

Case Study #4 - Validation of Biomarker Correlation with Clinical Outcome on FDA Approved Targeted Therapies

Monitoring pharmacodynamic endpoints early in clinical studies can facilitate go / no-go decisions. Scientists at ApoCell developed a proprietary quantitative process for measuring biomarkers related to drug target inhibition, cell signaling, and apoptosis in patient specimens. These biomarker assays have routinely demonstrated significant correlation with clinical outcome including predicting the degree of response on FDA approved drugs. Pharmacodynamic analyses of key biomarkers in endothelial and/or tumor cells reveal that these endpoints may be beneficial in assessing potential therapeutic benefit.

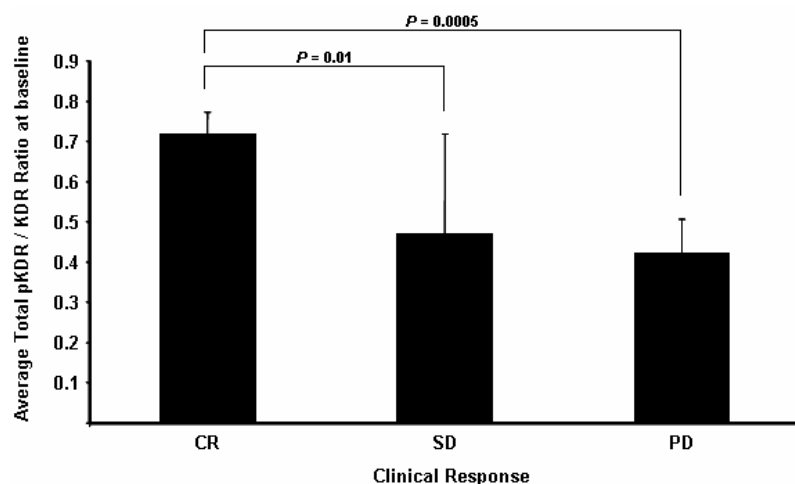
Sutent - In a phase I / II trial, pharmacodynamic analysis of Sutent demonstrated that the change in levels of pVEGFR-2 and pPDGFR-b biomarkers correlated with clinical outcome. Apoptosis in tumor cells and endothelial cells significantly correlated with clinical outcome.

Table 1. Change in RTK activity: correlation with clinical benefit

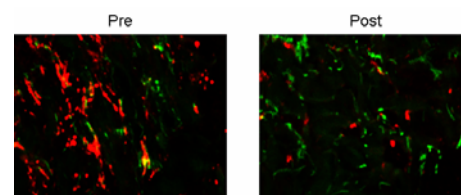
Clinical response	Number of patients	Δ p-PDGFR- β	Δ p-VEGFR-2
Clinical benefit (PR or SD >6 months)	8	18.2% \downarrow (P=0.006) (42% \downarrow [P=0.008]) [†]	26.7% \downarrow (P=0.02)
PR	2	26.1% \downarrow (P=0.001)	–
SD >6 months	6	13.9% \downarrow (P=0.04)	–
PD (SD <6 months)	12	9.9% \uparrow (P=0.06) (23% \uparrow [P=0.443]) [†]	9.6% \uparrow (P=0.02)

[†]Change in p-PDGFR- β activity in tumor-associated endothelial cells.

p = phosphorylated; PD = progressive disease; PR = partial response; SD = stable disease.



Avastin + Tarceva – In a Phase I / II trial, pharmacodynamic analysis of Avastin + Tarceva revealed that quantifying pKDR/KDR levels using ApoCell's proprietary process significantly predicted clinical outcome, including degree of response.



Pre-treatment Marker	pkit (Y721)	pkit (Y703)	Total kit	p-PDGFR α	p-DGFR β
Fold difference- Responder vs. Non-responder	77 \uparrow	36 \uparrow	1.16	30 \downarrow	16 \downarrow

Gleevec – In a Phase II study, pharmacodynamic analysis of Gleevec revealed that hyperphosphorylation of a specific tyrosine kinase in the Kit receptor predicted a complete clinical response. In contrast, we found

that the levels of phospho-PDGFR α or - β in the non-responders are higher than that of the responder. Together, these data suggest that the phospho-Y721-c-kit mediated oncogenic pathway is the driving force for the tumorigenesis of melanoma in the responder.

ApoCell's analytical process may be used to help monitor the pharmacodynamic effects of investigational agents and even predict clinical response of drugs with similar targets.

Reference

1. EORTC-NCI-AACR International Conference on Molecular Targets and Cancer Therapeutics, Abstract #57, Prague, Czech Republic, 2006