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Combination Therapies for Melanoma: A New Standard of Care?

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Abstract

Recent data have demonstrated improved survival with targeted and immune therapies in patients with advanced melanoma, leading to much excitement amongst the oncology community and the widespread use of these drugs in combination regimens. However, the place of these combination therapies in the treatment of advanced melanoma remains to be fully determined. In this perspectives article we critically review the available data and outline the rationale for these combinations being adopted as the standard of care for patients with advanced melanoma in the future.

1. Introduction

Melanoma is responsible for most skin cancer deaths, and its incidence continues to rise year after year.[1] For many years, metastatic melanoma was widely believed to be intractable to most conventional anticancer therapies and the prognosis was generally grim.[2] Recent years have seen the development of a remarkable series of systemic therapies for patients with unresectable metastatic melanoma.[3] These therapeutic advances can be divided into either 1) targeted therapies – kinase inhibitors that specifically inhibit the function of the most common genetic mutation that drives melanoma progression – or 2) immune therapies – therapeutic antibodies that relieve the inhibitory signals that impair immune cell recognition and destruction of the tumor in melanoma patients.[3] Although the adoption of both of these therapeutic modalities has been rapid, the clinical data is not yet fully mature. At this time the criteria for selecting the optimal therapy for any given patient remains to be determined. In this brief perspectives article we will discuss the pertinent clinical data on both targeted therapy and immune therapy in melanoma with the goal of defining the best frontline treatment strategies.

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Compliance with ethical standards

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2.1 Combinations with targeted therapy

The development of molecular targeted therapy for melanoma stemmed from the observation that approximately 50% of all of cutaneous melanomas harbored activating mutations in the serine/threonine kinase BRAF.[4] Early experimental studies demonstrated that mutant *BRAF* was a *bona fide* melanoma oncogene and that its inhibition through small molecule inhibitors was associated with reduced tumor growth.[5] BRAF inhibitor monotherapy progressed rapidly through clinical development, with the first BRAF inhibitor, vemurafenib, receiving FDA approval in 2011 (Table 1). Responses were only seen in patients whose melanomas harbored an activating position 600 (V600E, R or K) *BRAF* mutation.[6] Use of BRAF inhibitors was not recommended for patients whose melanomas harbored other driver oncogenes, and there was even some suggestion that BRAF inhibitors might accelerate the progression of *NRAS*-mutant melanomas.[7] In general, BRAF inhibitor monotherapy was well-tolerated, with side effects including pyrexia, rash, fatigue and alopecia.[6] Of special note, single agent BRAF inhibitor treatment was associated with the appearance of squamous skin tumors such as squamous cell carcinomas (SCC) and keratoacanthomas (KA), an unanticipated finding attributed to the paradoxical effects of BRAF inhibition in sub-clinical clones of *HRAS*-transformed keratinocytes.[7] At the same time it was noted that targeting MEK, the downstream effector of BRAF, using single-agent trametinib, also had activity (albeit less of an effect than BRAF inhibitor monotherapy) in patients with *BRAF*-mutant melanoma (median PFS 4.8 months). [8]

It was rapidly realized that, although impressive, responses seen to BRAF inhibitor monotherapy were usually transient, with long-term follow up of the phase 3 trial demonstrating a median progression-free survival (PFS) of 6.9 months.[9,10] In most cases, reactivation of the mitogen activated protein kinase (MAPK) pathway was found in the tumor specimens tested upon relapse.[11] With this in mind, strategies were developed to vertically target the MAPK pathway in melanoma using the combination of a BRAF and a MEK inhibitor. These studies, initially using the combination of dabrafenib and trametinib[12,13,14] and later vemurafenib plus cobimetinib[15] or encorafenib plus binimetinib,[16] showed the BRAF-MEK inhibitor combination to have greater efficacy and increased PFS compared to each BRAF inhibitor monotherapy evaluated (Table 1). Resistance (albeit delayed) was still seen to the BRAF-MEK inhibitor combination, with reactivation of the MAPK pathway still emerging as the major driver of resistance.[11] Interestingly the BRAF-MEK inhibitor combination was associated with a slightly different side-effect profile, with a reduced incidence of SCC/KA development being observed compared to those on BRAF inhibitor monotherapy.[7] Conversely, increased levels of pyrexia and chills were seen in patients receiving the dabrafenib-trametinib combination vs dabrafenib-placebo.[17] Mature clinical trial data are now available on the dabrafenib-trametinib combination that show a clear survival benefit for patients receiving the dabrafenib-trametinib combination vs patients randomized to receive dabrafenib plus a placebo (median overall survival 25.1 months vs 18.7, respectively) (Table 1).[13] The increased survival benefit of the combination was seen in virtually all subgroups analyzed, and included high tumor-burden patients (those with elevated serum LDH levels) as well as

