

**A Randomized, Double-blind, Phase 3 Trial of Elesclomol
in Combination with Paclitaxel versus Paclitaxel Alone
for Treatment of Patients with Stage IV Metastatic
Melanoma (SYMMETRY)**

Updated Results

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Disclosures

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Elesclomol

- 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 chemotherapies¹⁻³
- Preclinical *in vivo* studies demonstrated synergistic efficacy of paclitaxel and elesclomol in a variety of solid tumor models, including melanoma
- 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)⁴

1. Kirshner *et al.* (2008) *Molecular Cancer Therapy* 7:2319-2327

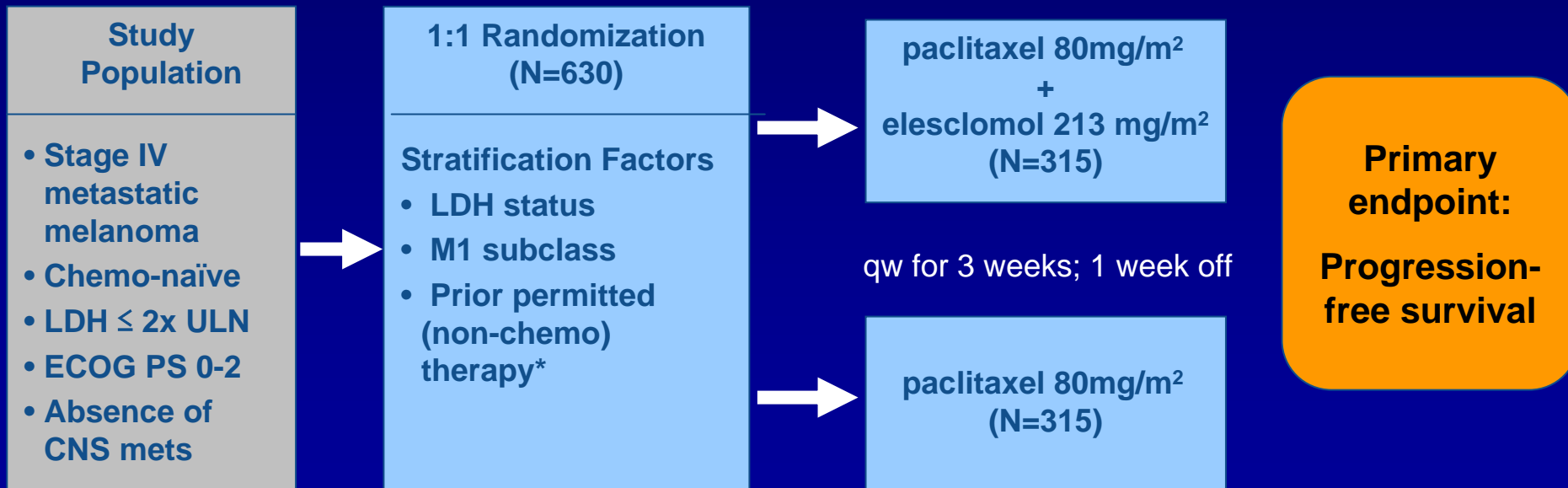
2. Kong *et al.* (2000) *Medical Hypothesis* 55:29-35; Pelicano *et al.* (2004) *Drug Resistance Updates* 7:97-110

3. Ramanathan *et al.* (2005) *Cancer Research* 65:8455-8460

4. O'Day *et al.* JCO in press

SYMMETRY study design

- 160 centers in 15 countries
- Tumor assessment at baseline and every 8 weeks (RECIST)
- No patient cross-over
- Same dose, schedule as Phase 2b trial
- Study Steering Committee: Steven O'Day, Axel Hauschild, Alexander Eggermont



