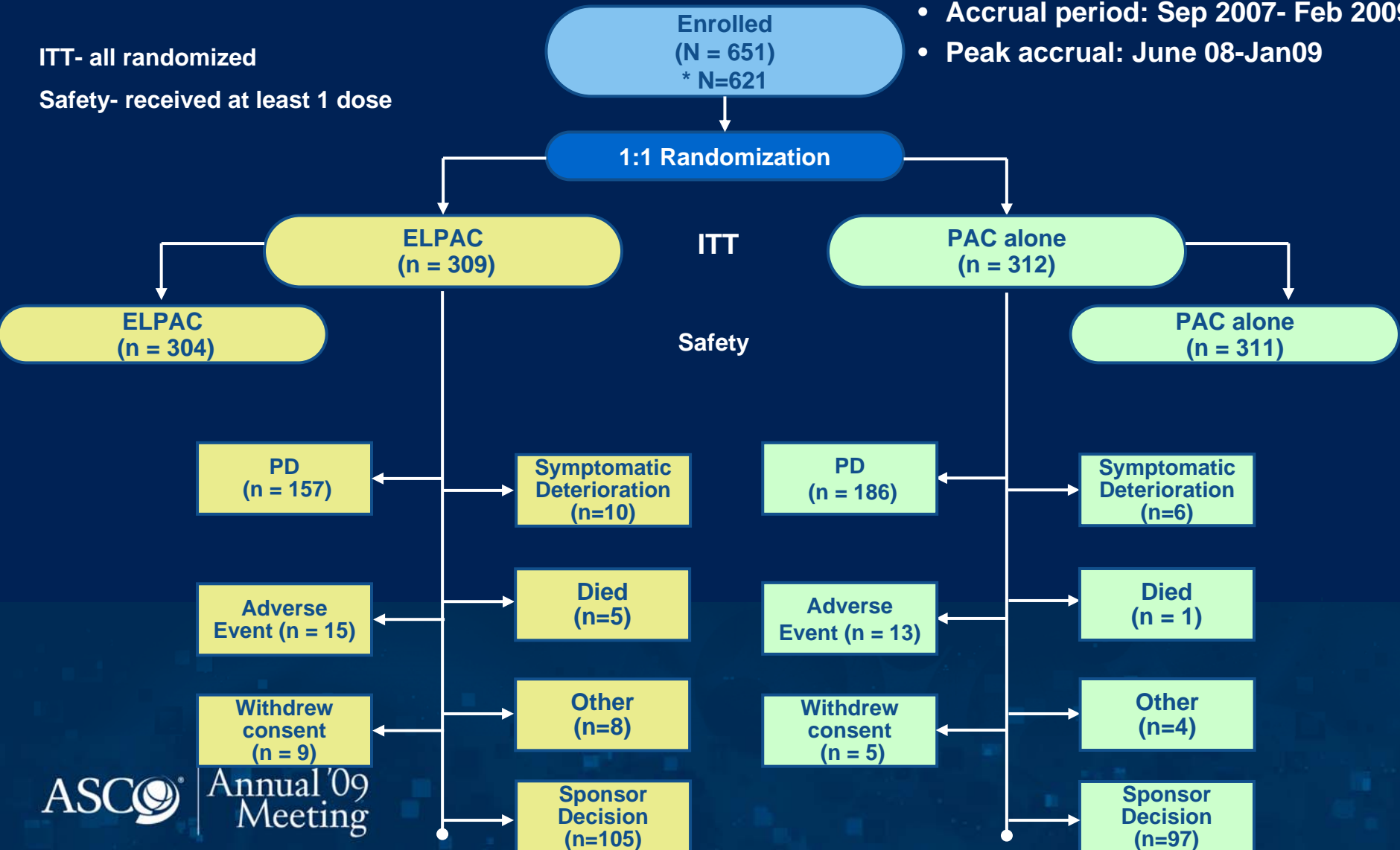
*Data cut April 2009

ITT- all randomized

Safety- received at least 1 dose

• Accrual period: Sep 2007- Feb 2009

• Peak accrual: June 08-Jan09



Demographics - ITT Population

	ELPAC (N=309)	PAC (N=312)
Age		
Mean (SD)	59.5 (13.60)	59.4 (13.07)
Median	60.0	60.0
Min, Max	21.0, 87.0	21.0, 87.0
Gender		
Male	182 (58.9%)	196 (62.8%)
Female	127 (41.1%)	116 (37.2%)
Geographic Region		
USA/Canada	99 (32%)	100 (32.1%)
South America	19 (6.1%)	21 (6.7%)
Western Europe/Australia	162 (52.4%)	157 (50.3%)
Rest of World	29 (9.4%)	34 (10.9%)