individuals whose melanomas harbored a V600K mutation. Use of the combination was also associated with an increase in both the objective response rate (69% compared to 53% for BRAF inhibitor monotherapy) and the median time to disease progression (11.0 months compared to 8.8 months for BRAF inhibitor monotherapy).[13] Perhaps most significant of all, the combination was better tolerated in many respects than monotherapy, with a dramatic reduction in the number of secondary SCC and/or KA lesions observed.¹⁴ At this time, three randomized phase III clinical trials have demonstrated the BRAF-MEK inhibitor combination to show improved response (increased PFS and OS) compared to BRAF inhibitor monotherapy.[13,14,15]

2.2 Combinations with immune therapy

The immune system has long been an interest of those who treat melanoma patients. Some of the first therapies with proven efficacy against melanoma, such as high dose interleukin (IL-2), have been immunologic, and involved nonspecific stimulation of the immune system. The use of high dose IL-2 came at the cost of low response rates (objective response rate ~15–20%, complete response rate ~5%) and significant toxicity, and required hospitalization for safe administration.[18] A more successful approach has been to relieve the inhibitory effects of the tumor upon the immune system through the blockade of some of the many inhibitory immune checkpoints.[3,19] Therapeutic strategies have now been designed to inhibit some of these important immune system checkpoints using blocking antibodies. The first approach to be validated clinically was the inhibition of the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), a cell surface protein that blocks the function of cytotoxic T-cells.[20] In melanoma patients, inhibition of CTLA-4 using ipilimumab was associated with a response rate of 11% and improved overall survival rate compared to a vaccine comparator (Table 2).[21] A subsequent pooled analysis of data from several ipilimumab clinical trials showed that 22% of treated patients were still alive at 3-years, and responses lasting over a decade have been observed in some patients treated with anti-CTLA-4 antibody therapies.[22,23] Use of CTLA-4 targeted antibodies was also associated with severe immune-related adverse effects in up to 20% of those treated.[21] The low response rates and high levels of toxicity associated with anti-CTLA-4 monotherapy make patient selection a critical issue. Attempts to define biomarkers of response to anti-CTLA-4 therapy have centered upon whole exome sequencing of pre-treatment biopsies of tumor and normal tissue. The emerging evidence suggests that total tumor mutational load, neoantigen load and the expression of cytolytic markers (such as granzyme B and perforin) in the immune environment are predictive of therapeutic response.[24,25] Studies in mice have also provocatively suggested that the constitution of the host microbiome may also influence response to immune therapies.[26,27]. Significant advances in biomarker-driven patient selection for immune therapies are expected over the coming years.

Better selectivity seems to be achieved when checkpoints found more exclusively in the tumor microenvironment, such as the programmed death (PD)-1 receptor and its ligands PD-L1 and PD-L2, are targeted.[28] As monotherapy, the anti-PD-1 antibodies nivolumab or pembrolizumab (originally referred to as lambrolizumab) are associated with response rates of 30–40%, with the majority of those responding experiencing responses of >1 year.[29,30] In phase 3 trials, nivolumab was found to have superior efficacy to chemotherapy in patients

with unresectable metastatic melanoma regardless of their tumors' *BRAF* mutation status or prior treatment with ipilimumab (Table 2).[31,32] Nivolumab showed good efficacy in patients who progressed on ipilimumab or *BRAF*-mutant melanoma patients who failed on *BRAF* inhibitor therapy. Pembrolizumab was also found to outperform chemotherapy and was associated with higher response rates and longer progression-free and overall survival than single-agent ipilimumab.[33,34]

