Predicting clinical response based on \textit{ex vivo} drug response in renal cell carcinoma using kinase activity profiling

Rob Ruijtenbeek\textsuperscript{1}, Liesbeth Houkes-van Kerkhoff\textsuperscript{1}, Riet Hilhorst\textsuperscript{1}, Peter Mulders\textsuperscript{2}, Jeannette Oosterwijk-Wakka\textsuperscript{2}, Lambertus Kiemeneij\textsuperscript{2}, Egbert Oosterwijk\textsuperscript{2}.
\textsuperscript{1}PamGene International B.V., 's-Hertogenbosch, Netherlands; \textsuperscript{2}Radboud University Medical Center, Nijmegen, Netherlands

\textbf{Abstract}

\textbf{Introduction}

Sunitinib, a potent multikinase inhibitor, is one of the first line treatments for metastatic renal cell carcinoma (mRCC). Because sunitinib responses and toxicity are highly variable, there is a need for biomarkers predicting sunitinib response or predicting the optimal sequence preference when using alternative tyrosine kinase inhibitors.

\textbf{Aim of the study}

\begin{itemize}
  \item To investigate the correlation between \textit{ex vivo} drug response and clinical response in mRCC.
  \item To explore alternative treatment options.
\end{itemize}

\textbf{PamChip\textsuperscript{®} kinase assay}

\begin{itemize}
  \item Drug treatment: PKI/TKI
  \item Time
  \item Kinase activity
  \item Tumor response
  \item Prediction Biomarkers
\end{itemize}

\textbf{Optimisation of assay conditions}

\begin{itemize}
  \item Non-kinase
  \item Drug added
  \item ex vivo
  \item Drug response
  \item Kinase activity
  \item Kinase activity
\end{itemize}

\textbf{Time course of study}

\begin{itemize}
  \item Drug treatment: PKI/TKI
  \item Time
  \item Kinase activity
  \item Tumor response
  \item Prediction Biomarkers
\end{itemize}

\textbf{Profile s not correlate with clinical sunitinib response}

\begin{itemize}
  \item Non-kinase
  \item Drug added
  \item ex vivo
  \item Drug response
  \item Kinase activity
\end{itemize}

\textbf{Sunitinib responders (more than 6 months)} show more inhibition than non-responders

\begin{itemize}
  \item Profiles
  \item Kinase activity
  \item Inhibition by drug
\end{itemize}

\textbf{Pharmacological profiling}

\begin{itemize}
  \item Non-kinase
  \item Drug added
  \item ex vivo
  \item Drug response
  \item Kinase activity
\end{itemize}

\textbf{Fig. 3} Tyrosine Kinase activity profiles, hierarchically clustered.

\textbf{Fig. 4} Inhibition profiles with 0.1µM sunitinib, hierarchically clustered per peptide. More inhibition is seen in responder samples.

\textbf{Fig. 5} Inhibition profiles with 0.5µM sunitinib. Inhibition is expressed with respect to mean per peptide.

\textbf{Fig. 6} Exploring alternative treatment options with a sunitinib responder and non-responder sample for inhibition effect of axitinib, crenolanib, crizotinib, erlotinib, imatinib, masitinib, pazopanib, sorafenib, sunitinib and tivozanib. Different TKI concentrations are used so potency information is not shown.

\textbf{Summary}

\begin{itemize}
  \item The \textit{ex vivo} sunitinib effect is positively correlated with clinical responses especially in the subgroup which received sunitinib as 1st line treatment (4 responders vs. 4 non-responders) (Fig. 5).
  \item Pathway analysis of the peptides significantly (p<0.05) less phosphorylated upon \textit{ex vivo} sunitinib treatment (18 of 105) revealed sunitinib target involvement (e.g. VEGFR, PDGFR) (Fig. 7).
  \item \textit{Ex vivo} erlotinib, axitinib, crenolanib or crizotinib showed reversed inhibition patterns i.e. more inhibition in the non-responder than in the responder sample (Fig. 6).
\end{itemize}

Contact: ruijtenbeek@pamgene.com

This study has received funding from the European Union’s Seventh Framework Programme (FP7/2007-2013) under grant agreement no 259939.