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Identification of new prognostic biomarkers for Stage III metastatic melanoma patients

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Accurately predicting disease outcome among patients bearing Stage III metastatic melanoma is complex. However, current advances in personalized medicine call for ever more precise prognostic assessments, as these have a significant impact not only on the design and analysis of clinical trials, but also on therapeutic decision-making.

Prior to 2010, a few treatment options (and no effective systemic therapy) were available for patients with metastatic melanoma. Since then, clinical trials have demonstrated the efficacy of a number of new systemic treatments for metastatic melanoma patients, generating some optimism for the future. Targeting the mitogen-activated protein kinase (MAPK) signaling pathway has proven effective in advanced stage patients bearing $BRAF^{V600}$-mutant melanoma. In particular, BRAF and MEK inhibitors employed as standalone therapeutic interventions have been shown to significantly improve progression-free survival, and combinatorial therapies were even more effective.[1] Novel immunotherapeutic agents such as anti-CTLA4 (ipilimumab) and anti-PD1 monoclonal antibodies, which enhance antitumor immune responses by blocking the immunosuppressive effects of regulatory T cells, have also been shown to induce durable clinical responses in patients with metastatic melanoma.[2,3] Now that these therapeutic approaches have proven to be effective in patients bearing systemic disease, an important question is whether or not they will also be efficient when administered in an adjuvant setting to patients with high risk, clinically localized primary melanoma or bearing metastases in regional lymph nodes only.

The current version of the American Joint Committee on Cancer (AJCC) Melanoma Staging System (as of 2010) was based on the analysis of prognostic factors in a large number of melanoma patients treated in centers throughout the world. It is fundamental for clinical trials that patients are accurately stratified according to risk. Otherwise, possible clinical benefits to patients from a specific risk group may be masked by a "dilution" effect, originating from patients in whom the therapy was poorly effective. However, melanoma patients exhibiting highly variable disease outcomes even within individual AJCC staging subcategories.[4] With the aim of identifying ever more accurate prognostic biomarkers in patients with AJCC Stage III melanomas, we recently performed a comprehensive clinical, pathologic, and molecular analysis of a cohort of such patients for whom long-term clinical follow-up data were available. Multivariate analyses revealed that various clinical and pathological factors including disease Stage II at presentation, the presence of a nodular component in the primary lesion, a reduced cell size, and pigmentation within nodal metastases and the absence of *BRAF*/*NRAS* mutations were all independent predictors of improved disease outcome. In addition, our study identified a gene expression signature involving 46 distinct transcripts that was independently associated with good clinical outcome (**Fig. 1**). Of note, this immune-related gene signature was also associated with good prognosis in 2 independent AJCC Stage III melanoma patient cohorts.

Perhaps the most advanced use of prognostic gene expression signatures in a clinical setting involves breast carcinoma. In this scenario, the Oncotype Dx® RT-PCR assay (Genomic Health Inc.) is being used to identify patients with estrogen receptor-positive (ER^+) and lymph node-negative lesions that are at high risk of distant recurrence, and hence who may benefit from systemic therapy. However, there is some skepticism on whether such signatures actually enhance clinical decision-making, fully justifying their costs. The combined prognostic model developed from our data performed better in predicting disease outcome than any single variable taken alone.[5] As this and similar models are refined, for instance by the addition of expanded somatic mutation profiles, the rates of classification errors are likely to decrease further. Of note, these rates are already superior to those of prognostic assessments based on AJCC criteria only, at least among Stage III melanoma patients. It would be reasonable to begin testing in a prospective fashion how well these models inform clinical decision-making procedures and using

