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Predictive and on-treatment monitoring biomarkers in advanced melanoma: Moving toward personalized medicine

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ABSTRACT

The treatment armamentarium for patients with metastatic melanoma has increased substantially over the past decade with the regulatory approval of targeted BRAF + MEK inhibitors and immune checkpoint inhibitors, which have vastly improved long-term outcomes. Recently, these advances have been rapidly translated to the high-risk adjuvant setting. Primary and acquired resistance to both immune and molecularly targeted agents, however, remains a challenge. Therefore, biomarkers predictive of response to therapy that can be assessed prior to initiation of treatment and early during the course of therapy are critical. Equally important is on-treatment biomarker monitoring that may predict the likelihood of treatment failure and disease relapse. This review will summarize recent advances in the understanding of biomarkers for patients with advanced melanoma, emphasizing emerging baseline predictive factors and on-treatment monitoring of biomarkers that aim to establish truly personalized treatment.

Introduction

Melanoma incidence is increasing globally, with 351,880 cases reported in 2015 [1]. In the United States alone, an estimated 91,270 new cases and 9320 deaths were predicted in 2017 [2]. The treatment of unresectable or metastatic melanoma has been transformed by the introduction of novel molecularly targeted and immune therapies [3–6]. The discovery of driver oncogenes has facilitated the clinical development of targeted therapies, ushering in the era of personalized medicine. In melanoma, this has been exemplified by the success of agents targeting BRAF and downstream MEK proteins in patients with activating *BRAF* mutations [7–11]. Furthermore, immune checkpoint inhibitors, including anti–cytotoxic T-lymphocyte–associated antigen 4 (anti–CTLA-4) and anti–programmed death 1 (anti–PD-1) inhibitors, have demonstrated substantial benefit as treatment options for patients with melanoma, regardless of their oncogenic driver mutation status [12–14]. For example, recent 5-year overall survival (OS) results from a phase 2 trial of patients with *BRAF* V600–mutant unresectable or metastatic melanoma treated with dabrafenib + trametinib demonstrated a median OS of 25.0 months and a 5-year OS rate of 28% in patients receiving the approved label dose [15]. Similar results have been observed in patients treated with anti–PD-1 monotherapy or a combination of anti–PD-1 and anti–CTLA-4 agents. A recent OS analysis of the phase 3 KEYNOTE-006 trial showed a 33-month OS rate of 50% in patients receiving pembrolizumab monotherapy [16]. In the phase 3 CheckMate 067 trial, patients treated with nivolumab monotherapy or nivolumab + ipilimumab had 3-year OS rates of 52% and 58%, respectively [14].

Despite the increases in 5-year OS with these new agents, many patients still do not achieve long-term disease remission and control [14,15]. Primary and acquired resistance remains a major barrier to successful melanoma treatment and, ultimately, long-term remission. Patients are considered to have primary resistance to therapy when no clinical benefit is observed following treatment. This form of resistance also includes hyperprogressive disease in which patients experience ≥2-fold increase in tumor growth rate and worsening clinical status [17–19]. Acquired resistance differs in that disease progression occurs after a period of tumor response. Although the rate of primary resistance to targeted agents in patients with *BRAF* V600–mutated melanoma is very low, approximately half of patients will develop acquired resistance to combination BRAF + MEK inhibition within 9–12 months [10,11]. Conversely, although immune checkpoint inhibition can produce durable outcomes in some patients, the rate of primary resistance within the first 6 months is relatively high [20,21].

Understanding the biology behind these clinical outcomes will be key to personalized therapy. It is paramount that clinicians determine the optimum treatment for each patient, using biomarkers that may guide the targeting of a specific therapeutic agent toward those who

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have the capacity to respond while saving others the burdens of unwanted toxicities and costs in the absence of predicted benefit. At present, validated biomarkers predictive of response to available therapies are limited to *BRAF* mutation status and remain a critical need to aid in treatment selection [22]. Emerging technological advances combined with a growing knowledge of tumor biology present the opportunity to evaluate on-treatment markers that could help to predict outcomes, provide an early indication of response or progression, and aid in the understanding of therapeutic resistance.

The present review will summarize recent advances in the understanding of biomarkers for melanoma, with an emphasis on emerging baseline predictive biomarkers and on-treatment monitoring that could help shape the future of personalized melanoma treatment.

Biomarkers in melanoma

Biomarkers may be either prognostic or predictive in nature (Fig. 1). A prognostic biomarker provides insight into the overall disease outcome of a patient but does not predict the likelihood of benefit from a treatment. Predictive biomarkers, on the other hand, provide insight into the probability of therapeutic response of a patient's disease to a particular treatment.

