

Serum Cathepsin B (CB) Is Prognostic and May Predict Response to Therapy in Chemotherapy-naïve PS2 Advanced NSCLC Patients Treated on Two Concurrent Phase III Trials of Paclitaxel Poliglumex (PPX) vs Control Treatments (STELLAR 3 and 4)

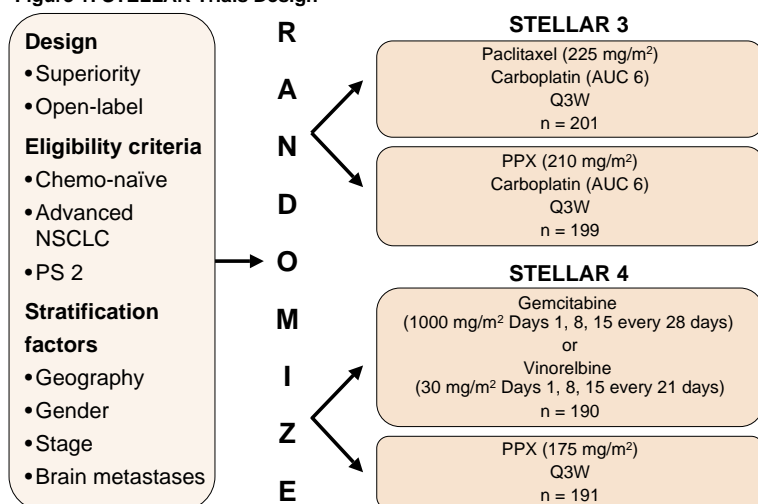
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Background

- Cathepsin B (CB) is an estrogen-regulated lysosomal cysteine protease produced by cancer cells and tumor-associated macrophages. This peptidase is prognostic in several epithelial cancers and is the predominant metabolizing enzyme for paclitaxel poliglumex (PPX, CT-2103).
- Estrogen-mediated elevation of CB appears to mediate PPX activity against human tumor xenografts in mice¹ and is postulated to contribute to the differential response to PPX in pre- and post-menopausal women.
- STELLAR 3 and 4 (PGT303 and 304) were concurrent phase III trials of first-line PPX vs. standard therapy for patients meeting identical entry criteria. All patients had performance status (PS) 2 and had stage IIIB/IV or recurrent non-small cell lung cancer (NSCLC) without prior chemotherapy. Combined analysis identified estrogen as both prognostic and predictive of response to and survival after PPX in women on the two trials.
- To investigate the hypothesis that CB is prognostic and plays an important role in PPX activity in NSCLC, we analyzed CB levels in baseline serum samples from STELLAR 3 and 4 study patients and examined the correlation between CB and survival.

- STELLAR 3 and 4 were large randomized phase III trials of paclitaxel poliglumex (PPX) based therapy compared to standard chemotherapy for first-line treatment of PS 2 patients with NSCLC² (Figure 1)

Figure 1: STELLAR Trials Design



Methods

- Stored baseline serum was assayed for CB by a highly specific ELISA (ICON Laboratories; Farmingdale NY).
 - Pretreatment serum samples were analyzed from 396 male and 3 female patients (293 of the 400 patients in STELLAR 3 and 106 of the 381 patients in STELLAR 4)
 - Samples from 50 normal subjects (25 men and 25 women) were also tested to establish a normal range
- Patients were categorized as high or low CB based on whether their values were above or below the breakpoint seen at the median value, 64 ng/ml (Table 1).
- Overall survival for the combined STELLAR 3 and 4 datasets was analyzed using Kaplan-Meier Methods, and survival curves were compared using the log-rank test.

Table 1: Basis for establishing breakpoint (64 ng/ml) for Cathepsin B Levels

	Normal samples	Patients in STELLAR 3 and 4
N	50	399
Mean (ng/ml)	50.9	71.01
SD (ng/ml)	19.4	29.2
Median (ng/ml)	46	64.1
Range (ng/ml)	(24.7, 105.97)	(28.9, 292.8)