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

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%) |

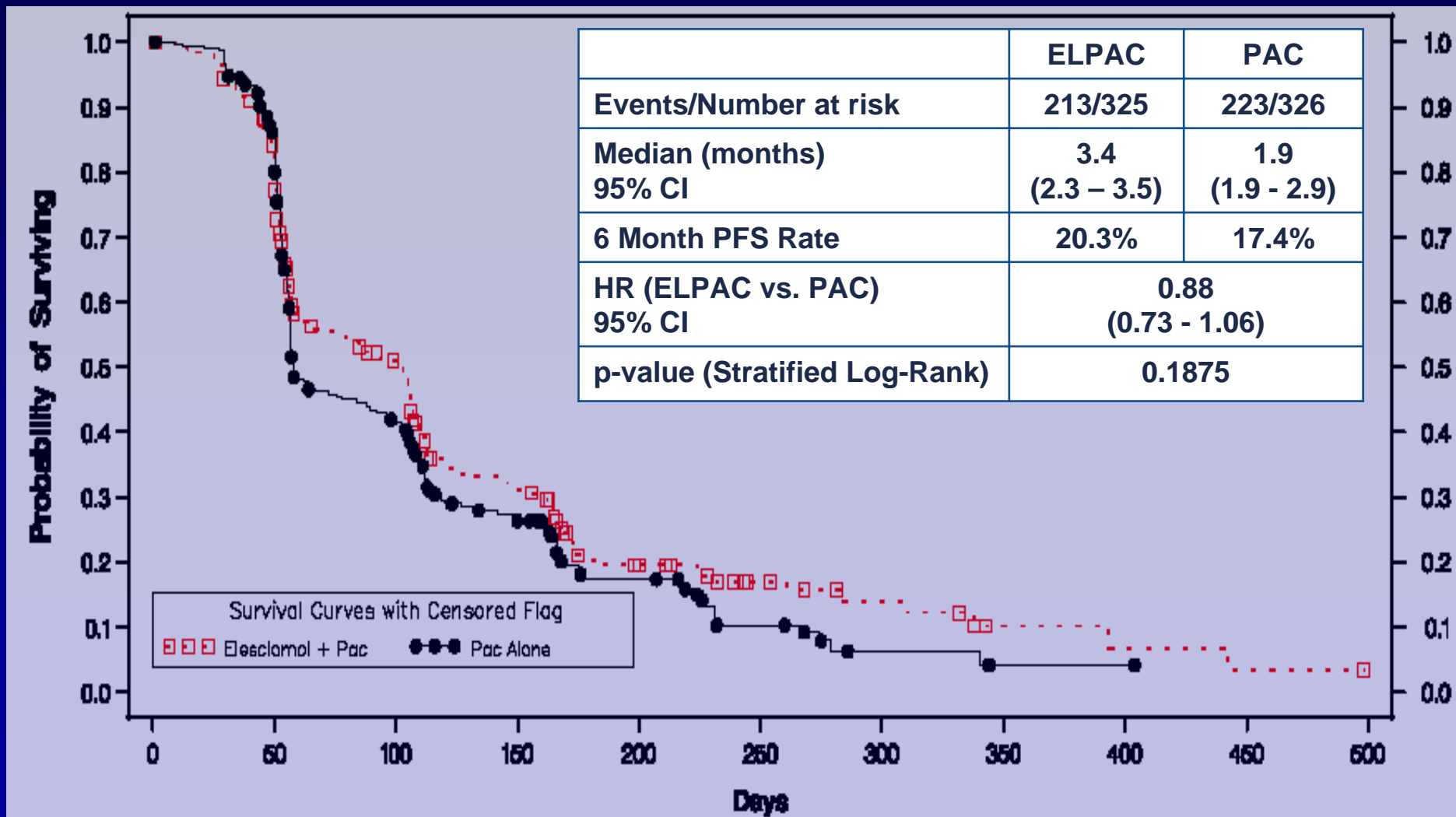
Baseline Disease Characteristics

| | ELPAC (N=325) | PAC (N=326) |
|---------------------------------------|------------------|----------------|
| M classification | | |
| M1a | 27 (8.3%) | 38 (11.7%) |
| M1b | 94 (28.9%) | 75 (23.0%) |
| M1c | 204 (62.8%) | 213 (65.3%) |
| LDH | | |
| Normal (<234 U/L) | 218 (67.1%) | 225 (69.0%) |
| Elevated (≥ 234 U/L) | 107 (32.9%) | 101 (31.0%) |
| ECOG PS | | |
| 0 | 233 (71.7%) | 251 (77.0%) |
| 1 | 83 (25.5%) | 68 (20.9%) |
| 2 | 9 (2.8%) | 7 (2.1%) |
| Prior Permitted 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%) |

