P3-019 NT: Cytotoxic Chemotherapy Posters, Wed, Sept 5 – Thur, Sept 6

Serum Cathepsin B (CB) is prognostic and may predict response to therapy in chemotherapy-naive 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: STELLAR 3 and 4 are concurrently run phase III trials of first-line PPX vs standard therapy for patients meeting identical entry criteria. Patients all had performance status 2 and had stage IIIB/IV or recurrent NSCLC without prior chemotherapy. Combined analysis identified estrogen as both prognostic and predictive of response to PPX in women on the two trials. 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). Estrogen-mediated elevation of CB appears to mediate PPX activity against human tumor xenografts in mice (Di Giovine, et. al., European Journal of Cancer Supplements, Volume 4, No.12, page 191, 2006) and is postulated to explain the differential response to PPX in pre and post-menopausal women. To investigate this hypothesis, we analyzed CB levels in serum samples from STELLAR 3 and 4 study patients and correlated results with survival.

Methods: Pretreatment serum samples were analyzed from 450 patients (STELLAR 3, n=315; STELLAR 4, n=135). STELLAR 3 patients received doublet chemotherapy (carboplatin with either PPX or paclitaxel) while STELLAR 4 patients received singlet therapy (PPX or investigator's choice of gemcitabine or vinorelbine). Serum was assayed for CB by highly specific ELISA (ICON labs). 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). Correlation of CB with survival was evaluated by log rank for pooled patients from the two studies.

Results: Analysis by treatment arm: median survival (MS) was worse for patients with high CB on the control arms of STELLAR 3 and 4. For non-PPX treated patients, if CB was above 64 ng/ml MS was 174 days compared to 234 days for patients with CB at or below 64 ng/ml (HR 1.36, P=.022). For patients treated with PPX, this survival disadvantage for high CB was not seen (MS 220 vs 249 days, HR 0.96, P=.82). Analysis by CB level: patients with high CB exhibited a trend in favor of improved survival with PPX compared to control treatments (MS 220 vs 174 days, HR 0.80, P=.13). Patients with CB 64 ng/ml or less had similar survival whether treated with PPX or control treatments (249 vs 234 days, HR 1.12, P=.474).

Conclusions: Serum CB appears to be a prognostic biomarker for NSCLC with inferior survival in patients with high levels. CB may also be predictive of response to targeted paclitaxel in the form of PPX based on retrospective analysis of STELLAR 3 and 4. Analysis of serum CB should be built in to prospective trials and could be considered as a stratification factor for future studies of PPX.

Novel Therapeutics: Immunotherapy/Vaccines

P3-020 NT: Immunotherapy/Vaccines Posters, Wed, Sept 5 – Thur, Sept 6

Combined CCL19/IL-7 treatment eradicates tumors in murine models of lung cancer

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Background: Effective anti-tumor responses require both antigen presenting cells and lymphocyte effectors. Although lung cancers express tumor antigens, they are ineffective as antigen presenting cells because tumor cells often have limited expression of MHC Ags and lack co-stimulatory molecules.

It has been demonstrated that local and systemic administration of chemokines or cytokines as stimulators of the immune response is beneficial as potent anti-cancer strategy. Epstein Barr virus-induced molecule 1 ligand chemokine (ELC/CCL19) is a CC chemokine that strongly chemoattracts both dendritic cells (DC) and T lymphocytes. Interleukin-7 (IL-7) amplifies the longevity of the tumor antigen specific T cells and NK effectors. In this study we evaluated the anti-tumor efficacy of combined CCL19/IL-7 treatment in two murine lung cancer models.

Methods: 105 L1C2 and 3LL cells have been injected into the right flank of Balb/C and C57/Bl6 mice respectively. Five days after injection mice have been treated intratumorally with injection of recombinant ELC/CCL19 (0.5μg/dose) three times per week and Interleukin 7 (200ng/dose) daily for 2 weeks. For the evaluation of anti-tumor responses, tumors were harvested three weeks after combined treatment and assessed for H&E staining to analyze tumor infiltrating T cell subsets by flow cytometry. Tumors were evaluated for the production of IL-10, IL-12, GM-CSF, IFNγ, TGFβ, by ELISA and PGE2 by enzyme immunoassay (EIA) in the supernatants after an overnight culture.

Results: In the C57/Bl6 mice there was a dramatic inhibition of tumor growth compared to diluent treated controls, in 5 out of 6 Balb/C mice we even observed a complete tumor eradication. Flow cytometric analysis showed a significant increase in both CD4 and CD8 subsets as well as dendritic cells. However, there was a decrease in CD4+CD25+ T regulatory cells in the tumor infiltrating lymphocytes of combined treated mice. Tumor tissue cytokine profiles showed a shift towards immunostimulatory molecules.

Conclusions: Combination of CCL19 and IL-7 treatment leads to a dramatic reduction of tumor growth and confirms the impact of chemokines and cytokines in the development of an effective anticancer-immunotherapy and the importance of targeting multiple pathways.