P-value (2 sample t-test) all normal samples to STELLAR patients: <0.0001

Results

Figure 2: STELLAR 3 and 4 Control Group by CB Levels

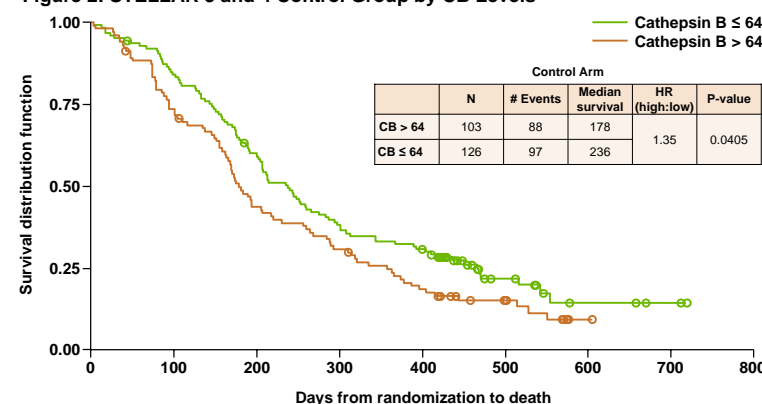


Figure 3: STELLAR 3 and 4 PPX Group by CB Levels

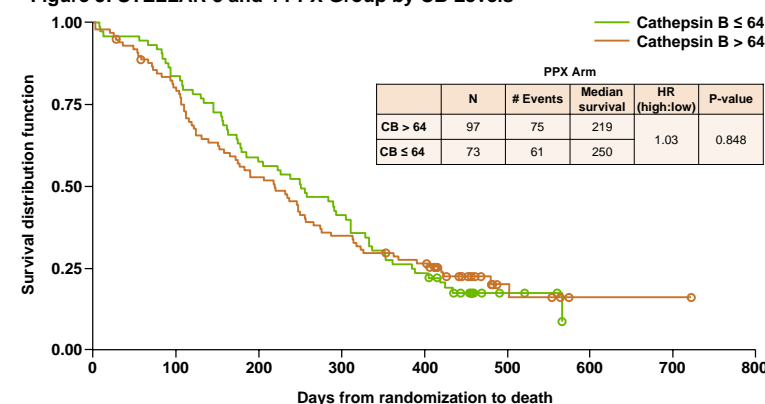


Figure 4: STELLAR 3 and 4 Combined by CB > 64

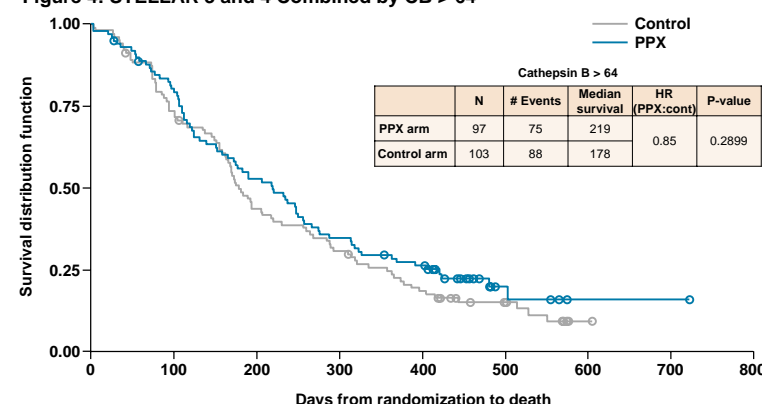
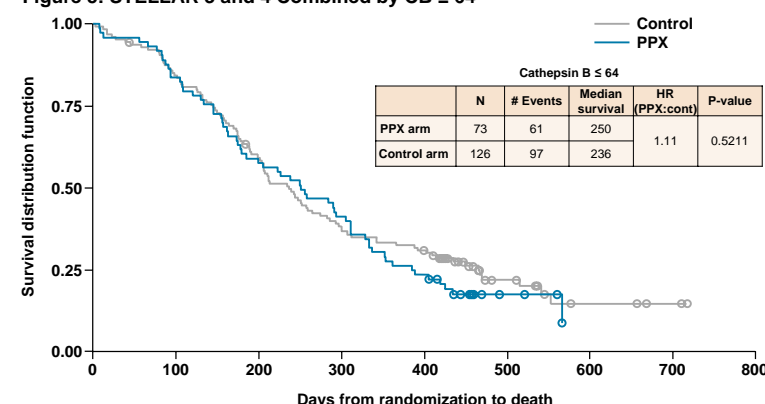


Figure 5: STELLAR 3 and 4 Combined by CB ≤ 64



Conclusion

- Serum CB levels are higher in patients with advanced NSCLC than in control samples from individuals without cancer.
- Serum CB appears to be a prognostic biomarker for PS 2 NSCLC patients treated with conventional chemotherapy with shorter survival in patients with higher levels. Treatment with PPX in this predominantly male study population was able to overcome the adverse prognostic effect of high CB.
- Retrospective analysis of STELLAR 3 and 4 supports the hypothesis based on preclinical data that CB may enhance the efficacy of PPX against NSCLC, at least in a male population. This should be validated in prospective trials including more females and in conjunction with analysis of estradiol status.
- Prospectively targeting patients with high levels of serum CB is of interest in future studies of PPX.

References

1. Di Giovine, et. al., *European Journal of Cancer Supplements*, Volume 4, No.12, page 191, 2006
 2. *J Clin Oncol* 2006, 24(18S):7038; *J Clin Oncol* 2006, 24:59-63