TUMOR AGNOSTIC CD8 IMMUNE-PHENOTYPE RELATED GENE SIGNATURE DEFINES CLINICAL OUTCOME ACROSS EARLY AND LATE PHASE CLINICAL TRIALS

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Background A key question in cancer immunotherapy is the general immune status of the patient’s tumor-microenvironment prior to therapy. The patient’s underlying tumor immune-contexture may therefore a) guide the therapeutic intervention and b) help to identify potential resistance mechanisms to immune-therapies. The most commonly used classification of the patients’ immune status is based on the CD8 tumor infiltrating lymphocytes status referring to either ‘cold’ or ‘hot’ tumors.

Methods In this study, we systematically analyzed the CD8 immune-phenotype in 628 patients from 11 Phase 1 clinical trials using immunohistochemistry (IHC) and matched gene expression profiling by RNA-seq. The CD8 immune-phenotype was classified by pathologist assessment into cold (CD8 deserts) and hot (CD8 excluded and inflamed) tumors using CD8+/Ki67+ IHC staining in epithelial and stromal areas of the tumor.

Results In total, we observed 193 inflamed, 144 excluded, and 291 desert CD8 immune-phenotype from 49 different indications. The main source of tumor biopsy tissues was liver metastasis (N=174), lymph node (N=51) and lung tumor tissue (N=69). Further, we developed a RNA-seq based classification as a surrogate to the IHC based CD8 immune-phenotype classification. Using regularized logistic regression (ElasticNet), we identified a 92 gene signature that accurately predicts the CD8 immune-phenotype in primary and metastatic samples (AUC inflamed = 0.846; AUC Excluded = 0.712; AUC Desert = 0.853). Using our new gene signature, we demonstrate prolonged overall survival (ORR) of patients with CD8 inflamed tumors across The Cancer Genome Atlas (TCGA; Hazard-Ratio 0.89; 95%CI [0.80–0.98]) as well as a better ORR to Checkpoint inhibitors (CPI) in the randomized Phase III OAK study in Non-Small-Cell lung cancer patients (Hazard-Ratio 0.75; 95%CI [0.58–0.97]).

Conclusions In summary, we identified a novel prognostic and predictive gene signature accurately predicting the IHC based CD8 immune-phenotype in primary and metastatic tumor samples. Survival analysis indicated that the predicted CD8 inflamed phenotype results in prolonged survival in independent patient cohorts. Our analysis provides important insights and a new precision immune phenotyping tool to characterize the impact of the tissue origin with regards to the tumor microenvironment. The new signature enables multiplex analyses and may be used for retrospective, reverse translation approaches as well as for prospective patient enrichment to identify resistance mechanisms to cancer immunotherapy.

Ethics Approval All patients provided written informed consent. The trials were approved by each center’s ethics committee or institutional review board and were performed in compliance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice.