Development and validation of baseline predictive biomarkers for response to immuno-checkpoint treatments in the context of multiline and multitherapy cohorts using EpiSwitch™ epigenetic profiling

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INTRODUCTION

• The EpiSwitch biomarker discovery platform detects systemic changes in the cellular-genomic architecture using a technology and FDA-approved biomarker platform (Figure 1). It identifies and monitors chromosome conformation significance (CCS), key regulatory properties that integrate environmental cues and genetic alterations into the genomic regulatory machinery.

• CCSs are also known as gene loops, chromosome domains, or long-range interactions.

• CCSs have low off-rates and only change when a physically signaled transition to a new phenotype occurs or because of genetic alterations. They can be measured in changes in other cellular entities, such as DNA methylation and histone and protein expression.

• We profiled patients with non-small cell lung cancer (NSCLC) and melanoma treated with antibodies (anti-PD-1 and anti-PD-L1) or pembrolizumab in combination with chemotherapy to discover baseline and predictive biomarkers.

• This work was sponsored by Merck KGaA, Darmstadt, Germany, and Pfizer Inc., New York, NY, USA.

METHODS

• The classifiers were generated in 2 steps using a random cross-validation:
  - Step 1: identification of unstable association between biomarkers and response using Fisher exact test
  - Step 2: generation of multivariate model using XGBoost or regularized logistic regression

• A multivariate Cox proportional hazards model was built using 8 survival parameters supplemented with smoking history.

RESULTS

• The 3 NSCLC classifiers built using baseline profiles of overkilled treated patients achieved good generalization performance for predicting response in 1L and 2L patients. However, the composite classifier had unstable classification performance for predicting response in 1L NSCLC (see poster #F12).

• There was a significant difference in log-rank (P < 0.001) in progressive new survival (PFS) and overall survival (OS) between the predicted test response groups (Figure 2).

• This survival difference was not observed with PD-L1 when patients were stratified at different thresholds of PD-L1 positivity (Table 1) and in a multivariable logistic regression model (data not shown).

• Pembrolizumab + azacitidine demonstrated that:

• Pembrolizumab alone or pembrolizumab + pembrolizumab (PD-L1 ≥80%) showed a good overall survival (OS) when patients were stratified at different thresholds of PD-L1 positivity (Table 1) and in a multivariable logistic regression model (data not shown).

• The composite classifier had independent predictive power when assessing the content of multivariable Cox proportional hazards model (Table 2) and a multivariable logistic regression model (data not shown).

• Future work:

• Apply the classifiers to a broad independent test set that reflects real-world populations of a clinical trial and that also has a compensatory arm.

CONCLUSIONS

• Profiling patients who received overkilled or pembrolizumab with pembrolizumab demonstrated that:
  - It is possible to derive predictive signatures from baseline patient profiles that are applicable across agents with similar mechanisms, treatment lines, and indications.
  - The biomarkers assigned by the EpiSwitch platform had high effect size because the testing process requires a small number of samples to train the signatures were stored and used, provided good generalization on test sets with high accuracy, and had independent predictive power.

• The single-arm design did not allow differentiation between the prognostic and predictive values of the classifiers.

• Future work:

• Apply the classifiers to a broad independent test set that reflects real-world populations of a clinical trial and that also has a compensatory arm.

• We also demonstrated that classifiers could be built with powerful predictive performance across indications and combination treatments (Figure 4).

• As observed in the overkilled and pembrolizumab 3 NSCLC datasets, the pembrolizumab monotherapy and combination treatment had better performance, suggesting potential differences in nonresponsive patients (Figure 5).

REFERENCES

5. Merck KGaA, Darmstadt, Germany, and Pfizer Inc., New York, NY, USA.

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Figure 1. EpiSwitch biomarker methodology: from discovery to clinical assay

Figure 2. Generation of indication-agnostic NSCLC classifier

Figure 3. OS plots for classifier predictions

Figure 4. Survival plots for PD-L1 subgroups

Figure 5. Application of monotherapy signatures to predict response across indications and for treatment combinations

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