Baseline Disease Characteristics

	ELPAC (N=309)	PAC (N=312)
M classification		
M1a	25 (8.1%)	38 (12.2%)
M1b	90 (29.1%)	70 (22.4%)
M1c	194 (62.8%)	204 (65.4%)
LDH		
Normal (<234 U/L)	209 (67.6%)	215 (68.9%)
Elevated (\geq 234 U/L)	100 (32.4%)	97 (31.1%)
ECOG PS		
0	219 (70.9%)	241 (77.2%)
1	81 (26.2%)	65 (20.8%)
2	9 (2.8%)	6 (1.9%)
Prior Permitted Treatment*		
No Prior Treatment	223 (72.2%)	206 (66.0%)
Prior D/C due to PD	42 (13.6%)	59 (18.9%)
Prior D/C due to other reasons	44 (14.2%)	47 (15.1%)

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

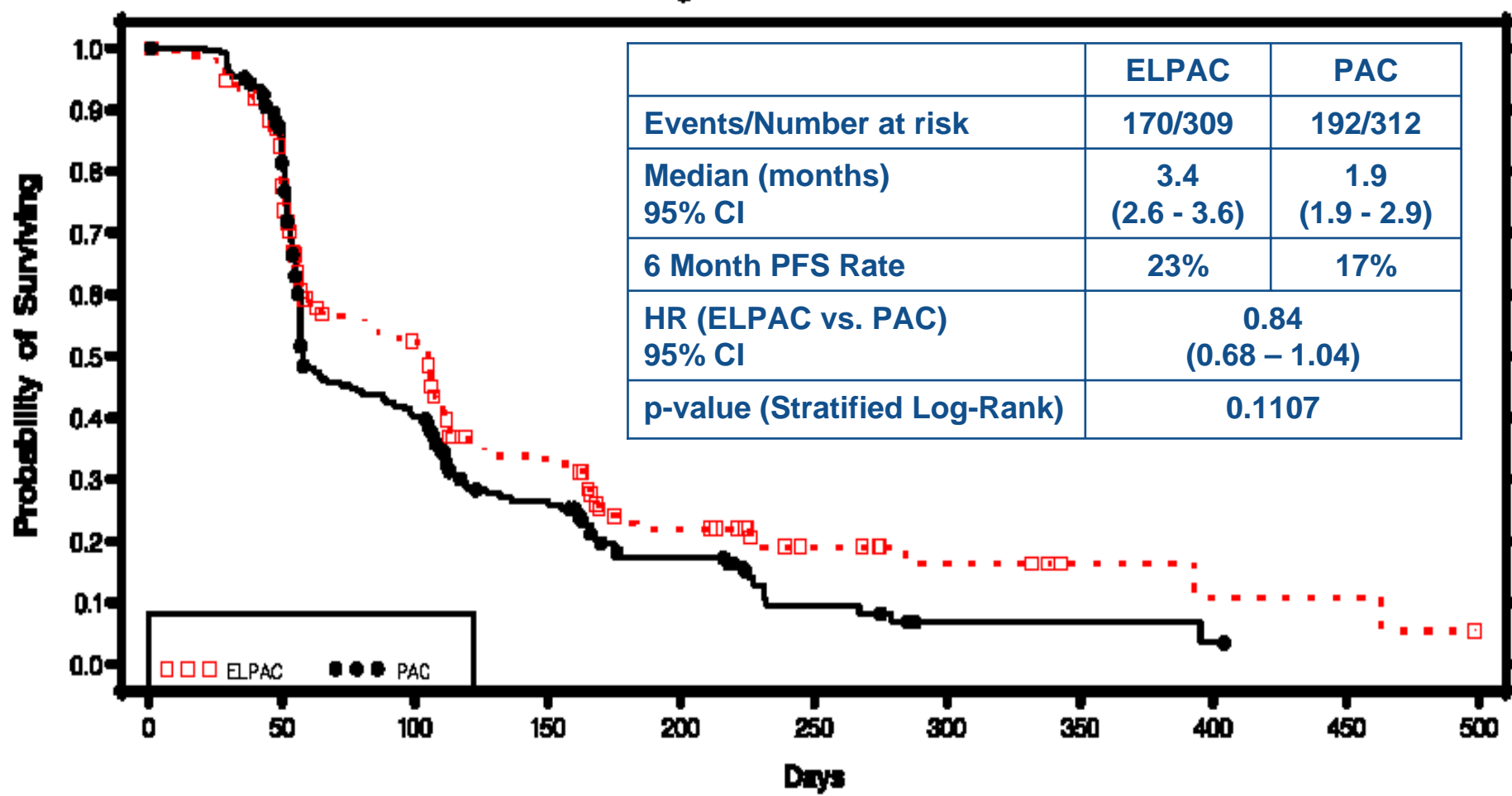
Early termination of the SYMMETRY study

- On February 23, 2009, DMC conducted an ad hoc interim analysis and recommended un-blinding of the SYMMETRY study
 - Data analysis indicated primary endpoint (PFS) would not be met
 - Early OS data analysis indicated unexplained imbalance in deaths favoring the control arm (80 vs. 53)
- Sponsor decided to discontinue treatment in the SYMMETRY study
 - All subjects had been accrued at this time; treatment was discontinued for 241 patients (36% of ITT)

PFS Analysis Methodology

- The protocol assumption was that treatment with ELPAC would extend PFS by two months (3 vs. 5)
 - 2-sided alpha 0.05, power 90%
 - required number of PFS events = 164
- There were a total of 219 PFS events at the time of the February 23rd, 2009 DMC meeting which exceeded the required number of events by 34%
- Follow-up for disease progression stopped at time of study stop; patients were censored at last valid tumor assessment prior to stopping the treatment phase of the study on February 26th, 2009