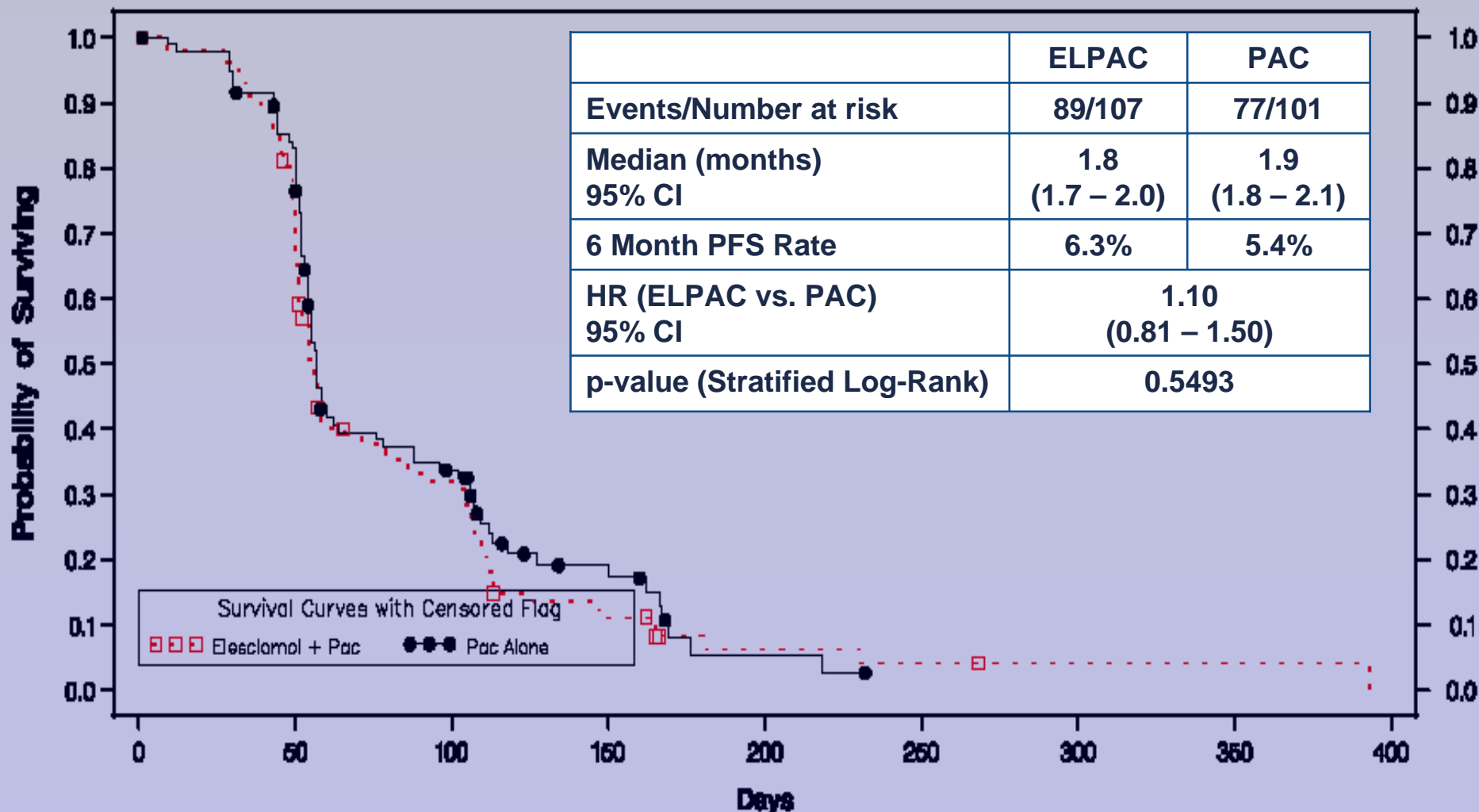
Phase 3 Study Termination

- On February 23, 2009, DMC conducted an ad hoc interim analysis and recommended unblinding 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)
- Sponsors decided to discontinue treatment in the SYMMETRY study
 - All subjects had been accrued at this time; treatment was discontinued for 242 patients (37% of ITT)

