Are we entering the era of combination therapy for melanoma?

“The concept of harnessing the immune system to initiate an antitumor response has dramatically changed the approach to therapy for melanoma and many other malignancies.”

Justine V Cohen¹ & Ryan J Sullivan^{*1}

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Unprecedented responses to newly available treatments for metastatic melanoma have dramatically changed the therapeutic landscape of this disease during the last decade, highlighted by eight new US FDA approved therapies since 2011. Two approaches include modulation of the immune system with checkpoint inhibitors and targeting oncogenic drivers of melanoma using BRAF and MEK inhibitors (BRAFi and MEKi). As these therapies show more promise, the number of clinical trials exploring various combinations continues to increase. There are compelling preclinical and clinical data that provide a rationale for combining targeted agents and immune checkpoint inhibitors. While trials are ongoing, early results appear favorable. Significant challenges consist of determining optimal dosage, timing and sequencing, identification of candidates for new combinations, and attempting to individualize therapy while balancing toxicity with clinical benefit.

More than half of melanomas harbor a *BRAF*^{V600E} mutation, which constitutively activates the mitogen activated protein

kinase (MAPK) pathway and increases metastatic disease potential [1]. Agents that target the *BRAF* oncogene, such as vemurafenib and dabrafenib are associated with rapid responses at rates exceeding 50% in patients with *BRAF*-mutated melanoma [2,3]. However resistance develops in most patients within 6 months of starting therapy. The mechanism of resistance is often MAPK pathway reactivation, a finding that has inspired the development of combinatorial therapy with BRAFi and MEKi. There are now three randomized Phase III trials demonstrating similar toxicity yet superior response, progression-free survival and overall survival (OS) of two BRAF/MEK inhibitor combinations, dabrafenib/trametinib and vemurafenib/cobimetinib, compared with single-agent BRAFi therapy [4,5]. A third combination, encorafenib/binimetinib, has shown promising data in a Phase I/II trial and is being tested in a Phase III trial (NCT01543698) [6]. The majority of patients, however, consistently develop resistance to these combinations within 12 months, prompting investigation of

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• *BRAF* • immunotherapy • targeted therapy

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¹Cancer Center – Massachusetts General Hospital, Boston, MA, USA

^{*}Author for correspondence: Tel.: +1 617 724 4000; Fax: +1 617 643 1740; rsullivan7@mgh.harvard.edu

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new and potentially more effective therapeutic combinations.

The concept of harnessing the immune system to initiate an antitumor response has dramatically changed the approach to therapy for melanoma and many other malignancies. Modulators of the PD-1 receptor on the surface of T lymphocytes and its ligand, PD-L1, on the surface of tumors, as well as inhibitors of the CTLA-4 surface molecule on T lymphocytes have been tested as mono- and combination therapies for metastatic melanoma. These immune-modulating antibodies, compared with targeted therapies, offer lower response rates (10–15% with anti-CTLA-4 and 30–40% with anti-PD-1) but with more durability (10-year OS of 20% for anti-CTLA-4, 2-year OS of 60% with first-line pembrolizumab and 4-year OS of 32% with first-line nivolumab) [7–10]. The combination of anti-CTLA-4 and anti-PD1 showed response rates of 57.6% in a Phase III trial and gained FDA approval in 2015; though the widespread use of this combination has been limited by its substantial toxicity [10].

The ultimate effectiveness of combination therapies is dependent on the complementary effects of agents, on the underlying tumor biology and/or on the immune systems interaction with the tumor. There now are compelling preclinical and emerging clinical findings regarding improved outcomes for combinations of immune-modulating antibodies and combinations of targeted therapies. Specifically, MAPK inhibition, via downregulation of the MAPK pathway, results in modulation of the tumor-immune microenvironment. As early as 2010, data suggested that BRAF and MEK inhibition in melanoma cell lines led to enhanced recognition of melanocyte antigens and improved reactivity to antigen-specific T lymphocytes [11]. Following this, multiple groups confirmed that patients with metastatic melanoma treated with either BRAFi or combination BRAFi–MEKi had a decrease in intratumoral cytokines IL-6 and IL-8, an increase in CD8⁺ T cells, increased expression of effector function molecules (perforin and granzymes) and an early, temporal increase of immune-inhibitory markers PD-1, PD-L1 and TIM3 [12–14]. Preclinically, MAPK pathway inhibition activates CD8 T cells, which secrete IFN- γ and TNF- α , in *BRAF*-mutant murine melanoma. The combination of targeted therapy and immune checkpoint inhibitors in preclinical models predictably increased CD8⁺