The evident lack of cross-resistance between inhibitors of the CTLA-4 and PD-1 immune checkpoints led to the evaluation of combination immune therapies.[35] A phase 2 study of 142 treatment-naïve, *BRAF* wild-type melanoma comparing nivolumab-ipilimumab combination therapy to ipilimumab monotherapy reported an objective response rate of 61% to the combination, with 16% of patients achieving a complete response (Table 2).[36] At the time of publication the median response duration had not been reached. The rate of serious adverse events was 54%, significantly higher than that seen with ipilimumab monotherapy.[36] In a double-blind, randomized phase 3 trial of previously untreated patients with unresectable metastatic *BRAF*-mutant or *BRAF* wild-type melanoma, the combination of nivolumab and ipilimumab was associated with a progression-free survival of 11.5 months compared to 2.9 and 6.9 months for single-agent ipilimumab and nivolumab, respectively.[37] Activity was seen with the combination in tumors that were both positive and negative for PD-L1 expression; greater duration of response was observed in the PD-L1 negative group with the nivolumab-ipilimumab combination, compared to nivolumab monotherapy (11.2 months vs 5.3 months).[37] The increased efficacy to the combination came at the expense of greater toxicity, with treatment related adverse effects observed in 55% of those receiving the combination, in 27% of those on ipilimumab monotherapy, but only in 16% of those on nivolumab monotherapy.[37] At present, no data are available to determine whether a survival advantage exists for the combination of nivolumab and ipilimumab compared to nivolumab alone, and indeed the number of observed deaths was virtually identical for the combination arm and the nivolumab arm.[38] Trials of anti-PD-1 or anti-CTLA-4 antibodies combined with therapeutics targeting other immune regulatory checkpoints are also under investigation. Ipilimumab showed an improvement in overall survival (17.5 versus 12.7 months) when combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) as compared to ipilimumab alone in a randomized phase 2 trial.[39] Combinations of checkpoint inhibitors with agonistic antibodies such as CD40 or CD137 antibodies (NCT02253992, NCT01103635) are also ongoing.

3. Where to start?

The development of two potentially effective and very different therapeutic approaches has both improved and complicated the melanoma treatment landscape. At this point in time, there are no long-term data directly comparing targeted therapy and immunotherapy for their ability to achieve durable survival in patients with unresectable metastatic melanoma harboring a *BRAF* V600 mutation; therefore, the standard of care for first-line treatment of these patients remains to be defined. Each modality offers distinct advantages, with targeted therapy showing a rapid time to response and generally less toxic off-target effects, and immunotherapy offering the possibility of increased durability of benefit in all patients irrespective of tumor genotype. Recent data on the long-term follow up of patients receiving

combined BRAF-MEK inhibitor therapy has suggested that the ability of targeted therapies to induce durable overall survival may not be as different as from immunotherapeutics as initially believed. Although the optimal path forwards remains to be determined, some important guiding principles have already emerged. The first consideration is whether the patients' tumor has a *BRAF* V600 mutation. Although BRAF status is the necessary criterion for receiving BRAF-MEK inhibitor therapy, it does not mean these drugs should always be used as the frontline therapy in *BRAF*-mutant melanoma patients. Single agent or combination immune therapy is effective in patients whose melanomas harbor a *BRAF* mutation, and the possibility exists of achieving a durable response to immunotherapy while retaining targeted therapy as a future option in the event of immunotherapy failure.

It is widely believed that the relatively rapid response seen to BRAF-MEK inhibitor therapy makes it an ideal first choice for patients with *BRAF*-mutant melanoma who exhibit rapid disease progression kinetics. Again this may be a little more nuanced as it is clear that while responses to ipilimumab monotherapy are often delayed in onset, there is evidence that the ipilimumab-nivolumab combination works significantly faster. There is also data showing that the BRAF-MEK inhibitor combination may be more effective in patients with slower disease progression, with an increased PFS being observed in patients who were stratified on the basis of lower serum LDH levels. A further consideration for the use of BRAF-MEK inhibitor therapy is whether to treat beyond disease progression. There is already evidence that treatment of patients beyond first disease progression, as seen in the BREAK-3 trial using dabrafenib, was associated with a greater overall survival than that seen in the BRIM-3 trial of vemurafenib, where treatment was discontinued upon disease progression. [9,10]