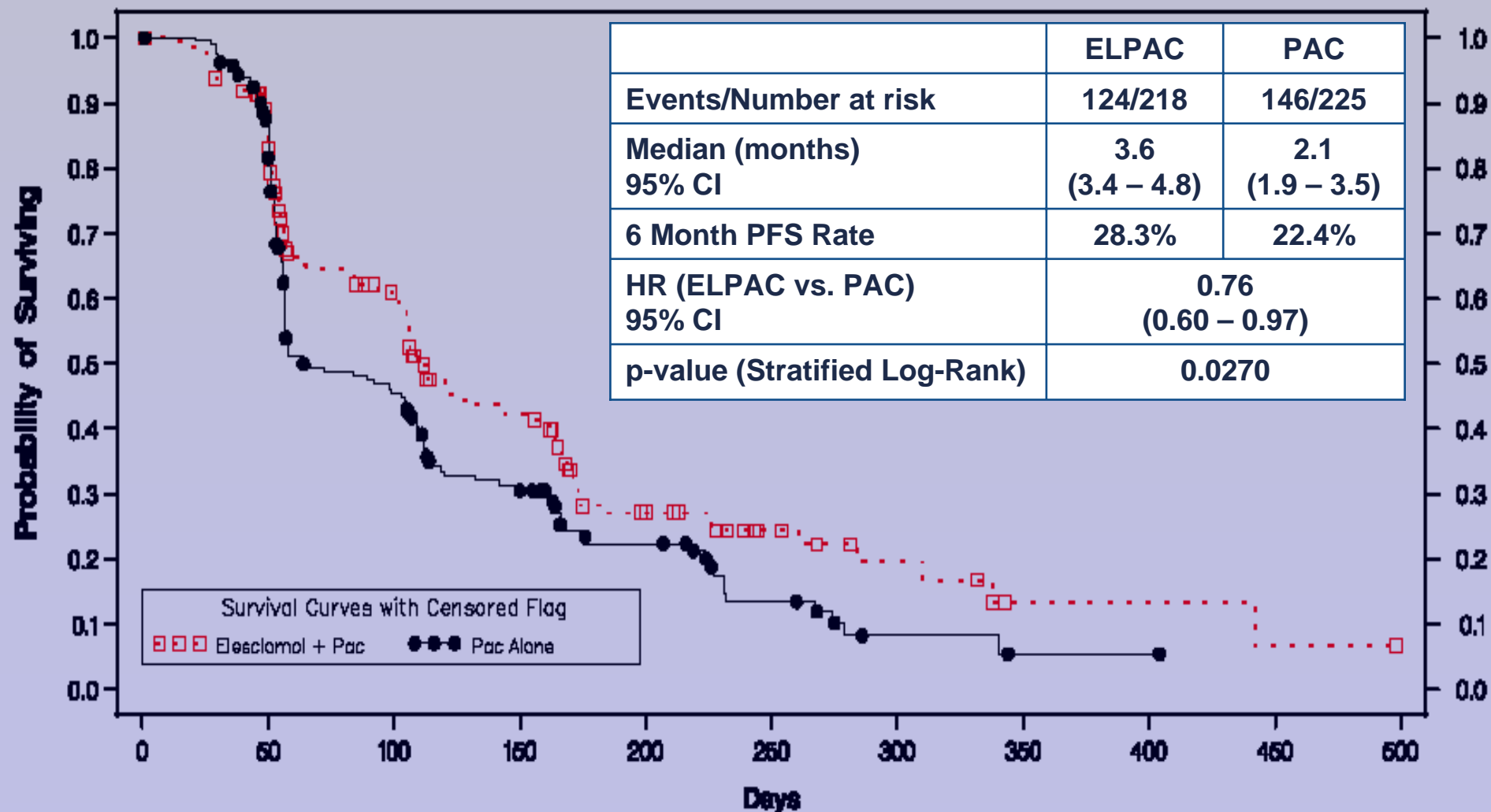
Progression-Free Survival (ITT Population)



