EDITORIAL

For reprint orders, please contact: reprints@futuremedicine.com

Melanoma Management

Where to start with systemic melanoma therapy?

"As new combination strategies evolve for melanoma, the selection of appropriate therapies and the management of toxicities will become a major challenge for treating oncologists and patients."

Geoffrey T Gibney[1], Vernon K Sondak[1] & Keiran SM Smalley*[1,2]

Recent years have seen unparalleled advances in the development of new systemic therapies for the treatment of unresectable metastatic melanoma. These novel therapies fall into two camps – targeted therapies and immune-based therapies – each with its' own strengths and weaknesses. The development of targeted therapies in melanoma followed the 2002 discovery that approximately half of all cutaneous melanomas harbored activating mutations in the serine/threonine kinase *BRAF* [1]. Mutant *BRAF* was identified as being a key oncogenic player in melanoma through its effects on the MAPK pathway. A wealth of preclinical data have now established the MAPK pathway as a driver of many of the processes required for melanoma development, including uncontrolled growth, invasion and dissemination [2]. In the clinic, strategies to target mutant *BRAF* through small-molecule inhibitors such as vemurafenib and dabrafenib have been highly successful and often lead to rapid objective responses in the majority of patients [3,4]. One drawback of BRAF inhibitors has been their relatively short duration of benefit – especially when used in the single-agent setting. Long-term follow up of the Phase III trials of vemurafenib and dabrafenib have demonstrated that median progression-free survival (mPFS) is 6.9 months [5,6]. Recognition of the nearly uniform reactivation of the MAPK pathway in melanoma patients failing single-agent BRAF inhibition led to the development of trials combining BRAF and MEK inhibitors [7]. Combination of dabrafenib with the MEK inhibitor trametinib has shown prolonged mPFS compared with dabrafenib alone [8]. On the basis of these encouraging data, the BRAF/MEK inhibitor combination received accelerated US FDA approval in January of 2014. Although a limited number of individuals have shown durable responses (>3 years) with vemurafenib monotherapy [9], the majority of patients are unlikely to achieve durable remissions from targeted BRAF therapy, even in combination.

While targeted therapy is a recent development, melanoma has been a disease that has long fascinated immunologists. Some of the earliest, albeit limited, successes in systemic melanoma therapy were immune therapies. High-dose IL-2 was FDA

KEYWORDS

• BRAF • combination therapy • CTLA-4 • melanoma • NRAS • PD-1

[1]The Department of Cutaneous Oncology, The Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, Tampa, FL, USA

[2]The Department of Molecular Oncology, The Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, Tampa, FL, USA

*Author for correspondence: Tel.: +1 8137458725; Fax: +1 8134498260; keiran.smalley@moffitt.org

Future Medicine part of fsg

approved in 1998 for treatment of metastatic melanoma. Under physiological conditions, the immune system is tightly regulated through a network of 'checkpoints' that serve to avoid aberrant immune activation and the resultant attack of normal tissues (autoimmunity). These regulatory mechanisms are co-opted by cancer cells to avoid immune recognition and/or destruction. Therapeutic strategies have now been developed to target and block these immune inhibitory checkpoints. One of the first checkpoints to be successfully targeted in melanoma was cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), a cell surface protein that shuts down the activation of T cells through competition with the T-cell receptor costimulatory protein CD28 for engagement of the B7 class of molecules expressed on antigen-presenting cells. Treatment of melanoma patients with ipilimumab, an antibody directed against CTLA-4, demonstrated an objective response rate of 11% and improved overall survival rates, both superior to the gp100 vaccine control arm [10]. Although significant immune-related side effects can occur in up to 20% of patients, they are generally manageable with steroids and supportive care [10]. It is noteworthy that a pooled analysis of ipilimumab-treated patients has shown 22% of metastatic melanoma patients were alive at 3 years with a plateau of the survival curves extending through 10 years [11]. As of yet, no predictive biomarkers for patient selection have been identified.

"While targeted therapy is a recent development, melanoma has been a disease that has long fascinated immunologists."

A further strategy to exploit the immune system by overcoming a tumor escape strategy is targeting the programed death-1 (PD-1) receptor, as well as its ligands PD-L1 and PD-L2. The observation that PD-1 ligands, especially PD-L1, are expressed largely in the tumor microenvironment suggests this strategy may offer greater tumor selectivity and fewer off-target effects over inhibition of CTLA-4. In the Phase I study of nivolumab (an anti-PD-1 antibody), an objective response rate of 28% was observed across all dose levels in the metastatic melanoma cohort, and durable responses (>1 year) occurred in the majority of responding patients [12]. Response rates as high as in the range of 38% have been observed in further studies of anti-PD1 therapy [13]. On the basis of the anti-CTLA4 and anti-PD1 therapy results and their likely complementary modes of action, a Phase I clinical trial of ipilimumab in combination with nivolumab was conducted [14]. While this combination was associated with a 40% objective response rate, tumor regression was often rapid, with ≥80% decreases in tumor burden seen in 16 out of 21 responding patients by 12 weeks. However, the combination immunotherapy was associated with significant side effects in 53% of patients. A randomized Phase III trial is now ongoing to compare nivolumab or nivolumab with ipilimumab to ipilimumab alone in metastatic melanoma patients (ClinicalTrials.gov identifier: NCT01844505).