It has recently been suggested that disease kinetics need to be a consideration in determining the frontline therapeutic strategy to pursue – particularly in *BRAF*-mutant melanoma. This idea, which was recently described in a paper by Grob and colleagues[40] suggested the adoption of different strategies depending upon the speed of disease progression (slow vs fast). The kinetics of disease progression would need to be assessed through sequential scans, 4–12 weeks apart, while also accounting for other factors such as serum LDH levels, rapidly growing brain metastases, etc. The goal in each case would be to develop a treatment schedule that balanced toxicity, the likelihood of best response and the overall risk to the patient. Under this scheme, patients with fast disease kinetics would be treated aggressively with the intention of preventing risk to life (through the adoption of fast-acting therapy), while accepting a higher level of toxicity. In patients with slower disease progression, less toxic schedules could be considered such as intermittent dosing with either BRAF-MEK inhibitors or anti-PD-1 antibodies. Trials looking at intermittent dosing schedules of BRAF-MEK inhibitors are currently ongoing (NCT02196181, NCT02263898). The goal of treatment in patients with slower growing disease would be to maintain quality of life, minimize toxicity and to ensure prolonged survival.

4. Combinations of targeted and immune therapies

A promising area of research that may abrogate the need to determine which therapeutic to start with, is clinical studies which combine both targeted and immune therapies. BRAF-

MEK inhibitors modulate the immune microenvironment in tumor biopsies and increase CD8 positive T cells and melanoma differentiation antigens like MART-1 and gp100, which may have a role in T cell recognition.[41,42] Clinical trials are ongoing to determine if the combination of BRAF-MEK inhibitors with immunotherapeutics lead to higher frequency of long-lasting responses in patients with advanced *BRAF*-mutant melanoma, without causing intolerable toxicity. In a phase 1 trial of ipilimumab combined with dabrafenib with and without trametinib in *BRAF*-mutated melanoma patients, two out of seven patients on the triple-agent combination developed grade 3 colitis complicated by perforation.[43] Enrollment to the triple combination arm was halted, while the dabrafenib and ipilimumab combination arm is ongoing. The combination of dabrafenib and trametinib with the anti-PD-L1 antibody durvalumab (MEDI4736) is under investigation in another trial.[44] Tumor biopsies from the patients have revealed evidence of immune activation post-treatment, with increased frequency of tumor-infiltrating CD8+ T cells post-treatment. For the 26 *BRAF*-mutated advanced melanoma patients treated with dabrafenib, trametinib and MEDI4726, a 69% response rate was obtained, and 16 out of 18 responding patients have ongoing responses. Exacerbation of immune-related adverse events was not observed. While a response rate of 69% does not appear to be higher than what is expected from BRAF-MEK inhibitor therapy alone, future data on durability of these responses, along with overall survival will help determine how beneficial the combination of targeted and immunotherapies may be. A different ongoing phase 1/2 trial, KEYNOTE-022 (NCT02130466), is looking at the combination of pembrolizumab with dabrafenib and trametinib.

5. Conclusions

Although many significant advances have been made in the development of therapeutic strategies for melanoma, treatment failure leaves few good therapeutic options for many patients who may have had good but not durable responses. This is true both for *BRAF* wild-type patients who have failed ipilimumab and nivolumab and *BRAF* mutant melanoma patients have failed both BRAF-MEK inhibitor therapy and immunotherapy regimens. Currently, a clinical trial is probably the best option for these patients, a situation likely familiar to those who have treated melanoma patients for many years. Although great progress has been made, much remains to be done before advanced melanoma can be reduced to the level of a chronic disease. The field has evolved rapidly over the past 5 years and continues to do so. The future standard of care for melanoma is likely to be highly personalized and based upon combination of tumor genetics, immune endpoints and disease kinetics. Further advances in the field will depend heavily upon the continued strong interactions between basic scientists and clinicians whose work to date has been an inspiration for the entire oncology community.