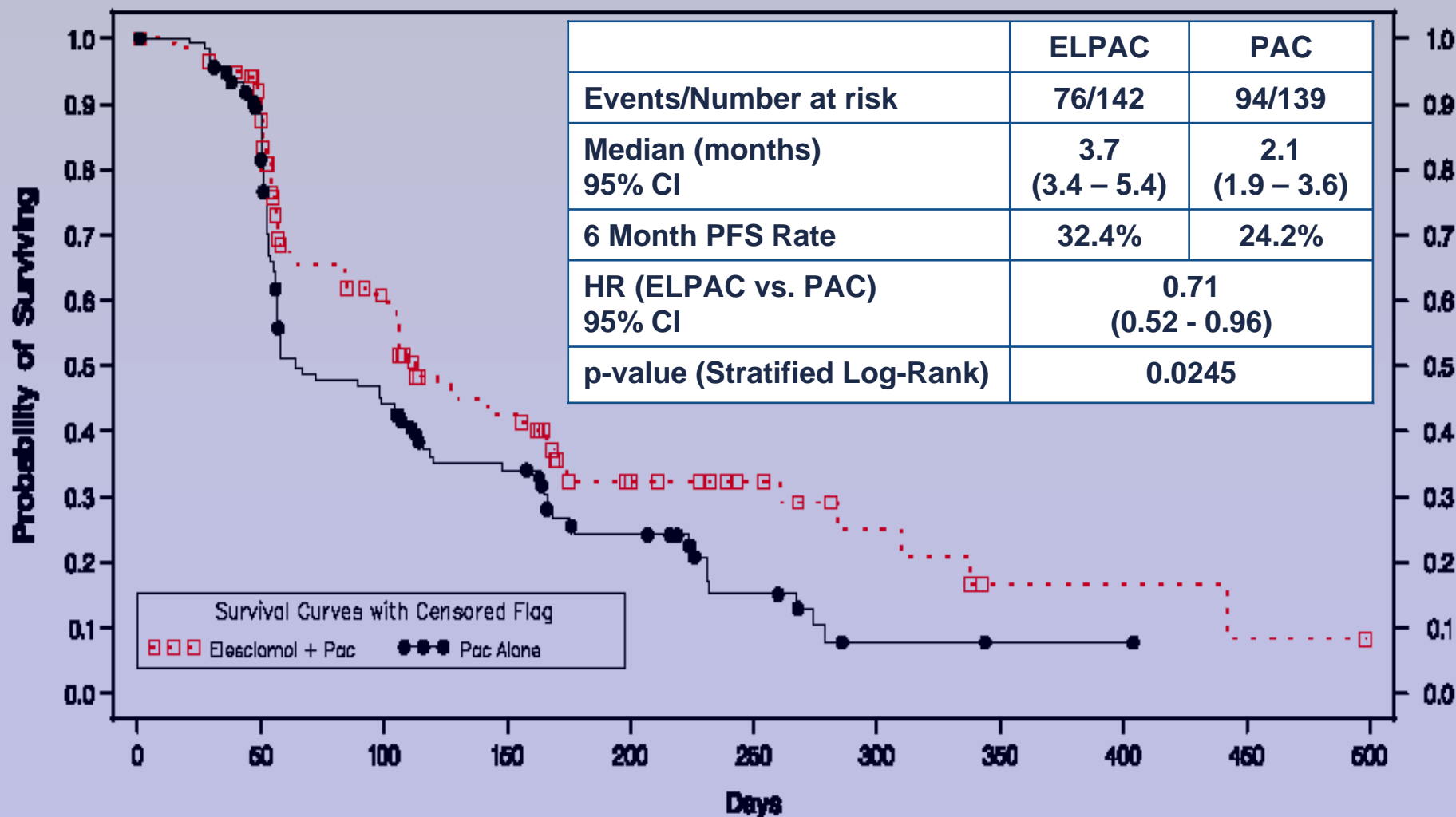
Progression-Free Survival (ITT Population) High LDH patients (N=208/651; 32%)



Progression-Free Survival (ITT Population) Normal LDH patients (N=443/651; 68%)



Progression-Free Survival (ITT Population) Low LDH ($\leq 0.8 \times \text{ULN}$) (N=281/651; 43%)



PFS Outcomes by LDH Subgroup: Summary ITT Population

| | High LDH ($\geq 1x$ ULN) | Normal LDH ($< 1x$ ULN) | Low LDH ($\leq 0.8x$ ULN) |
|---------|------------------------------|-----------------------------|-------------------------------|
| % pts | 32% | 68% | 43% |
| HR | 1.10 | 0.76 | 0.71 |
| P-value | 0.5493 | 0.0270 | 0.0245 |

- High LDH patients: no activity seen
- Normal/low LDH patients: signs of clinical benefit