For the first time, patients with metastatic melanoma and their treating oncologists can choose among several potentially active therapies. The question of which therapy to initiate in a treatment-naive unresectable metastatic melanoma patient has become a legitimate question. There are a number of issues to consider. One of the first is whether the patient's tumor harbors an activating *BRAF* mutation? In the case of *BRAF* wild-type melanoma, immune therapy would be the natural frontline choice [15]. This includes melanoma tumors that harbor other oncogenic alterations. Although there is evidence of clinical benefit for the use of MEK inhibitors in *NRAS* and *GNAQ*/*GNA11* mutant melanoma patients, as well as c-KIT inhibitors in *c-KIT* mutant melanoma patients, the disease control is modest relegating these agents to generally second- or third-line strategies [16].

In patients with *BRAF* mutant melanoma, an important consideration is the extent and pace of their disease. Since BRAF inhibitors generally work rapidly and can provide symptomatic relief in days, patients with more aggressive disease may benefit most from starting with a BRAF-targeted strategy. On the contrary, *BRAF* mutant melanoma patients with limited and/or slowly progressive disease, may benefit more from starting with immunotherapy because of the possibility of long-term disease control, albeit at a slower onset of response. Indeed, better clinical outcomes in *BRAF* mutant melanoma patients have been reported in patients initially treated with ipilimumab, followed by a BRAF inhibitor at progression [17]. With further development of combination immunotherapy (e.g., ipilimumab plus nivolumab), both rapid and durable responses may be achievable [14], which may impact treatment decisions in *BRAF* mutant melanoma patients with advanced, symptomatic disease.

Another appealing strategy is to combine targeted therapies with immune therapies with the goals of rapidly shrinking the disease

while maximizing the possibility of a durable long-term response. There is already preclinical evidence that inhibition of BRAF leads to the adoption of a more immune-favorable tumor microenvironment [18]. In melanoma patients, treatment with BRAF inhibitors increases the expression of melanoma antigens and is associated with increased $CD8^+$ T-cell infiltration [18]. At the same time, BRAF inhibition also unexpectedly increased the expression of multiple immunosuppressive molecules on the melanoma cells, including PD-1, PD-L1 and TIM3, suggesting there may be some blunting of the potential immune response [19]. Further analysis showed failure of BRAF inhibitor therapy to be associated with decreased $CD8^+$ T-cell infiltration, a loss of melanoma antigen expression and the increased expression of the immune inhibitory molecule PD-L1 [19]. Together, these data suggest a role for increased immune surveillance in the antitumor responses seen to BRAF inhibition and that treatment failure leads to a reversal of immune recognition. Based on these findings, clinical studies have been initiated to explore the hypothesis.

The success of combined targeted and immune therapies will likely depend upon the correct scheduling and timing of the two therapeutic modalities to ensure that the maximal benefit can be achieved. New toxicities are also likely to appear as new drug combinations are evaluated. A Phase I trial has been conducted to explore concurrent vemurafenib and ipilimumab therapies in metastatic *BRAF* mutant melanoma patients (ClinicalTrials.gov identifier: NCT01400451). To date, the only published data from the trial is the increased rate of hepatotoxicity seen in the first and second cohorts of the trial, which led to an early closure [20]. Another similar trial with dabrafenib ± trametinib in combination with ipilimumab is ongoing in *BRAF* mutant melanoma patients (ClinicalTrials.gov identifier: NCT01767454). An alternative strategy is to use BRAF inhibitors as a debulking agent, as well as to enhance immunogenicity, followed by an immune therapy to 'clean up' any residual tumor. This may maximize clinical benefit to patients, while mitigating some of the toxicity issues that arise with concurrent therapy. This strategy is being tested in two different clinical trials – one with vemurafenib followed by ipilimumab (ClinicalTrials.gov identifier: NCT01673854) and a second with vemurafenib followed by adoptive cell therapy (ClinicalTrials.gov identifier: NCT01659151).

As new combination strategies evolve for melanoma, the selection of appropriate therapies and the management of toxicities will become a major challenge for treating oncologists and patients. We have seen the rapid development of selective BRAF inhibitor therapy single agents, only now to be usurped by the combination of BRAF and MEK inhibitors 3 years later. A similar movement towards combination immunotherapy appears to be imminent with early promising data for combined anti-CTLA4 and anti-PD1 agents. We may see even further strides towards combined targeted and immune therapy approaches based on ongoing studies.