The earliest clinical markers that helped to inform prognosis were based on baseline clinical characteristics, including serum levels of lactate dehydrogenase (LDH), a marker of tumor burden [23]. In its role to catalyze pyruvate into lactate, LDH can be a marker of cancer metabolic activity and increased glucose uptake by tumor cells highly dependent on the anaerobic glycolytic pathway [24]. LDH has been shown to be a negative prognostic marker, regardless of treatment received, even with modern-age therapies [15,25–28]. Elevated LDH is traditionally associated with poor OS compared with normal LDH and is an important marker in determining staging of patients with distant metastases in the American Joint Committee on Cancer (AJCC) staging system of melanoma [29]. Of the approximately 30% of patients with long-term survival (4–5 years following treatment initiation) on BRAF + MEK inhibitors, few had high LDH prior to starting therapy [15]. Similar to serum LDH, levels of S100B in the serum have consistently demonstrated prognostic value in both the metastatic [30,31] and high-risk resected settings [32]. Gene expression profiling, while still in its infancy, has shown some validity as a prognostic biomarker assay that may complement existing techniques in patients with melanoma [33–35].

Biomarkers predictive for response to therapy aid in clinical decision making and provide an evidenced-based rationale to inform treatment decisions. The most notable and well-characterized predictive biomarker in patients with metastatic melanoma is the presence of a *BRAF* V600 mutation, which is highly predictive for response to BRAF ± MEK inhibition with low rates of primary resistance [7,8,11]. Response to BRAF + MEK inhibitors is approximately 70% in selected patients, with < 10% of patients having a best response of progressive disease [11,36–38].

Additional oncogenic driver mutations have been described that could be predictive of benefit from targeted agents (eg, *NRAS*, *NF-1, c-KIT*) [39–43]. Nevertheless, *BRAF* V600 mutation remains the only validated predictive marker for patients with melanoma; however, several other markers are currently being evaluated in clinical studies that may one day help inform treatment decisions.

Emerging predictive biomarkers

Evidence is emerging for the potential predictive value of several biomarkers for response to or progression on either targeted therapy or immune checkpoint inhibition.

Targeted therapy

Multiple baseline analyses have demonstrated that patients with *BRAF* V600E mutations often have concomitant molecular alterations in other genes that may predict response to therapy [44,45]. For example, overall mutation burden, which has been linked to neoantigen formation and enhanced tumor immunogenicity [46], was associated with longer OS in patients treated with dabrafenib + trametinib and a trend toward longer OS in patients treated with vemurafenib + cobimetinib [44,45]. In terms of specific genes, mutation and deletion of the tumor suppressor gene *CDKN2A* were significantly associated with poorer OS and progression-free survival (PFS) in patients treated with dabrafenib + trametinib [44]. Two further potential markers were identified in the coBRIM trial of vemurafenib + cobimetinib: immune response

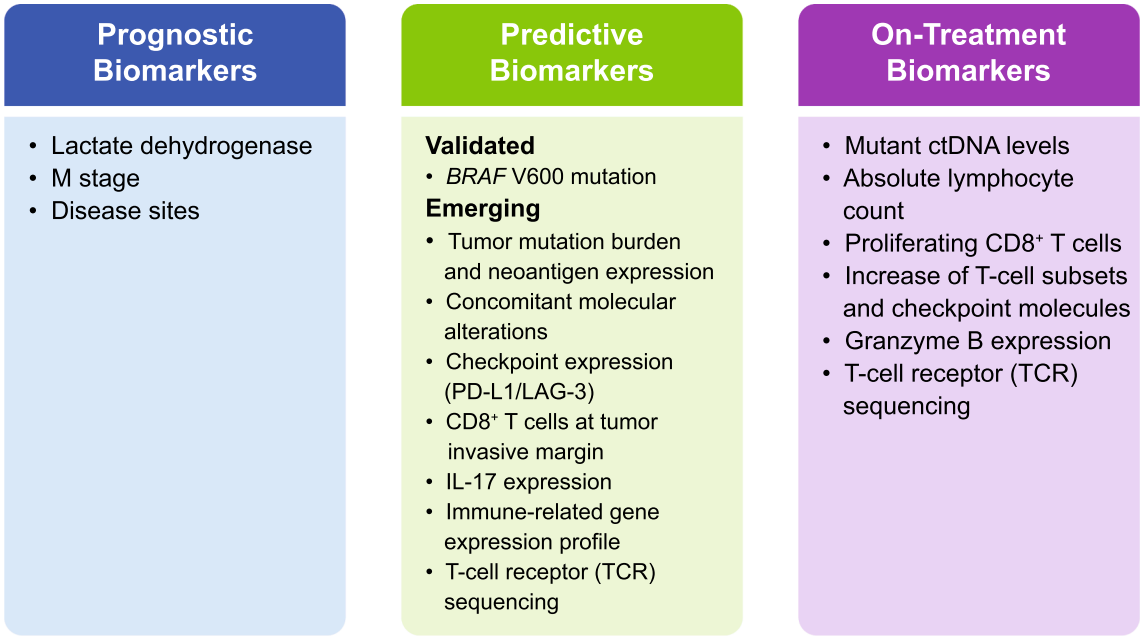

Fig. 1. Prognostic, predictive, and on-treatment biomarkers in metastatic melanoma. ctDNA, circulating tumor DNA; IL, interleukin; LAG-3, lymphocyte-activation gene 3; PD-L1, programmed death-ligand 1.