

Serum free estradiol (E2) levels are prognostic in men with chemotherapy-naïve advanced non-small cell lung cancer (NSCLC) and performance status (PS) of 2

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Background

- Women with NSCLC have better stage-for-stage survival than men with the same disease.
- Older women in particular have a better outcome than the general population.
- E2 levels > 30 pg/mL confer a survival disadvantage to women with advanced NSCLC treated on two large randomized clinical trials (STELLAR 3 and 4) suggesting an adverse effect of E2 on prognosis for women with NSCLC.¹
- Levels of E2, produced from testosterone by aromatase, are often higher in men than in un-supplemented postmenopausal women.²
- The hypothesis that E2 will have the same adverse effect on prognosis in men with advanced NSCLC as in women with the disease was explored by a retrospective analysis of male participants in the STELLAR 3 and 4 studies.

- Survival was significantly worse for men with E2 values higher than the median compared to those below the median (Figure 2). Hazard ratios showed a 54% increase in the probability of death in men with high estradiol level (Table 1).
- Survival and hazard ratio for men with E2 above or below 0.41 pg/ml were similar whether men received PPX or control therapies (Table 1, Figures 3 and 4).

Table 1: Summary of Overall Survival by E2 Level and Treatment Arm

	HR	Log Rank P	Median Survival (days)
PPX and Control: E2 >0.41: E2 ≤0.41	1.54	0.0007	212 vs. 259
Control Only: E2 >0.41: E2 ≤0.41	1.48	0.022	206 vs. 255
PPX Only: E2 >0.41: E2 ≤0.41	1.61	0.012	222 vs. 275
E2 >0.41: PPX: Control	0.97	0.839	222 vs. 206

Results

Figure 2: Overall Survival of Men by E2 level (>0.41 pg/mL vs ≤ 0.41 pg/mL) in STELLAR 3 and STELLAR 4

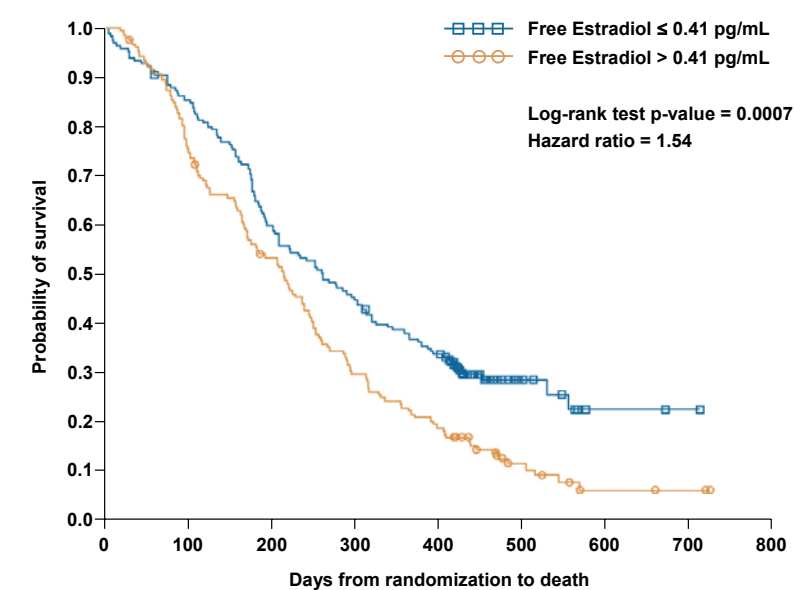


Figure 4: Overall Survival of Men with E2 ≤ 0.41 by treatment arm in STELLAR 3 and STELLAR 4

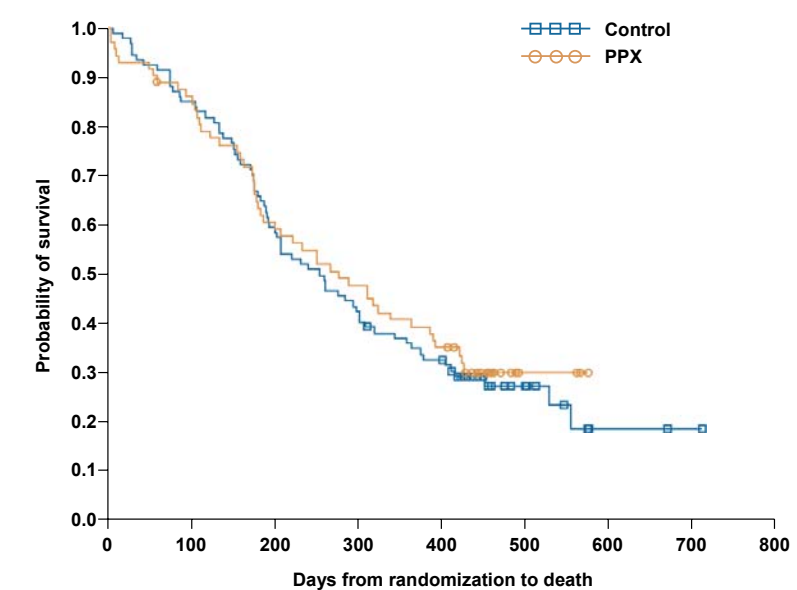
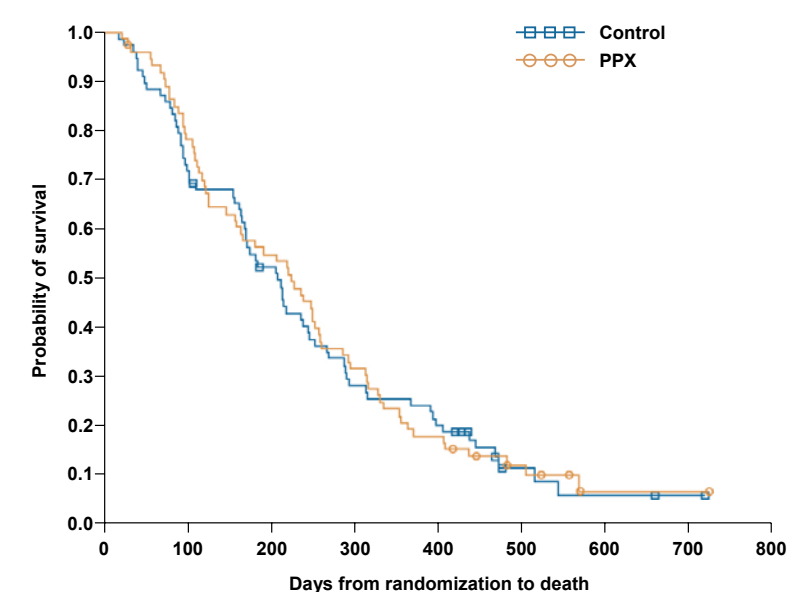


