**Figure Captions**

**Fig. 1:** **Workflow of the nested cross-validation approach.** cvAUC: cross-validated area under the curve. cv: cross validation.

**Fig. 2:** **Log-2 miRNA expression in melanoma patients grouped by immunotherapy response.** Expression has been determined by FirePlex®-assay. Crossbars show mean ± sd. Statistics: unequal variances t-test (Welch’s t-test). Grey: Non-responder. Blue: Responder. \*: p<0.05.

**Fig. 3:** **Log-2 serum marker concentration.** Crossbars show mean ± sd. Statistics: unequal variances t-test (welch’s t-test). Grey: Non-responder. Blue: Responder. CRP: c-reactive protein. LDH: lactate dehydrogenase. \*: p<0.05; \*\*: p<0.01; \*\*\*: p<0.001.

**Fig. 4:** **Development of a machine learning model. (A):** *Model selection based on cvAUC.*Calculation of cross-validated AUC as described in the workflow passage (Fig. 1). Blue dots indicate the mean cvAUC for each model. Error bars indicate 95% confidence intervals. (**B):***Model evaluation in the outer loop of nested cross validation.*Application of the *relaxedLasso* model on the test set in the outer loop resulted in different performances in each iteration (grey lines). Red dottet line: random classifier. Blue line: combined ROC curve for the cross validation process. AUC: area under the curve. Values in parentheses indicate 95% confidence interval for the AUC. (**C):** *Feature importance in the feature selection process.*Features used in more than 50% of the iterations in the first LASSO regression were considered important. Grey: features below the 50% threshold. Blue: features above the 50% threshold. Red dotted line indicates 50%. Significantly changed features are depicted in red.