tumor infiltrating lymphocytes and resulted in their improved function as reflected in the production of granzyme B, IFN γ and TNF α [15]. Improved responses and prolonged survival were also seen. Given the early immune environment changes with BRAF/MEK inhibition (10–14 days) [12], it may be ideal to time immunotherapy either concurrently or sequentially following targeted therapy. Details on the scheduling and dose of potential combinations have yet to be determined, although several ongoing trials are focused specifically on these challenges.

The first Phase I trial, in 2011, testing the synergism of targeted therapy (vemurafenib) and immunotherapy (ipilimumab) was terminated early due to unexpected hepatotoxicity [16]. It was unclear if the amplified hepatotoxicity was secondary to that particular combination or if the combination of a BRAFi and an immune-modulating antibody was excessively toxic. Subsequently, a BRAFi (dabrafenib) with or without an MEKi (trametinib) and ipilimumab was tested in a Phase I trial (NCT01767454) [17]. Again, the triple-combination arm was stopped early because of toxicity (colitis and bowel perforation); however, the dabrafenib/ipilimumab arm is ongoing. Ribas *et al.* [18] presented interim results of a trial with anti-PD-L1 (durvalumab or MEDI4736) plus dabrafenib and trametinib (NCT02027961) at the American Society for Clinical Oncology in 2015. Twenty six patients with *BRAF*-mutated melanoma in arm A received the triple combination. The overall response rate (ORR) was 69%, approximating the combination of BRAFi/MEKi. The disease control rate was 100%, with the promise of a longer response duration. Long-term data are still unknown since the follow-up was 7.1 months at the time of presentation. Notably, arm B included patients with *BRAF* wild-type melanoma and produced an ORR in this group of 21% and a disease control rate of 79%. Arm C tested the sequential administration of trametinib followed by durvalumab plus dabrafenib, with an ORR of 13% and disease control rate of 80%. These results are most promising in the triple-combination arm for patients with *BRAF*-mutated melanoma. Toxicities were similar to those expected with the same individual agents. KEYNOTE-022 (NCT02130466) is evaluating the combination of pembrolizumab with dabrafenib and trametinib. Results from the Phase I part of the study were presented at the American Society

for Clinical Oncology in 2016 [19]. 67% of patients developed grade 3–4 immune-related adverse events and 33% required discontinuation of treatment. Early data analysis showed an ORR in 15 patients of 60%. The Phase II study is ongoing. Interim results of a Phase IB study of an anti-PD-L1 (atezolizumab or MPDL3280) plus vemurafenib were presented at the Society of Melanoma Research in 2015 (NCT01656642) [20]. The objective response rate was 76% and toxicities were reportedly manageable and reversible. Again, we await results regarding duration of response. The triple combination of atezolizumab plus a BRAFi/MEKi combination (vemurafenib/cobimetinib) is also being studied in this trial.

Tumor heterogeneity and resistance in melanoma precludes a single-faceted therapeutic approach. We unquestionably have entered an era of combination therapy, with three combinations (two targeted, one immune) gaining approval in the past 3 years. The next step is determining the value of combined oncogenic and immune targeting, and emerging preclinical and clinical experience supports this approach. The canonical thinking is that immune checkpoint inhibitors (both alone and in combination) produce gradual, yet, durable responses, and targeted therapies (both alone and in

combination) result in rapid, albeit short-lived responses. While there are some data that suggest this is an oversimplified view, the fact is that the synergistic potential with these two classes of therapy in combination is very promising. Challenges include toxicities, timing and dosing. Meticulous vigilance for new adverse effects, both predictable and unpredictable, will be required with the introduction of any new combination. The potential clinical benefit (i.e., durable responses) must outweigh the risks. Additionally, research advances focused on the detection of predictive biomarkers may further optimize patient selection. Ultimately, we are moving toward a more personalized approach in the treatment of cancer, which will undoubtedly involve combination therapy. Melanoma is squarely in the cross hairs of leading-edge research to overcome current hurdles.

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