

Clinical response to the MAGE-A3 immunotherapeutic in metastatic melanoma patients is associated with a specific gene profile present prior to treatment

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Abstract

patients with a higher likelihood of response to MAGE-A3 ASCI treatment.

Objectives

Gene expression profiling by microarrays is used to identify biomarkers predictive of the observed clinical activity of the MAGE-A3 Antigen-Specific Cancer Immunotherapeutic (ASCI) recorded in a Phase II study in metastatic melanoma (EORTC 16032-18031).

Clinical activity to MAGE-A3 ASCI treatment in metastatic melanoma patients and a gene signature discriminating between clinical benefit and non clinical benefit patients were previously demonstrated (ASCO 2008). The predictive signature improved significantly the median time to treatment failure (2.3 months in the GS (-) and 10.3 months in the GS (+) population.

Here we report on a new improved classifier to select patients with a higher likelihood of clinical response to treatment.

Methods

75 patients with progressive, unresectable stage III or stage IV M1a MAGEA3 (+) melanomas, were randomized as 1st line therapy between immunization with MAGE-A3 recombinant protein combined with GSK Adjuvant Systems AS15 or AS02B. Gene expression profiling was performed on tumor biopsies taken prior to any immunization.

Results

Supervised classification experiments were conducted on a subset of 62 patients. A multivariate gene selection process was embedded in the estimation of a mathematical predictive model (linear support vector machine). Using bootstrap resamplings, gene selection was repeated on 30 independent sample sets. A final gene signature of 33 probes was derived from genes appearing most frequently after the various resamplings. The vast majority of the identified genes are immune-related. The final classifier correctly predicts clinical response with 91% sensitivity, 95% specificity and 91% positive predictive value. These performances were estimated on new independent resamplings of the same data.

Conclusions

The gene signatures found in metastatic melanoma patients are strongly correlated with the response to the MAGE-A3 ASCI treatment, reflecting an immune microenvironment in the tumor present prior to any therapeutic intervention. Such signatures and associated classifier could be used to select