An Analysis of the CK2 Pathway in PBMCs, CTCs, And Plasma in Patients with Solid Tumors

APOCELL molecular profiling & diagnostics

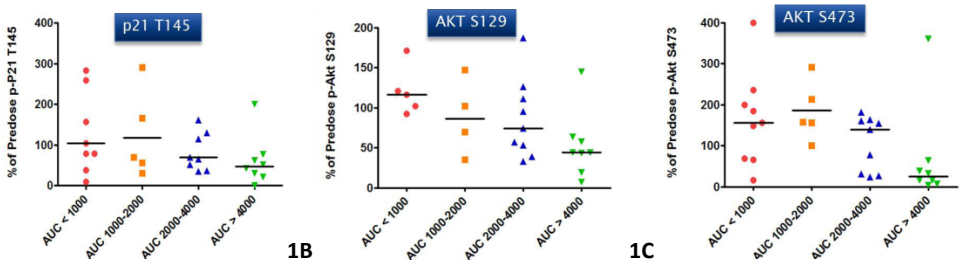
Clinical Application: Pharmacodynamic Assessment of a CK2 Inhibitor

Key Words: PBMCs, CTCs, plasma, biomarker expression, pharmacodynamics

Background: CK2 protein kinase is a constitutively active enzyme that mediates signaling in multiple pathways including oncogene and cytokine signaling. CK2 is an attractive target for anticancer therapy due to its overexpression in most cancer types and its importance to the survival and maintenance of the cancer phenotype. ApoCell was contracted to monitor the pharmacodynamics of a first-in-class CK2-inhibitor, CX-4945, by measuring changes in a CK2 specific biomarker in patient peripheral blood mononuclear cells (PBMCs), circulating tumor cells (CTCs), and plasma.

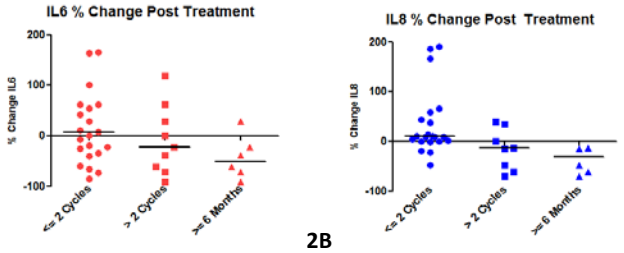
Methods: Patient blood samples were received by ApoCell and PBMCs were isolated via Ficoll-Paque density gradient centrifugation. PBMCs were cytospun to slides and stained for DAPI, CD45, and three primary biomarkers – pAKT (S129), pAKT (S473), and p-p21 (T145). An additional tube of blood was processed on the CellSearch® Profile kit for CTC enumeration. CellSearch®-isolated cells were cytospun and stained with DAPI, Cytokeratin (CK), and CD45. Both sets of slides were then analyzed by Laser Scanning Cytometry (LSC). PBMCs were classified as cells exhibiting a DAPI+/CD45+ phenotype – each biomarker of interest was examined in these cells – and CTCs were classified as cells exhibiting a phenotype of DAPI+/CK+/CD45-. Plasma samples were analyzed via ELISA for IL-6 and IL-8 across the course of treatment.

Results:



1A 1B 1C

Figure 1. Biomarker Expression Levels in PBMCs. PK-PD relationships were analyzed using the expression levels of p-p21 (A), pAKT (S129) (B), and pAKT (S473) (C) in PBMCs after one week of treatment. Treatment in a drug exposure (AUC) related manner caused strong reduction in each biomarker, indicating pathway inhibition.



2A 2B

Figure 2. IL-6 and IL-8 Levels in Plasma. The percent change in the expression of IL-6 (A) and IL-8 (B) in patient plasma is shown here; duration of disease stabilization was associated with a percent decrease in both IL-6 and IL-8 levels.

CTC counts of eight patients of various cancer types (colon, osteosarcoma, NSCLC, SCLC, breast, uterine sarcoma) were analyzed and showed a trend toward reduced CTC counts over the course of treatment.

Impact: CX-4945 inhibited the phosphorylation of S129 on Akt – a CK2 specific site – demonstrating that CX-4945 hit its molecular target and pAKT (S129) can serve as a target biomarker for evaluating the pharmacodynamic activity of CX-4945. Reductions in the interleukin biomarkers and CTC counts were associated with stable disease.

References: 1. Marschke, R.F., et al. "Findings from the Phase I Clinical Trials of CX-4945, an Orally Available inhibitor of CK2." ASCO, 2011.

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