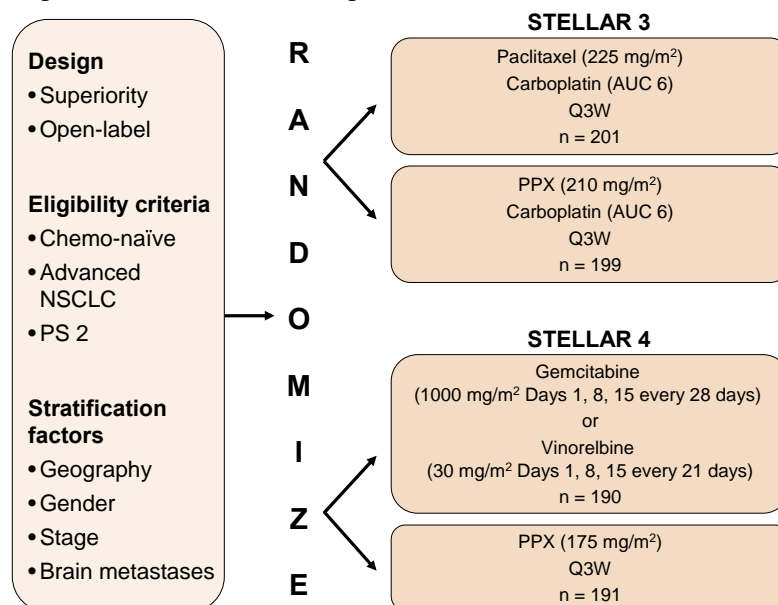
Figure 3: Overall Survival of Men with E2 > 0.41 by treatment arm in STELLAR 3 and STELLAR 4



Methods

- The STELLAR 3 and 4 trials were large, phase III, open-label, randomized trials of paclitaxel poliglumex (PPX) in combination with carboplatin (C) versus paclitaxel (P)/C and single-agent PPX versus vinorelbine (V) or gemcitabine (G) respectively, for first-line treatment of PS 2 patients with advanced NSCLC.^{3,4}
- E2 levels from male participants in STELLAR 3 and 4 were assessed retrospectively from stored serum samples.
- Free serum E2 levels were measured before chemotherapy using a radioimmuno-assay in samples from 318 of 583 men enrolled in the STELLAR 3 and 4 trials. This assay differs from that used in the prior analysis of estradiol in female patients on these studies in that total E2 was assayed in the previous studies.
- The relationship between free E2 levels and survival was evaluated by log rank test. Patients were categorized as high or low E2 based on values above or below the median (0.41 pg/mL; range: 0.1-2.95). The assay range for normal men is 0.2-0.5 pg/mL. The normal ranges for women are: follicular = 0.34-1.26 pg/mL; luteal = 0.80-3.45 pg/mL, menopausal = 0.12-0.39 pg/mL.

Figure 1: STELLAR Trials Design



Conclusion

- Free serum E2 levels are prognostic in men as well as women with advanced NSCLC.
- In a previous analysis in women on the STELLAR 3 and 4 studies (using a different assay so E2 range cannot be compared directly with the current data) premenopausal E2 levels conferred a survival advantage for treatment with PPX compared to control.¹
- Men with higher levels of free E2 have shorter survival, consistent with the shorter survival noted in premenopausal women when compared to older women but in this analysis PPX did not mitigate the disadvantage of higher E2 as it did in women.
- Clinical exploration of anti-E2 therapy should be considered in men as well as in women with advanced NSCLC.

References

1. *J Clin Oncol.* 2006, 24(18S):7039.
2. *Ann Intern Med.* 2000, 133:951-63.
3. *J Clin Oncol.* 2005, 23(16S):7011.
4. *Eur J Cancer.* 2005, S3(2):324.