Objective Tumor Response

Investigator assessment

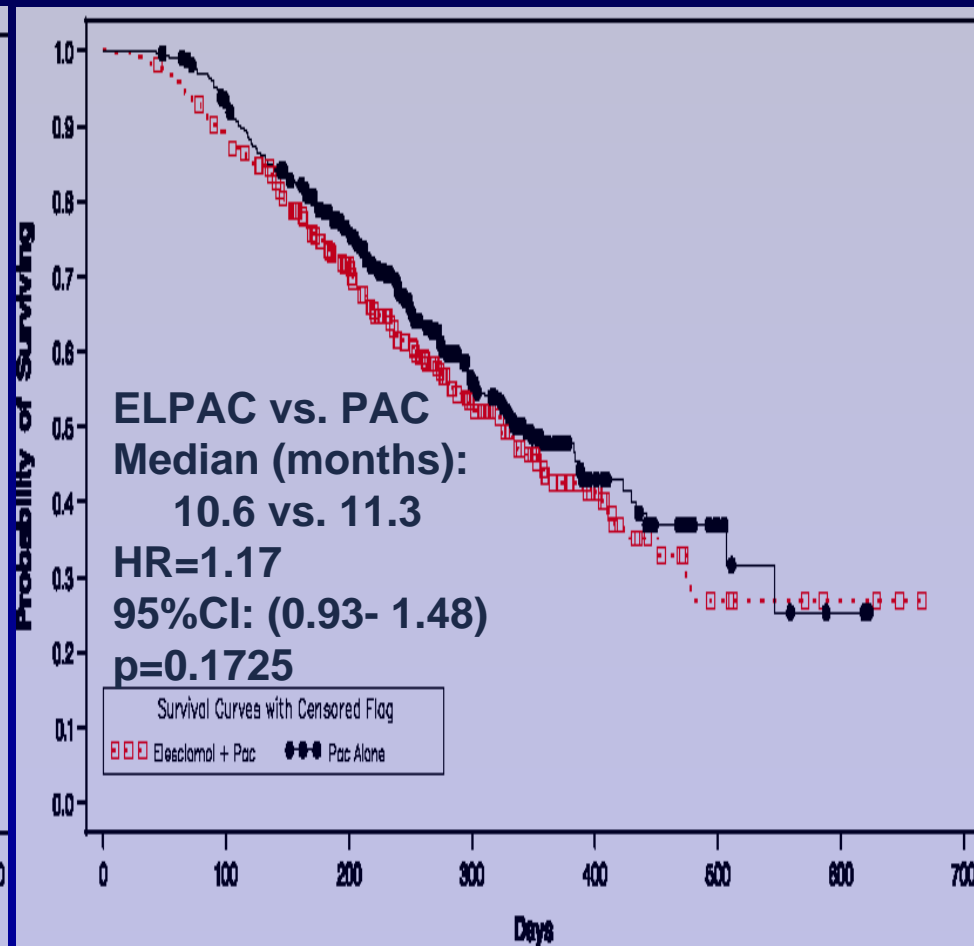
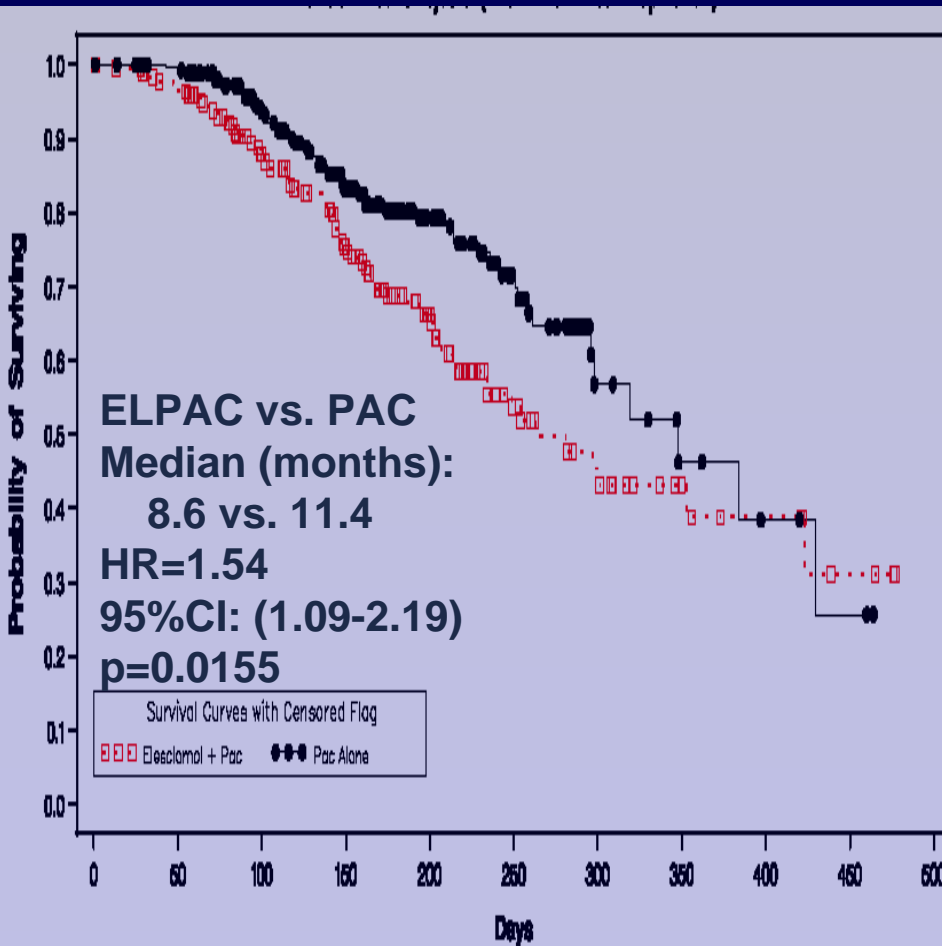
Subjects with at least 1 follow-up assessment