Progression-Free Survival - ITT Population

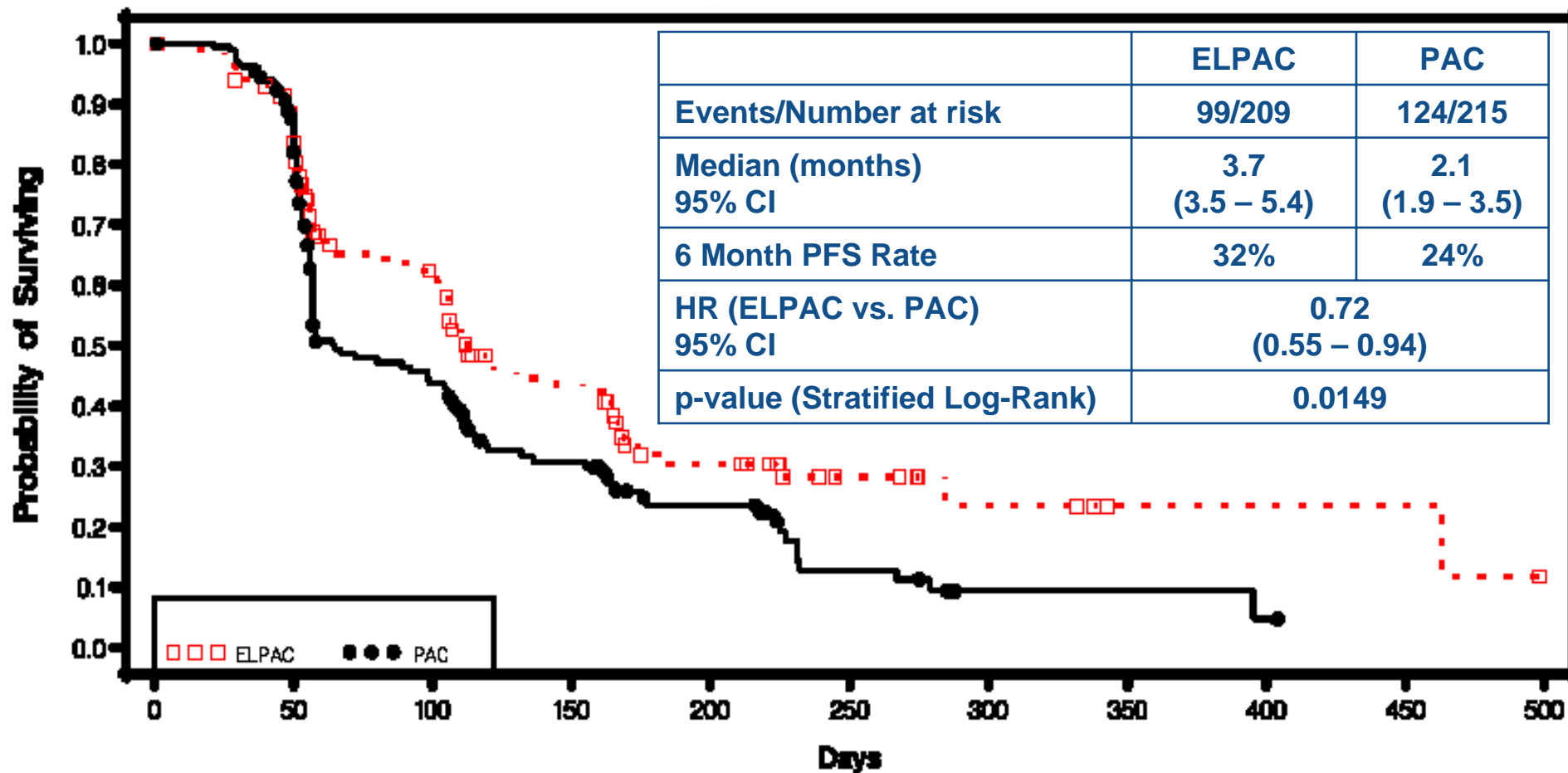


Subjects at Risk

PAC	312	200	87	42	20	8	2	2	1	0	0
ELPAC	309	187	107	53	21	10	6	3	2	2	0

Progression-Free Survival - ITT Population

Normal LDH* (N=424/621; 68%)

