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Systemic therapy for previously untreated advanced *BRAF*-mutated melanoma: navigating a shifting landscape

“Given the rapid changes in [*BRAF*-mutated melanoma], with promising treatment options on the horizon, head-to-head trials examining efficacy, safety and cost-effectiveness will be crucial for treatment and funding decisions in the future.”

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Treatment of advanced cutaneous melanoma has rapidly evolved over recent years. This aggressive form of skin cancer, when not amenable to surgical resection due to locoregional or distant spread of tumor, has been associated with very poor prognosis [1]. Until recently, advanced melanoma was considered a fatal diagnosis with very few exceptions. Historically, high-dose IL-2 was offered to highly selected patients with limited comorbidity and excellent functional status for a small chance of durable disease control; however, this therapy is associated with severe, sometimes, life-threatening toxicity [2]. Cytotoxic chemotherapy was the standard of care for decades despite a lack of evidence indicating survival benefit [3].

Two major advances in this field have revolutionized the treatment landscape. With the development of molecularly targeted agents and immunotherapies, chemotherapy has largely been replaced as a first-line systemic treatment. Mutation in the *BRAF* (V600) gene has been identified as a highly prevalent oncogene leading to constitutive activation of the RAF/MEK/ERK cell signaling pathway [4]. Present in 40–60% of cutaneous melanoma cases [4,5], the protein product of this oncogene can be selectively targeted to arrest malignant cell growth. Targeted therapeutic agents including the tyrosine kinase inhibitors vemurafenib and dabrafenib have shown significant antineoplastic activity and

clinical benefit for patients with advanced, *BRAF*-mutated melanoma [6,7]. Clinical responses with these small-molecule agents, however, are of limited duration, in part due to reactivation of the MAPK pathway leading to drug resistance [8]. Additionally, secondary skin malignancies can develop due to paradoxical activation of this pathway in cells with nonmutated *BRAF* [9]. Specific inhibitors of the MEK protein (which lies downstream of *BRAF*) including trametinib and cobimetinib have been developed, and the former has shown some clinical benefit as monotherapy [10]. The combination of *BRAF* and MEK inhibition, as compared with single-agent inhibition, has shown prolonged responses by delaying drug resistance and decreased incidence of skin-related adverse events [8,11]. Thus, the repertoire of targeted therapies has expanded.

The second breakthrough was the discovery of immune-checkpoints or co-regulatory molecules responsible for dampening immune response. Mechanisms to suppress T-cell activation are important to avoid autoimmunity after an infectious insult, yet these protective mechanisms can be exploited by tumor cells to avoid immune attack. In fact, immune evasion is now recognized as one of the hallmarks of cancer. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell-death protein 1 (PD-1) have been characterized as important immune-checkpoints [12,13].

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Immunomodulatory monoclonal antibodies have been developed to interfere with the activity of CTLA-4 (ipilimumab and tremelimumab) and PD-1 (nivolumab and pembrolizumab), allowing T-cell activation and proliferation with anticancer effect. These therapeutic agents have shown survival benefit for advanced melanoma regardless of *BRAF* mutation status [14,15]. Monotherapy with an immune-checkpoint inhibitor has improved survival compared with chemotherapy [16]. The combination of CTLA-4 and PD-1-directed therapy compared with monotherapy has shown promise in early outcomes, and overall survival data are eagerly awaited [17].

The development of targeted and immune-checkpoint inhibitors for advanced melanoma has occurred in parallel. Numerous novel treatments have shown clinical benefit in high-quality randomized controlled trials (RCTs), and many have entered routine clinical practice after receiving regulatory approval. For treatment-naïve patients with advanced *BRAF*-mutated melanoma, there are now multiple effective treatment options available. The lack of head-to-head comparisons between targeted and immunotherapies, however, has left patients and clinicians without evidence to inform decisions on optimal first-line systemic treatment.

In some circumstances, clinical factors dictate treatment choice. For example, in the face of rapidly advancing visceral disease, high disease-related symptom burden or poor performance status due to tumor burden, targeted therapy may be favored for rapid disease stabilization [18]. Clinical experience has shown that such patients can experience swift recovery, but tumor response may be short-lived. In these patients, immunotherapy is not ideal because response is expected to have slower onset. Additionally, there is risk of pseudoprogression with tumors temporarily increasing in size before response occurs [19]. In the setting of brain metastases, small-molecule targeted therapies were thought to cross the blood–brain barrier more easily than monoclonal antibodies and, therefore, targeted therapies were previously favored over immunotherapies in this patient population. Mounting evidence suggests both targeted and immune-checkpoint inhibitors can be effective in this setting, contributing to the uncertainty in choosing first-line treatment for this group of patients [20,21].