| Response Category | All Randomized (N=595) | | LDH Normal (<1x ULN) (N=407) | | LDH Elevated (≥1x ULN) N=(188) | |
|--------------------------------------|-------------------------|-----------------------|------------------------------|-----------------------|--------------------------------|----------------------|
| | ELPAC N (%) N=297 | PAC N (%) N=298 | ELPAC N (%) N=202 | PAC N (%) N=205 | ELPAC N (%) N=95 | PAC N (%) N=93 |
| CR | 2 (0.7) | 0 | 2 (1.0) | 0 | 0 | 0 |
| PR | 20 (6.7) | 13 (4.4) | 15 (7.4) | 8 (3.9) | 5 (5.3) | 5 (5.4) |
| ORR (CR+PR) | 22 (7.4) | 13 (4.4) | 17 (8.4) | 8 (3.9) | 5 (5.3) | 5 (5.4) |
| ORR p-value | 0.1207 | | 0.0651 | | 0.9999 | |
| Clinical Benefit (CR, PR, SD ≥6 mo.) | 64 (21.5) | 53 (17.8) | 55 (27.2) | 41 (20.0) | 9 (9.5) | 12 (12.9) |

Overall Survival: Feb 2009 vs. Sep 2009 (ITT)

Feb 2009: 80% censored

Sep 2009: 55% censored



OS outcomes by LDH subgroup (Sep 2009, ITT)

| | High LDH ($\geq 1x$ ULN) N=208 | Normal LDH ($< 1x$ ULN) N=443 | Low LDH ($\leq 0.8x$ ULN) N=281 |
|----------------------|---------------------------------------|--------------------------------------|--|
| % OS events censored | 34% | 65% | 68% |
| Median OS (months) | ELPAC: 5.9 PAC: 7.9 | ELPAC: 13.6 PAC: 13.9 | ELPAC: Not Ach. PAC: 14.5 |
| HR (95% C.I.) | 1.49 (1.05-2.11) | 0.99 (0.72-1.36) | 0.88 (0.58-1.34) |

OS outcome appears to correlate with LDH level

N.B.: OS data still evolving, not yet mature in normal/low LDH groups

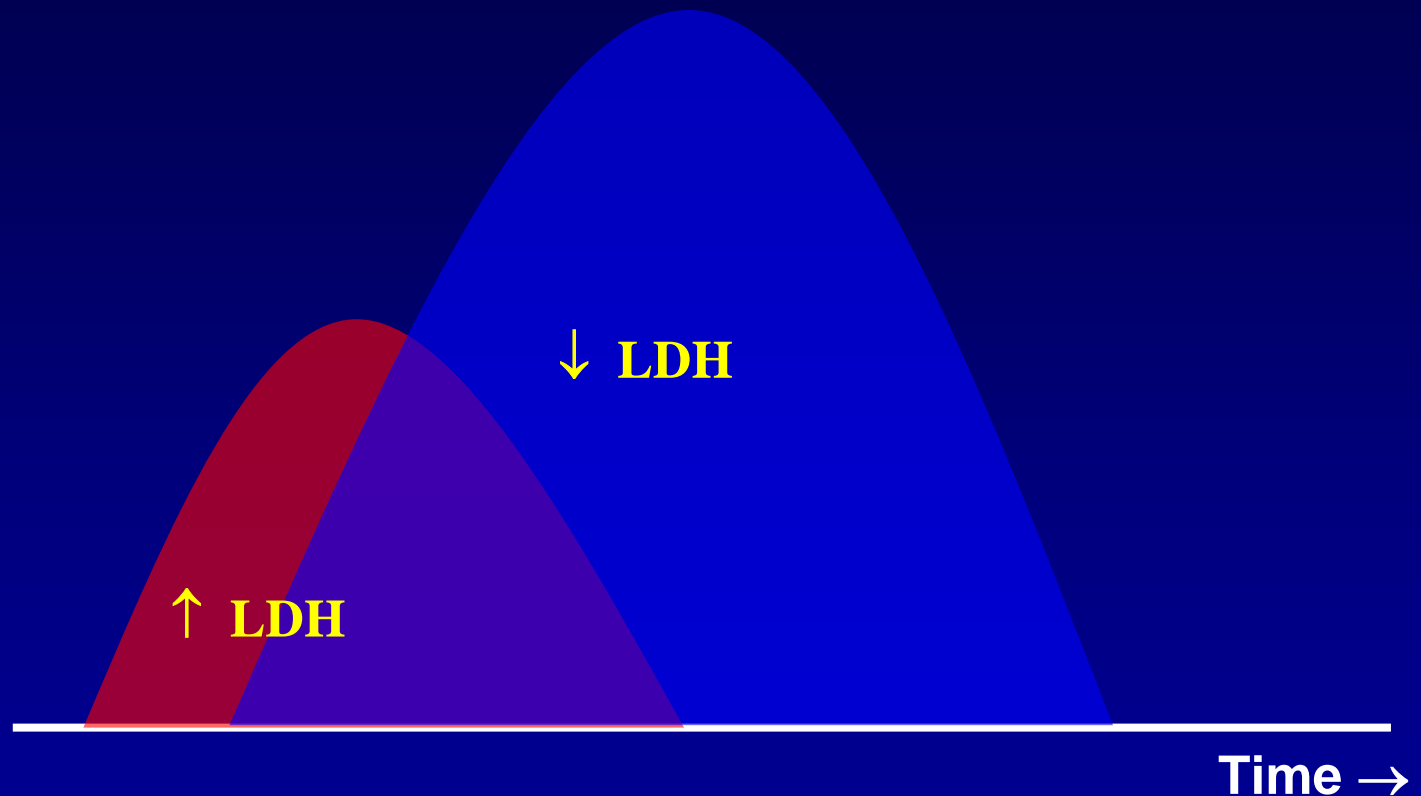
Sensitivity Analysis: Impact of Early Study Termination in Feb09 on OS Outcomes