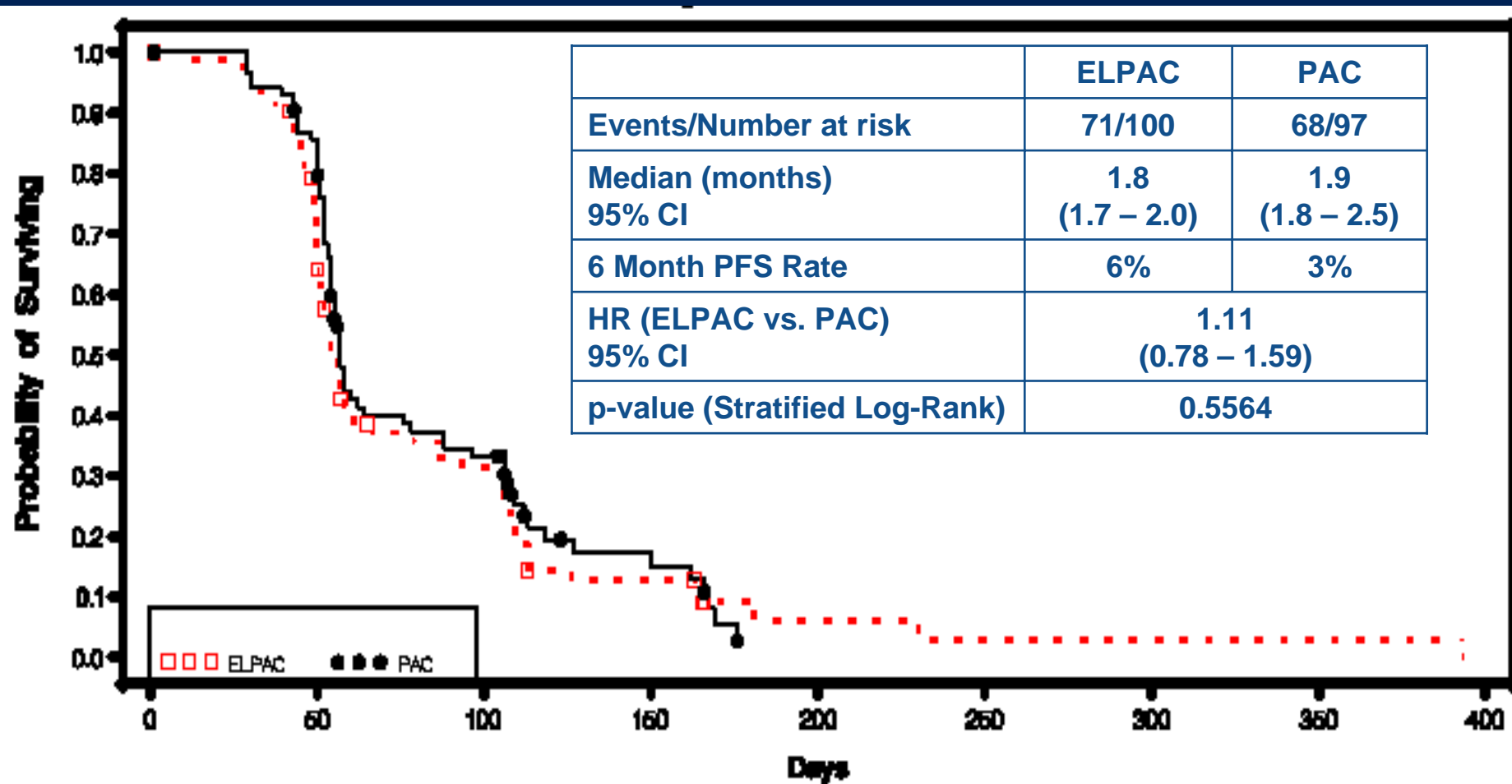


Subjects at Risk

PAC	215	136	62	35	20	8	2	2	1	0	0
ELPAC	209	138	85	45	19	9	5	2	2	2	0

Progression-Free Survival - ITT Population

High LDH* (N=197/621; 32%)



Subjects at Risk

PAC	97	64	25	7	0	0	0	0	0
ELPAC	100	49	22	8	2	1	1	1	0

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* High LDH: ≥ 234 U/L ($\geq 1x$ ULN)
Pre-specified exploratory analysis

M1c subgroup PFS results
HR=0.93, p=0.5686

Overall Survival: Not Yet Mature Currently Favors PAC Arm

ITT Population (N=651)			
Data Cut	% censored	HR (CI)	p-value
Feb 2009	80%	1.62* (1.14 - 2.31)	0.0068
April 2009	72%	1.31 (0.98 - 1.76)	0.0719

Pts enrolled as of Sep 1, 2008 (N=300)			
Data Cut	% censored	HR (CI)	p-value
Feb 2009	63%	1.28 (0.88 - 1.87)	0.1930
April 2009	54%	1.22 (0.87 - 1.71)	0.2552

Summary of Adverse Events Safety Population

Patients with at least one:	ELPAC (N=304) N (%)	PAC (N=311) N (%)
AE	262 (86.2)	267 (85.9)
NCI CTC Grade ≥ 3 AE	113 (37.2)	92 (29.6)
SAE	62 (20.4)	54 (17.4)
AE leading to treatment discontinuation	32 (10.5)	26 (8.4)
AE leading to death*	19 (5.8)	6 (1.8)

*Based on Drug Safety database as of 10 April 2009 (N=651)

Many of the AEs leading to death in both arms were related to disease progression

Adverse Events occurring in $\geq 10\%$ of patients

Preferred Term	NCI CTC Grades 1-4		NCI CTC Grade ≥ 3	
	ELPAC (N=304)	PAC (N=311)	ELPAC (N=304)	PAC (N=311)
	N (%)	N (%)	N (%)	N (%)
Alopecia	120 (39.5)	124 (39.9)	5 (1.6)	6 (1.9)
