Application of kinase activity profiles to predict upcoming TKI resistance in CML-patients

P.J. Boendera, J.J.W.M. Janssenb, L. Smitb, R. Ruijtenbeeka, A. van den Berga, R. de Wijna, G. Ossenkoppeleb, MD, PhD.
aPamGene International BV, 's-Hertogenbosch, the Netherlands, bVU University Medical Center, Amsterdam, the Netherlands

Study Design
Stored ("snapfrozen") mononuclear cell fractions, isolated by Ficoll-Paque centrifugation, of bone marrow of CML patients under continuous imatinib treatment and in various stages of their disease (see fig.1) were investigated. Samples of 15 imatinib sensitive and 13 imatinib resistant patients were tested on Tyrosine Kinase PamChip® Arrays (example data figure 2). The resulting data were analysed using the R-based package CMA ("Classification for MicroArrays") that enables the survey and evaluation of most usual classification methods with double cross-validation procedures.

Key Findings
We found differential kinase activity profiles in mononuclear cells from patients who became resistant vs. patients who remained sensitive (fig. 3). A model for prediction of resistance could be constructed. We used a Support Vector Machine (SVM) algorithm and data from 20 selected peptides, which demonstrated a sensitivity of 84% and a specificity 82%.

Differences in phosphorylation patterns as detected using PamGene’s peptide microarray technology with the aid of multivariate statistical analysis suggest the presence of an ongoing process in some CML-patients destined in due time to relapse in spite of continuous imatinib treatment independent of their BCR-Abl status.

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We regard these results to be a basis for further development of this kinase activity based test for response prediction to kinase inhibitors in CML patients. This opens new avenues into CML resistance research.

Background
Imatinib induces complete hematologic responses in virtually all patients, complete cytogenetic responses in almost 90% of patients and progression free survival in 83% of patients. Major molecular responses, attained by more than 60% of patients are durable. Unfortunately, not all patients achieve such a favorable response. Primary and secondary resistance develop in around 20% of cases. Predicting the development of this resistance would be of great clinical value.

Conclusion
Kinase activity profiles prepared with peptide arrays are a source of new information enabling prediction of CML patient prognosis under imatinib treatment.

References:
Boender P.J. et al., Paper $3425 and Poster presented at the ASH meeting 12-2010.