Patients enrolled as of Nov 1, 2008: opportunity to have received minimum 4 cycles by study termination Feb 26, 2009. (Nov 1 group: 83% patients off treatment by Feb 26; ITT group: 63% off treatment)

| | High LDH ($\geq 1x$ ULN) N=145 | Normal LDH ($< 1x$ ULN) N=277 | Low LDH ($\leq 0.8x$ ULN) N=174 |
|----------------------|---------------------------------------|--------------------------------------|--|
| % OS events censored | 26% | 54% | 59% |
| Median OS (months) | ELPAC: 5.4 PAC: 8.2 | ELPAC: 13.6 PAC: 12.7 | ELPAC: Not Ach. PAC: 13.9 |
| HR (95% C.I.) | 2.08 (1.37-3.15) | 0.95 (0.67-1.34) | 0.81 (0.51-1.30) |

Differential impact of LDH on OS outcome: persists

Mortality in LDH Patient Subgroups



Earlier analyses: more high LDH patient events
Later analyses: more low LDH patient events

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 \geq3 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) |

Adverse Events Occurring in $\geq 10\%$ 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) | 44 (13.5) |
| Peripheral Edema | 46 (14.2) | 39 (12.0) |
| Vomiting | 44 (13.6) | 33 (10.2) |

Adverse Events Occurring in $\geq 10\%$ of ELPAC Patients (continued)

| | ELPAC (N=323) N (%) | PAC (N=325) N (%) |
|-------------|---------------------------|-------------------------|
| Dyspnea | 43 (13.3) | 35 (10.8) |
| Pyrexia | 41 (12.7) | 22 (6.8) |
| Anorexia | 41 (12.7) | 26 (8.0) |
| Insomnia | 41 (12.7) | 36 (11.1) |
| Back Pain | 37 (11.5) | 45 (13.8) |
| Anemia | 35 (10.8) | 33 (10.2) |
| Parathesia | 35 (10.8) | 26 (8.0) |
| Arthralgia | 35 (10.8) | 27 (8.3) |
| Dyspepsia | 35 (10.8) | 23 (7.1) |
| Neutropenia | 34 (10.5) | 22 (6.8) |

Most Frequent \geq 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) |

Conclusions

- The SYMMETRY trial did not achieve the primary endpoint
- While OS data still evolving, clear message emerging: LDH is important predictor of both PFS and OS outcome for treatment with elesclomol in combination with paclitaxel
 - Patients with low or normal baseline LDH: improvement in PFS compared to PAC alone; no difference in OS observed to date (data still immature)
 - Patients with high baseline LDH: no PFS improvement; decrease in survival time compared to PAC alone
- Adverse event profile between ELPAC and PAC alone was comparable indicating treatment with elesclomol was well tolerated

Further investigation

- Updated survival data set expected to be presented by mid-2010, >12 months minimum follow-up
- LDH and elesclomol oxidative stress mechanism both relate to metabolic pathways; additional research is ongoing to investigate connection between the two. Further mechanism results will be presented at scientific meetings later this year (AACR-NCI-EORTC; ASH)

Acknowledgements

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| | | |
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