Tyrosine kinase activity profiling as a predictive biomarker for clinical benefit to immune checkpoint inhibition in advanced melanoma and NSCLC

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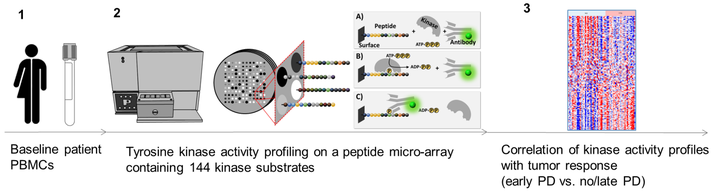
BACKGROUND

A substantial number of patients with cancer do not obtain clinical benefit from treatment with immune checkpoint inhibitors (ICIs). Previously, the potential role for tyrosine kinase activity profiles as a predictive biomarker for ICI response was shown [1,2]. In this ongoing multicenter prospective cohort study, tyrosine kinase activity profiles from peripheral blood mononuclear cells (PBMCs) are evaluated as a biomarker to predict tumor response to ICIs in patients with advanced stage melanoma or advanced stage non-small cell lung cancer (NSCLC).

METHODS

- 72 melanoma and 65 NSCLC patients treated with ICIs (first time)
- Classification analysis of the kinase activity profiles was based on binary grouping of patients with early progression vs. no/late progression and predictive performance was estimated using cross-validation
- Early progression was defined as progressive disease (PD) (RECIST v1.1) ≤24 weeks (melanoma cohort) and ≤12 weeks (NSCLC cohort)



REFERENCES

[1]D. Hurkmans et al. Blood-Based Multiplex Kinase Activity Profiling as a Predictive Marker for Clinical Response to Checkpoint Blockade in Advanced NSCLC. J. Thorac. Oncol., vol. 14, no. 10, p. S709, Oct. 2019.

[2]D. Hurkmans et al. Blood-based multiplex kinase activity profiling as a predictive marker for clinical response to checkpoint blockade in advanced melanoma. J. Clin. Onc, vol. 36, p. Suppl. Abstracts 9579, 2018.

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RESULTS

Significant differences in kinase activity between the early PD vs. no/late PD group were observed

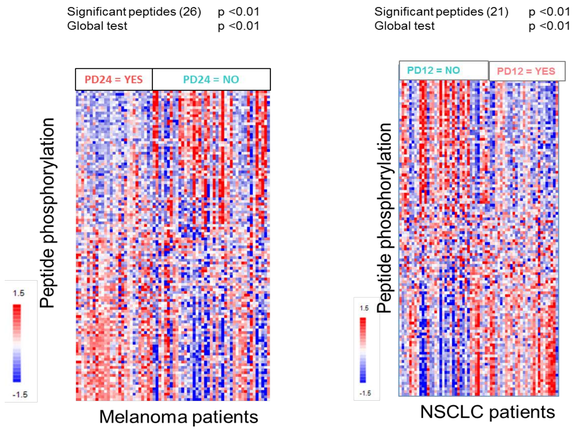

Figure 1. *Data visualization showing the correlation of the kinase activity profiles with PD. Rows represent kinase substrates. Columns represent different patients. The header indicates early progression (PD ≤24 weeks for melanoma (left) and ≤12 weeks for NSCLC (right)) after start of treatment with ICIs.*

A predictive model resulted in a correct classification rate of 71% (CI_{90}=61-80%) for the melanoma cohort and 70% for the NSCLC cohort (CI_{90}=59-79%)

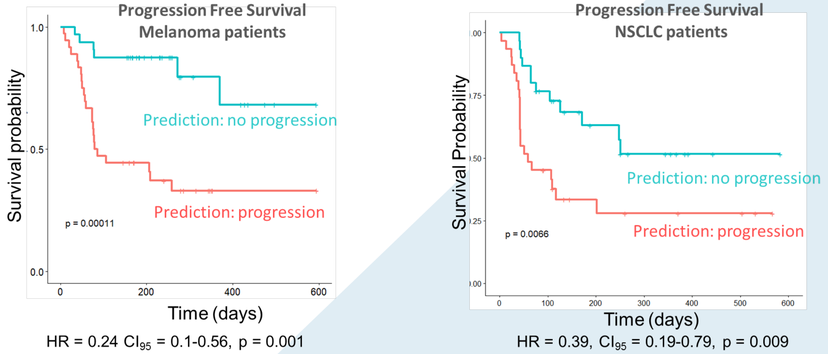

Figure 2. *Kaplan-Meier curves for the PFS (left melanoma, right NSCLC) based on the predicted late/no progression compared to early progression (≤24 weeks for melanoma and ≤12 weeks for NSCLC)*

Predictive performance may improve when combined with existing biomarkers. This is achieved when tyrosine kinase profile is combined with low tumor PD-L1 expression in NSCLC patients

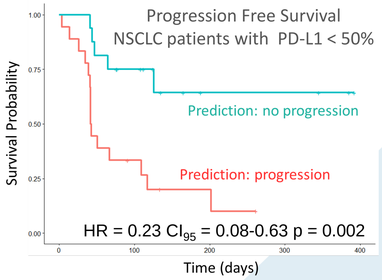

Figure 3. *Kaplan-Meier curves for the PFS based on the predicted late/no progression compared to early progression*

Baseline characteristics melanoma patients	
Age, *median (range)*	66 (56-74)
Sex, *n*	
Female	28
Male	44
Tumor stage, *n*	
IIIC	9
IV	63
Brain metastases for start treatment, *n*	
Yes	25
No	42
NA	5
LDH, *n*	
Normal (≤ 225 U/l)	43
1-2 ULN (226 - 450 U/l)	23
>2 ULN (≥451 U/l)	4
NA	2
WHO state	
0	41
1	27
2	4
Treatment regimen, *n*	
Nivolumab	36
Pembrolizumab	6
Nivolumab + Ipilimumab	30

Baseline characteristics NSCLC patients	
Age, *median (range)*	65 (58-71)
Sex, *n*	
Female	16
Male	49
WHO state	
0	12
1	51
2	2
PD-L1 expression, *n*	
<1%	17
1-49%	17
≥ 50%	28
NA	3
Primary tumor, *n*	
Adenocarcinoma	51
Squamous cell carcinoma	12
Large cell carcinoma	1
Other	1
Treatment regimen, *n*	
Nivolumab	29
Pembrolizumab	19
Pembrolizumab + chemotherapy	14
Other	3

Table 1: baseline characteristics of all melanoma patients (left, n=72) and all NSCLC patients (right, n=65)

DISCUSSION

- Kinase activity profiles discriminating between early PD vs. no/late PD are comparable between the melanoma and NSCLC cohort
- This blood based biomarker will be validated in an independent patient cohort

CONCLUSION

Tyrosine kinase activity profiling of baseline PBMCs can be used as a biomarker for prediction of early progression to immune checkpoint inhibitors in advanced stage melanoma and NSCLC patients

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K. de Joode has no conflicts of interest