"For the first time, patients with metastatic melanoma and their treating oncologists can choose among several potentially active therapies."

Financial & competing interests disclosure

Work in the Smalley laboratory is supported by R01 CA161107-01 from the NIH, and SPORE grant CA168536. VK Sondak is a paid consultant for Merck, GlaxoSmithKline, Bristol Myers Squibb, Novartis and Provectus. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Davies H, Bignell GR, Cox C *et al.* Mutations of the *BRAF* gene in human cancer. *Nature* 417(6892), 949–954 (2002).

2 Fedorenko IV, Paraiso KH, Smalley KS. Acquired and intrinsic BRAF inhibitor resistance in *BRAF* V600E mutant melanoma. *Biochem. Pharmacol.* 82(3), 201–209 (2011).

3 Hauschild A, Grob JJ, Demidov LV *et al.* Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, Phase 3 randomised controlled trial. *Lancet* 380(9839), 358–365 (2012).

4 Chapman PB, Hauschild A, Robert C *et al.* Improved survival with vemurafenib in melanoma with *BRAF* V600E mutation. *N. Engl. J. Med.* 364(26), 2507–2516 (2011).

5 Chapman PB, Hauschild A, Robert C *et al.* Updated overall survival (OS) results for BRIM-3, a Phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with *BRAF* V600E-mutated melanoma. *J. Clin. Oncol.* (Suppl.), Abstract 8502 (2012).

6 Hauschild A, Grob JJ, Demidov LV *et al.* An update on BREAK-3, a Phase III, randomized trial: dabrafenib (DAB) versus dacarbazine (DTIC) in patients with *BRAF* V600E-positive mutation metastatic melanoma (MM). *J. Clin. Oncol.* 31(Suppl.), Abstract 9013 (2013).

7 Paraiso KH, Fedorenko IV, Cantini LP *et al.* Recovery of phospho-ERK activity allows

melanoma cells to escape from BRAF inhibitor therapy. *Br. J. Cancer* 102(12), 1724–1730 (2010).

8 Flaherty KT, Infante JR, Daud A *et al.* Combined BRAF and MEK inhibition in melanoma with *BRAF* V600 mutations. *N. Engl. J. Med.* 367(18), 1694–1703 (2012).

9 Kim K, Amavaradi RK, Flaherty K *et al.* Significant long-term survival benefit demonstrated with vemurafenib in ongoing Phase I study. *Pigm. Cell Melanoma R.* 25(6), 866 (2012).

10 Hodi FS, O'day SJ, Mcdermott DF *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* 363(8), 711–723 (2010).

11 Schadendorf D, Hodi FS, Robert C *et al.* Pooled analysis of long-term survival data from Phase II and Phase III trials of ipilimumab in metastatic or locally advanced, unresectable melanoma. *Ann. Oncol.* European Cancer Congress, LBA 24 (2013).

12 Topalian SL, Hodi FS, Brahmer JR *et al.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N. Engl. J. Med.* 366(26), 2443–2454 (2012).

13 Hamid O, Robert C, Daud A *et al.* Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N. Engl. J. Med.* 369(2), 134–144 (2013).

14 Wolchok JD, Kluger H, Callahan MK *et al.* Nivolumab plus ipilimumab in advanced melanoma. *N. Engl. J. Med.* 369(2), 122–133 (2013).

15 Kaufman HL, Kirkwood JM, Hodi FS *et al.* The Society for Immunotherapy of Cancer consensus statement on tumour immunotherapy for the treatment of cutaneous melanoma. *Nat. Rev. Clin. Oncol.* 10(10), 588–598 (2013).

16 Ascierto PA, Schadendorf D, Berking C *et al.* MEK162 for patients with advanced melanoma harbouring *NRAS* or Val600 *BRAF* mutations: a non-randomised, open-label phase 2 study. *Lancet Oncol.* 14(3), 249–256 (2013).

17 Ascierto PA, Simeone E, Chiarion-Sileni V *et al.* Sequential treatment with ipilimumab and BRAF inhibitors in patients with metastatic melanoma: data from the Italian cohort of ipilimumab expanded access programme (EAP). *J. Clin. Oncol.* Abstract 9035 (2013).

18 Boni A, Cogdill AP, Dang P *et al.* Selective *BRAF* V600E inhibition enhances T-cell recognition of melanoma without affecting lymphocyte function. *Cancer Res.* 70(13), 5213–5219 (2010).

19 Frederick DT, Piris A, Cogdill AP *et al.* BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. *Clin. Cancer Res.* 19(5), 1225–1231 (2013).

20 Ribas A, Hodi FS, Callahan M, Konto C, Wolchok J. Hepatotoxicity with combination of vemurafenib and ipilimumab. *N. Engl. J. Med.* 368(14), 1365–1366 (2013).