In the absence of a compelling clinical circumstance to guide choice of treatment, patient-important factors must be considered. Targeted therapies are oral medications taken continuously until progression with the potential to impair quality of life due to daily side effects including skin-related adverse events, fatigue and fever. Immune-checkpoint inhibitors,

administered as intermittent infusions, may not cause daily symptoms and side effects, but have the potential to cause severe autoimmune toxicities, most notably, colitis. With more widespread use of such agents, a wide variety of immune-related adverse events have been documented, affecting almost any organ system in the body. Such toxicities often have delayed onset and can be life-threatening if not identified and managed appropriately [22].

Despite the toxicity risk, there has been much excitement about the durable remissions seen with use of immunotherapies. Around one in five patients seems to achieve long-term disease control with use of ipilimumab [23], and it is hoped that combined CTLA-4/PD-1-directed treatment will further improve patient-important outcomes. This represents a major paradigm shift for prognostication of advanced melanoma. Moreover, the unprecedented survival outcomes for melanoma patients have contributed to the fervor with which immune-checkpoint inhibitors are being tested in other cancer types. Successes have already been achieved in non-small-cell lung cancer, urothelial bladder cancer and renal cell carcinoma, among other tumor types [24–26]. Many trials are currently underway which could lead to additional new indications for immune-checkpoint inhibitors. With respect to *BRAF*-mutated melanoma, however, recently published long-term data from early clinical trials suggest that a proportion of patients treated in first line with targeted therapy also achieved durable disease control, adding to the uncertainty of optimal therapy [27].

It is unlikely that additional RCTs will be carried out for head-to-head comparison of single agent targeted or immunotherapies currently available for treatment-naïve patients. Rather, the focus of current inquiry is combinatorial strategies aiming to improve outcomes for melanoma patients by layering multiple drugs with potentially synergistic mechanisms of action. For instance, the combination of ipilimumab and bevacizumab, an antiangiogenic agent, is under investigation in a clinical trial (NCT01950390). A randomized Phase II trial has shown benefit of combined CTLA-4 inhibition and GM-CSF, a cytokine which augments antigen presentation and mitigates autoimmune toxicity [28]. A follow-up Phase II/III trial is testing the addition of GM-CSF to combined ipilimumab and nivolumab (NCT02339571). Optimal treatment sequence is another area of uncertainty, and this may be clarified by a current Phase III study that involves combined ipilimumab and nivolumab followed by combined dabrafenib and trametinib at progression, or the reverse treatment sequence (NCT02224781). Concurrent use of targeted therapies and a novel immune-checkpoint inhibitor is also the focus of a Phase III

trial (NCT02908672). With numerous combinations under investigation, there is optimism that a greater proportion of patients will derive long-term benefit, yet the treatment landscape may become increasingly crowded as a result.

The recent network meta-analysis (NMA) by Devji *et al.* identified and synthesized the evidence from 15 RCTs involving 6662 treatment-naïve patients with advanced melanoma to draw comparison between targeted therapy and immune-checkpoint inhibitors [29]. In light of the uncertainty toward optimal first-line treatment for patients with *BRAF*-mutated melanoma, this NMA estimated relative efficacy and safety for all possible pairwise comparisons between the included treatment options. Only treatment classes were compared since individual drug comparisons are too few to yield a robust analysis. This NMA found that PD-1 inhibition or combined BRAF/MEK inhibition significantly improves overall survival compared with other treatments, with no significant difference detected between them (hazard ratio: 1.02; 95% credible interval: 0.72–1.45). The rate of serious adverse events is lowest for PD-1 inhibition or chemotherapy. Thus, this analysis of current evidence suggests that PD-1 is an optimal choice for treatment-naïve patients who do not require a rapid tumor regression. Objective response is substantially more likely with BRAF/MEK inhibition compared with other treatments, which supports current clinical practice to offer targeted therapy in the first line for patients with bulky or highly symptomatic disease. Long-term results of landmark trials of combined CTLA-4/PD-1 inhibition are awaited. While this approach may have

the potential to further improve survival, the NMA found higher risk of serious adverse events with this combination [29].

Many of the novel therapies in treatment of advanced melanoma are costly. Particularly with combinations of multiple therapeutic agents, the financial burden is significant. In a resource-restricted healthcare environment, cost of care is an important factor in decision-making for patients and healthcare organizations. Cost-effectiveness of current treatment options is an area where more evidence is needed.

While the expanding armamentarium of systemic treatments for advanced, *BRAF*-mutated melanoma is encouraging for patients and clinicians, with each new drug approval, clinical decision-making becomes more complex. NMA of current evidence has provided a road map to navigate the evolving landscape of melanoma treatment. Given the rapid changes in this field, with promising treatment options on the horizon, head-to-head trials examining efficacy, safety and cost-effectiveness will be crucial for treatment and funding decisions in the future.

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