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Key points

- Combined targeted therapy (BRAF-MEK inhibition) and immune therapy (anti-CTLA-4-anti-PD-1 inhibition) leads to increased response rates and progression-free survival, and in some cases overall survival, in subsets of patients with advanced melanoma.
- Immune therapy and BRAF-MEK inhibitor therapy are both effective in patients whose melanomas harbor *BRAF* mutations. Disease kinetics and tumor burden may be an appropriate determinant of therapy selection for *BRAF*-mutant melanoma patients.
- Combined immune/targeted therapy regimes are currently being evaluated and may offer the possibility of long-term therapeutic responses, albeit with the likelihood of increased toxicity.

Table 1

Results from key melanoma clinical trials using molecularly targeted agents

Drug(s)	Target	Phase	Results	Adverse events (all grades)	Reference
Vemurafenib	BRAF	3	ORR 51% OS 65% (@12 months)	Arthralgia 51% Rash 43% Alopecia 39% Hand-foot syndrome 25% Skin papilloma 25%	[14]
Vemurafenib	BRAF	3	ORR 45% OS 73% (@9 months)	Arthralgia 40% Hyperkeratosis 29% Rash 35% Alopecia 30%	[15]
Dabrafenib	BRAF	3	ORR 53% OS 68% (@12 months) OS 42% (@24 months) mOS 18.7 months	Hyperkeratosis 33% Fatigue 28% Hand-foot syndrome 27% Alopecia 26% Skin papilloma 18%	[17]
Trametinib	MEK	3	PFS 4.8 months OS 81% (@6 months)	Rash 57% Diarrhea 43% Fatigue 26% Edema 26%	[8]
Dabrafenib + Trametinib	BRAF + MEK	2	ORR 76% OS 79% (@12 months)	Pyrexia 71% Chills 58% Fatigue 44% Nausea 40%	[12]
Dabrafenib + Trametinib	BRAF + MEK	3	ORR 69% OS 74% (@12 months) OS 51% (@24 months) mOS 25.1 Months	Pyrexia 52% Chills 28% Fatigue 27% Rash 24%	[17]
Dabrafenib + Trametinib	BRAF + MEK	3	ORR 64% OS 72% (@12 months)	Pyrexia 53% Nausea 35% Diarrhea 32% Chills 31%	[14]
Vemurafenib + Cobimetinib	BRAF + MEK	3	ORR 68% OS 81% (@9 months)	Diarrhea 50% Nausea 40% Rash 39% Arthralgia 32%	[15]
Encorafenib + Binimetinib	BRAF + MEK	1b/2	ORR 72% PFS 11.3 months	Nausea 44% Fatigue 44% Diarrhea 33% Vomiting 33%	[16]

Abbreviations used: ORR, objective response rate; OS, overall survival (at designated time point); PFS, progression-free survival (median).

Table 2

Results from key melanoma clinical trials on immune targeted agents.

Drug(s)	Target	Phase	Results	Adverse events (all grades)	Reference
Ipilimumab ± gp100	CTLA-4 vaccine	3	ORR 11% OS 10.1 months	Diarrhea 38% Fatigue 36%	[21]
Nivolumab	PD-1	1	ORR 41% PFS 55% (@24 weeks)	Rash 12% Pruritus 9% Vitiligo 3%	[29]
Pembrolizumab	PD-1	1	ORR 44%	Fatigue 30% Rash 21% Pruritus 21% Diarrhea 20%	[30]
Pembrolizumab	PD-1	3	PFS 47% (@ 6 months) OS 74% (@ 12 months)	Fatigue 21% Diarrhea 17% Rash 14% Pruritus 14%	[34]
Nivolumab + Ipilimumab	PD-1 CTLA-4	1	ORR 61%	Diarrhea 45% Rash 41% Fatigue 39% Pruritus 35% Colitis 23%	[36]
Nivolumab + Ipilimumab	PD-1 CTLA-4	3	PFS 11.5 months	Diarrhea 44% Rash 40% Fatigue 35% Pruritus 33% Colitis 12%	[37]
Ipilimumab + GM-CSF	CTLA-4 Immune cells	2	OS 68% (@ 12 months) PFS 3.1 months	Diarrhea 13% Rash 9% Colitis 6% Fatigue 6%	[39]

Abbreviations used: ORR, objective response rate; OS, overall survival (at designated time point or median if no time point given); PFS, progression-free survival (at designated time point or median if no time point given).