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“When any real progress is made, we unlearn and learn anew what we thought we knew before.” -Henry David Thoreau

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The dramatic progress recently made in the treatment of metastatic melanoma seemed unachievable only ten years ago. Until 2011, few effective therapies existed for metastatic melanoma and overall survival was on the order of months. Dacarbazine was FDA approved in 1975 and remains the only chemotherapy ever approved for melanoma, with response rates of up to 15%, but with limited durability [1]. Approval of high-dose interleukin-2 followed in 1998, with the potential for long-term durable responses in a minority of patients (up to 15%), but at the expense of significant toxicity [2]. After decades of drought, the advent of genomic profiling combined with breakthroughs in understanding immune escape mechanisms has led to approval of more effective therapies based on immunologic manipulation and identification of targetable oncogenic drivers [3]. Optimism in the field has soared since the 2011 FDA approval of the CTLA-4 inhibitor ipilimumab and the BRAF inhibitor vemurafenib, both of which provided unmatched options for disease control. Since then, dual immune checkpoint blockade with CTLA-4 and PD-1 inhibitors and vertical MAP kinase pathway inhibition with BRAF and MEK inhibitors are now standards of care. The challenges in melanoma therapeutics have shifted from finding an effective drug, to understanding which drug to use first, how to combine drugs to induce a synergistic anti-tumor effect, how to overcome primary or acquired drug resistance and how to mitigate treatment-related toxicity.

This comprehensive special issue is comprised of thoughtful perspectives from leading melanoma experts. Beginning with a focus on immunotherapy, Loo et al. review the use of single and dual agent immune checkpoint blockade in advanced melanoma and the ongoing research efforts to personalize these approaches. Hu-Lieskovan et al. build off this chapter to explore combination therapy strategies using CTLA-4 and/or PD-1 inhibitors as a backbone, while Giuroiu et al. segue into a discussion of novel drugs in early clinical development that target new immune molecules. An exploration of adjunctive therapies follows, including radiation's role in amplifying the anti-tumor immune response by Escorcia et al., and the use of and rationale for intratumoral approaches by Bommareddy et al. Merhavi-Shoham et al. review the experience with adoptive cell therapy including use of tumor infiltrating lymphocytes, T-cell receptor gene manipulation, and T-cells with genetically modified chimeric antigen receptors. The edition's focus then shifts to an update on molecularly targeted therapies by Iams et al. and Gibney et al., and transitions to current investigations for the management of melanoma brain metastases by Oliva et al.

Despite the groundbreaking progress that has transpired in systemic therapies for advanced melanoma over the past decade, multiple barriers remain, as highlighted in Izar et al.'s

commentary on clinical trial design and Sznol's reflection on the challenges of clinical research in melanoma. We have reached an unprecedented era in advanced melanoma in which objective response rates to front-line combination CTLA-4 and PD-1 immunotherapy reaches 57.7%, while response rates to monotherapy PD-1 inhibitors reach 43.7% [4]. This success has stimulated the rapid investigation and/or FDA approval of these drugs in other immunogenic malignancies. However, no reliable predictive biomarkers currently exist to aid in patient selection, and the rate of grade 3-4 toxicity remains high, potentially precluding patients from receiving subsequent immunotherapies. Even after melanoma progression on immunotherapy, other options include BRAF/MEK inhibition in the setting of a driver *BRAF* mutation, immunotherapy re-induction, or alternative immune therapies. Therefore, as patient and clinician access to numerous effective standard of care treatment options has dramatically increased, the pool of melanoma clinical trial participants can decrease. This is complicated by the lack of guidance for clinicians in choosing between the myriad of drugs currently under clinical investigation, either as second line therapies, or in combination with the current standards. Multi-institutional cooperation is warranted to prioritize the most impactful studies to facilitate effective patient accrual. Furthermore, therapeutic challenges are ongoing for special patient populations who have historically been excluded from some clinical trials, including the mucosal and ocular melanoma subtypes, and those patients with brain metastases.

The economic burden of these therapies cannot be overlooked. Single agent PD-1 inhibitors for the treatment of advanced melanoma patients can cost up to \$145,000 for six months of therapy (drug costs only), while the cost of dual CTLA-4 and PD-1 blockade can reach \$1,000,000 per patient, depending on the duration of therapy [5, 6]. These financial forecasts exclude the health care costs required to manage drug-related toxicities. Development of predictive biomarkers to understand which populations will benefit from these agents and clarification of the optimal dosing schedules and duration of therapy are the pressing questions currently under investigation to help identify financial sustainability strategies for these agents.

This special edition emphasizes the significant impact that decades of basic, translational, and clinical scientific research have had on melanoma. Current and future research activities and challenges reflect a major shift in paradigm from an era in which a 20% response rate and median progression free survival of six months were considered a benchmark for success. Melanoma has evolved from one of the most untreatable cancers to the “poster child” for advances in medicine, and the goal over the next decade should be to further raise the overall survival while minimizing toxicity and cost.

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