Fatigue	118 (38.8)	118 (37.9)	11 (3.6)	3 (<1)
Nausea	95 (31.3)	78 (25.1)	2 (<1)	2 (<1)
Diarrhea	76 (25.0)	67 (21.5)	4 (1.3)	0
Constipation	55 (18.1)	56 (18.0)	1 (<1)	0
Cough	44 (14.5)	41 (13.2)	1 (<1)	0
Headache	41 (13.5)	43 (13.8)	1 (<1)	1 (<1)
Asthenia	40 (13.2)	28 (9.0)	2 (<1)	2 (<1)
Rash	39 (12.8)	33 (10.6)	2 (<1)	0
Peripheral Neuropathy	38 (12.5)	37 (11.9)	6 (2.0)	4 (1.3)
Vomiting	37 (12.2)	27 (8.7)	4 (1.3)	4 (1.3)
Pyrexia	31 (10.2)	21 (6.8)	3 (<1)	0

No organ-specific toxicities have been identified that could explain the observed imbalance in deaths.

Conclusions

- Despite a trend in improvement of PFS, elesclomol in combination with paclitaxel (ELPAC) failed to demonstrate a statistically significant improvement when compared with paclitaxel alone in chemo-naive patients with metastatic melanoma
- There was a statistically significant increase in PFS with ELPAC in the subgroup of patients with normal LDH (68% of the ITT, pre-specified exploratory analysis)
- An imbalance in deaths favoring the paclitaxel arm was observed, leading to early study termination
- No organ-specific toxicities have been identified that explain the observed imbalance in deaths at this time; safety data is continuing to be evaluated
- At this point OS data is not mature; mature data will be presented at a future scientific meeting

Acknowledgements

- **SYMMETRY patients and their families**
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