Blood-based multiplex kinase activity profiling as a predictive marker for clinical response to checkpoint blockade in advanced melanoma


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Background

- There is an urgent need for response prediction to checkpoint inhibitor therapies.
- A significant proportion of patients does not benefit from the treatment, agents are costly and may cause serious toxicity.
- Kinase activity of peripheral blood cells (PBMCs) may reflect biological mechanisms underlying response to immunotherapy.

Methods

- Kinase activity profiles were generated by analyzing phosphorylation signatures of PBMC lysates on a peptide micro-array.
- The PamChip (PamGene, Netherlands) microarray comprises 144 different peptides derived from protein phosphorylation sites that are substrates for protein tyrosine kinase activity.
- Predictive models were trained using Partial Least Squares Discriminant Analysis (PLS-DA) with log-transformed (anti-CTLA4 or anti-PD1) PamChip data. Predictive performance of the models was evaluated by estimating the Correct Classification rate (CCR) using cross-validation.
- Binary grouping in responder and non-responder to therapy (table 2) was based on REIST V1.1.

Results

- In a multi-center effort, data were prospectively collected from anti-CTLA4- or anti-PD1 treated advanced melanoma patients (n=143; table 1).

Conclusions

- Kinase activity profiles of PBMC samples prior to checkpoint inhibitor therapy can predict the likelihood of response to anti-PD1 or anti-CTLA4 therapy.
- This assay may serve as a rapid and fast predictive liquid biomarker to stratify patients prior to treatment.
- Replicate collection tubes display a stable kinase activity profile, whereas EDTA interferes with kinase activity over time.
- Results suggest the involvement of immune receptor kinases, underlying the mechanism of response to checkpoint inhibitor therapy.

References

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