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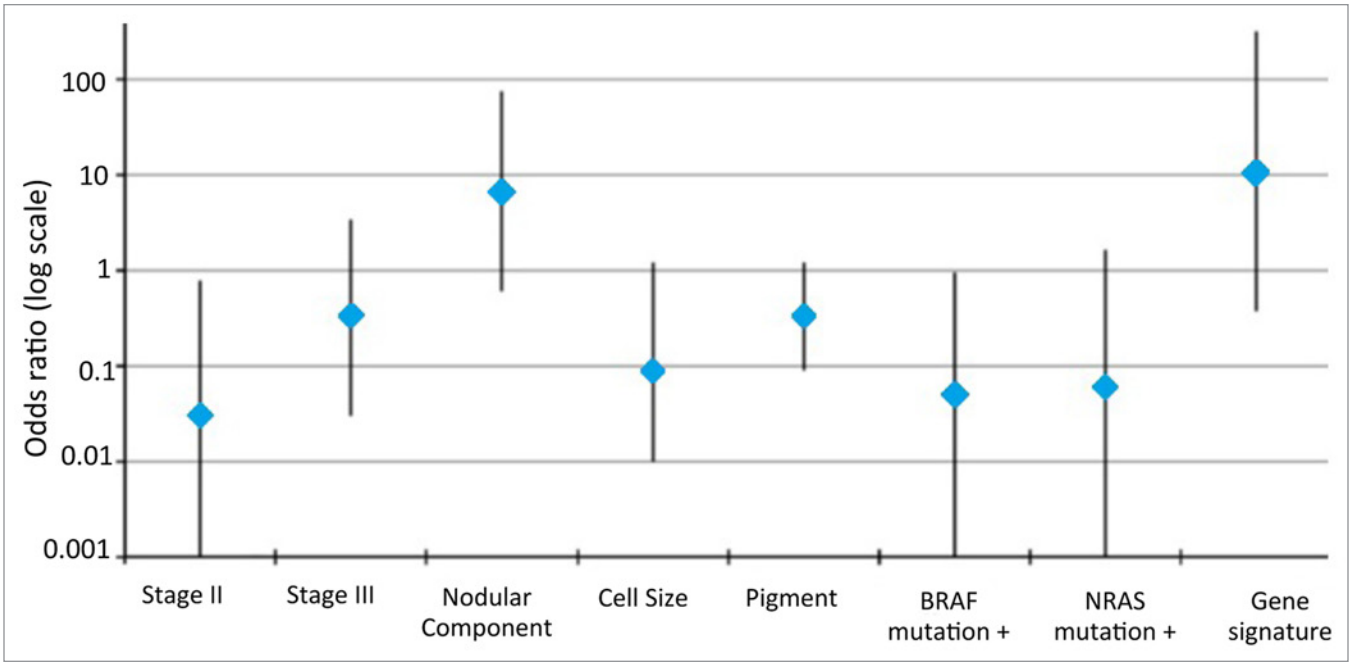

Figure 1. Factors independently associated with melanoma-specific survival fewer than 4 y on multivariable logistic regression analyses among AJCC Stage III patients. Data are presented as odds ratios with 90% confidence interval. Cell Size, large cell size in nodal metastases; Nodular Component, presence of a nodular component in primary lesions; Pigment, high degree of pigmentation in nodal metastases; Stage II, AJCC Stage II at presentation; Stage III, AJCC Stage III at presentation. Figure modified with permissions from Mann et al.[5]

them for the analysis of results from clinical trials. These or additional biomarkers might help clinicians to identify patients that are most likely to develop regional field node relapse upon surgery or relapse following surgery and radiotherapy. Recently, a randomized clinical trial involving 217 melanoma patients with high-risk regional node field disease demonstrated that adjuvant radiotherapy significantly improves regional node field control as compared with surgery alone ($P = 0.041$).[6] In a similar context, the identification of novel prognostic biomarkers may assist clinicians in the selection of patients for adjuvant radiotherapy, identifying those who are unlikely to obtain therapeutic benefits from the procedures, in whom potential side effects can be avoided.

Our results also highlight the importance of the interactions between melanoma cells and the immune system. We have previously shown that the intensity and distribution of an immune response (based on the number and localization of tumor-infiltrating lymphocytes) against primary melanomas strongly predict disease outcome.[7] The gene expression signature associated with improved prognosis in Stage III melanoma patients contained a predominance of immunological components, further substantiating the critical influence of immune responses on disease progression. The important role of the immune system in this context is also well exemplified by the so-called abscopal effect. Thus, a patient who had progressed on ipilimumab was treated with radiotherapy and not only the irradiated tumor, but also distant lesions responded.[8]

As we embark upon an exciting new era of expanding treatment options, it is imperative to utilize existing biomarkers and identify new ones that enable the prognosis of individual patients with metastatic melanoma to be determined ever more accurately. Only these building blocks will allow us to ensure that the most appropriate treatment is given to individual patients at the most suitable time, hence providing them with the best chances of a definitive cure.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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