1623 | RESPONSE AND SKIN TOXICITY RELATED PROTEIN SIGNATURE IN LATE STAGE MELANOMA PATIENTS AFTER ANTI-PD-1 TREATMENT

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INTRODUCTION

Skin toxicity after anti-PD1 treatment in melanoma patients is the most common type of immune related adverse events (irAEs) and has been associated with improved overall response rate and survival [1-3]. Nonetheless, not many mechanistic biomarkers have been identified so far, that could be associated with low-grade skin toxicity and good response rates. In order to address this need we have analyzed the proteome of 22 tumor samples from late stage melanoma patients receiving anti-PD-1 treatment as a first line treatment.

Figure 1: Cohort summary and survival analysis with regards to the response rate and skin toxicity

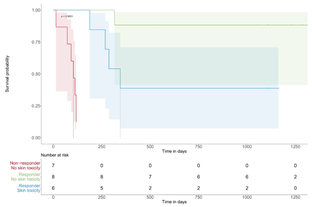
Skin toxicity is enriched (p-value < 0.05) in responder group defined as stable disease or better (**A**). Therefore, it has been used together with response for survival analysis (**B**).

Figure 1

A

		Non-responder	Responder	*p*-value
n		9	14	
Sex (%)	Female	6 (66.7)	5 (35.7)	0.31
	Male	3 (33.3)	9 (64.3)	
BRAF mutation (%)	Yes	2 (22.2)	5 (35.7)	0.82
	No	7 (77.8)	9 (64.3)	
LDH range (%)	135-225	2 (22.2)	10 (71.4)	0.06
	240-480	7 (77.8)	4 (28.6)	
Metastasis (%)	M0	1 (11.1)	0 (0.0)	0.37
	M1A	1 (11.1)	5 (35.7)	
	M1B	1 (11.1)	2 (14.3)	
	M1C	6 (66.7)	7 (50.0)	
Skin toxicity (%)	**Yes (grade ≤ 2)**	**0 (0.0)**	**8 (57.1)**	**0.03**
	No	**8 (100.0)**	**6 (42.9)**	
Treatment (%)	Nivolumab	8 (88.9)	9 (64.3)	0.41
	Pembrolizumab	1 (11.1)	5 (35.7)	

B



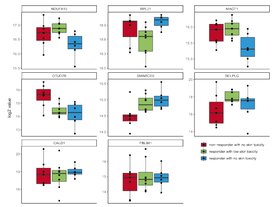
CONCLUSIONS

- **Low grade skin toxicity in melanoma patients treated with ant-PD-1 could be used as an additional response marker.**
- **Application of HRM™-MS technology for tissue samples yields unprecedented depth and allows for identification of response and toxicity related signatures.**
- **Proteomic and transcriptomic analysis provide a comprehensive picture of changes upon immune checkpoint inhibitor therapy and can be used for novel target selection.**
- **Identified minimal proteomic panel was sufficient for separation of subjects to non-responders, responders and responders with low grade skin toxicity.**
- **Identified proteins were mostly related to vesicle related transport, metabolism, inflammation and immune response.**

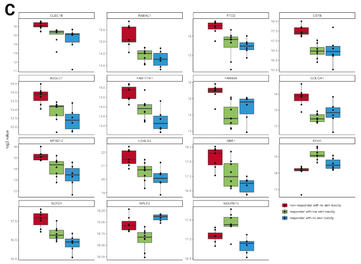
RESULTS

Figure 2

A



C



B

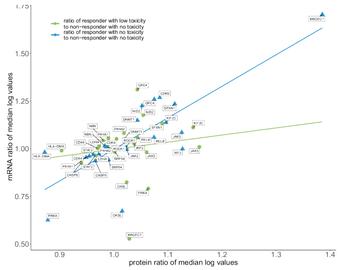


Figure 2: Selection of protein signature corresponding to response and skin toxicity

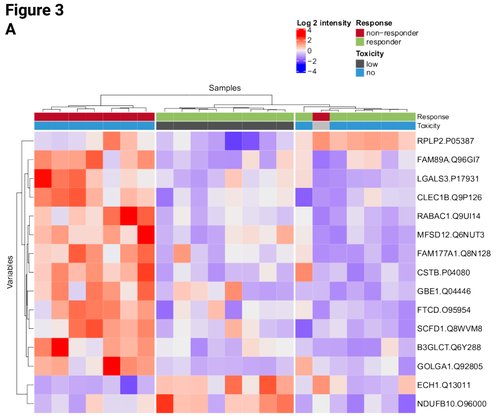
More than 8500 proteins were quantified across all samples. In order to identify the most relevant proteins for response and skin toxicity a supervised multivariate classification method was applied [4]. In total 899 proteins showed association with no response, response or response with low grade skin toxicity. Among these, eight were shared with the prognostic melanoma signature from The Human Protein Atlas [5] (**A**) and 23 were also measured using the PanCancer IO 360 panel (**B**). Proteins like JAK3 revealed similar trend between median protein and mRNA ratios to non-responders with no toxicity, however, others like MAGEC1 showed striking differences, pointing to important disease and response mechanics in mRNA and protein balance. Finally, the initially reported minimal predictive panel with 21 proteins was further optimized and reduced to 15 proteins (**C**).

Figure 3: Unsupervised clustering of subjects using the minimal panel

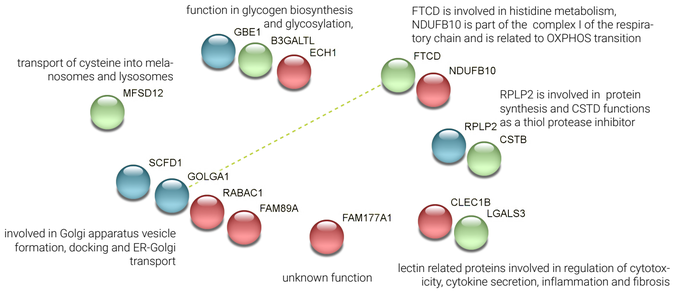
Unsupervised hierarchical clustering was successfully used to investigate if the selected proteins were able to group subjects into classes used for signature identification (**A**). STRING[6] analysis of the selected protein signature, with k-mean clustering indicated by color, shows a potential link between GOLGA1 and FTCD protein (**B**). Proteins are grouped based on functional similarity.

Figure 3

A



B



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[1] Nakamura, Biomarkers for Immune Checkpoint Inhibitor-Mediated Tumor Response and Adverse Events. Front Med. (2019) [2] Pavan et al., Circulating biomarkers and risk of immune-related adverse events (irAEs) in patients (pts) with advanced non-small cell lung cancer (aNSCLC) and metastatic melanoma (mMel). Annals of Oncology. (2019) [3] Gulati et al., Revisiting the association between skin toxicity and better response in advanced cancer patients treated with immune checkpoint inhibitors. J Transl Med. (2020) [4] Le Cao et al., mixOmics: Omics Data Integration Project. (2016), R package version 6.1.1. [5] Uhlen M et al., A pathology atlas of the human cancer transcriptome. Science. (2017), http://www.proteinatlas.org [6] Szklarczyk et al., STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Research. (2019)