Advancements in unresectable melanoma: a multidisciplinary perspective

“In September 2015, the US FDA approved the combination of nivolumab and ipilimumab for treatment of advanced melanoma after randomized Phase II and III clinical trials showed an increase in progression-free survival, compared with ipilimumab or nivolumab alone...”

Mary-Kate Malecek^{*1}, June K Robinson², Karl Bilimoria³, Jennifer N Choi², Jaehyuk Choi², Pedram Gerami², Timothy Kruser⁴, Timothy Kuzel⁵, Mary Martini², Jonathan B Strauss³, Jeffrey Wayne³, Jeffrey Sosman⁵ & Sunandana Chandra⁵

First draft submitted: 24 January 2016; Accepted for publication: 27 June 2016; Published online: 16 August 2016

With the progress of molecular targeted therapies and immune therapies made over the last few years, the treatment of many solid tumors has been transformed far beyond what could have been predicted. Perhaps the cohort of patients to most benefit from the latest advancements is those with advanced melanoma. Treatment options for advanced melanoma have historically been limited, and patients experienced dismal outcomes. Recently, there have been major breakthroughs in the developments of cancer therapy, from local treatment to radiation and systemic treatment, which have resulted in better response rates, increased progression-free survival and increased overall survival. Here, we aim to provide a commentary on the recent advances in

treatment of advanced melanoma, as well as describe the landscape of future therapeutic perspectives.

Advancements in systemic therapy

Up until 2011, the standard of care for unresectable melanoma was traditional chemotherapy with alkylating agents such as dacarbazine or temozolomide. Response rates to dacarbazine have been reported in clinical trials at 5–14%, with durability of only 3–6 months. Other alkylating agents and combination regimens of cytotoxic chemotherapy or biotherapy with interferon and/or IL-2 failed to show significant improvement in overall survival.

In March of 2011, ipilimumab was approved by the US FDA for the treatment

KEYWORDS

- clinical trials
- immunotherapy
- melanoma

“Recently, there have been major breakthroughs in the developments of cancer therapy...”

¹Department of Medicine, Northwestern University Feinberg School of Medicine, 251 East Huron Street, Galter Pavilion Suite 3-150, Chicago, IL 60611, USA

²Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

³Division of Surgical Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

⁴Department of Radiation Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

⁵Division of Medical Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

*Author for correspondence: mary.duncan@northwestern.edu

“...there are tantalizing hints of synergy between stereotactic body radiotherapy and targeted systemic agents such as anti-CTLA-4 antibodies or PD-1 inhibitors.”

of metastatic melanoma, and was the first therapy to show improvement in overall survival for this patient population. Ipilimumab is a monoclonal antibody against CTLA-4. CTLA-4, an immune checkpoint molecule, downregulates T-cell activation; however, ipilimumab binds CTLA-4 and functionally inhibits the immune system's innate ‘brake’, resulting in immune upregulation and an antitumor response. Ipilimumab was shown to increase overall survival to 10.1 months, compared with 6.4 months in the control arm with a hazard ratio of 0.66 ($p = 0.003$), in patients with metastatic melanoma with an overall response rate around 5–10% [1].

Simultaneously with the introduction of ipilimumab, targeted therapies were developed for the treatment of melanoma. Targeted therapies, an active area of drug development in medical oncology, refer to drugs that target specific genetic alterations or activated pathways identified in cancers that are critical to their proliferation and/or survival. By selectively targeting these alterations, these novel therapies can have a clinical benefit without many of the side effects seen with traditional cytotoxic chemotherapy. One of these ‘druggable’ targets identified in melanoma is the mutated *BRAF* gene (*BRAF*^{V600}), which occurs in about 50% of cutaneous melanomas. The serine–threonine kinase BRAF is a component of the MAPK pathway, which controls cell proliferation, differentiation and apoptosis. When an activating mutation at V600 is present, the proto-oncogene *BRAF* can drive the MAPK pathway and play a critical role in melanoma development [2].

In August 2011, vemurafenib, a selective BRAF inhibitor, was approved for use in advanced *BRAF*^{V600} mutant melanoma based on an Phase III trial that demonstrated an overall response rate of 48% in patients with previously untreated advanced melanoma [3]. In 2013, another selective BRAF inhibitor, dabrafenib, was approved by the FDA as a treatment for advanced melanoma based on an improvement in median progression-free survival compared with dacarbazine (5.1 vs 2.7 months), and response rates (50 vs 6%) [4].

Another downstream target in the MAP kinase pathway, MEK1 and MEK2, was studied as a means to inhibit BRAF activation of the MAPK pathway. The MEK inhibitor, trametinib, even as a single agent demonstrated superiority to dacarbazine in terms of response rate, progression-free survival and even overall survival, leading

to its single agent approval in *BRAF*^{V600} mutant melanoma. Based on its further inhibition of the MAPK pathway, it was thought to potentiate the effects of the BRAF inhibitor. Furthermore, in *BRAF* wild-type tissue, these selective BRAF inhibitors would paradoxically activate the MAPK kinase pathway causing cutaneous squamous cell cancers and keratocanthomas. In September 2015 dabrafenib in combination with trametinib was approved for use due to the improvement seen in response rate, progression-free survival and overall survival compared with dabrafenib alone (overall survival: 25.1 vs 18.7 months) [5]. Cobimetinib, an MEK inhibitor, was approved in November 2015 for use in combination with vemurafenib based on data that showed improved progression-free survival, response rates and overall survival benefit compared with vemurafenib alone [6]. A recent study noted an overall survival of over 2 years in patients treated with dabrafenib and trametinib, with approximately 20% progression-free survival at 3 years. Prolonged overall survival was associated with baseline features including a normal lactate dehydrogenase (LDH), fewer than three sites of metastasis and earlier stage disease [7].

Along with advances in targeted therapies, further discovery in immunomodulation resulted in the development of another type of checkpoint inhibitors, PD-1/PD-L1 inhibitors. The PD-1 receptor inhibits T cells when bound to its ligand (PD-L1 and PD-L2) on tumor and/or immune cells, which downregulates the anti-tumor immune response, and is a mechanism of adaptive resistance by allowing the tumor to evade the effects of activated T cells within the tumor microenvironment. Inhibition of the PD-1/PD-L1 axis enhances the immune response, and in September 2014, the FDA approved pembrolizumab for unresectable melanoma that previously failed ipilimumab and BRAF inhibitors in *BRAF* mutant-positive melanoma patients. In previously treated patients, pembrolizumab increased progression-free survival and 12-month survival rates compared with ipilimumab, and resulted in increased response rates (around 30%), as well as a lower incidence of treatment related adverse events [8]. In December 2014, the FDA approved a second PD-1 inhibitor, nivolumab, for treatment of advanced melanoma for patients who had failed first-line therapy with ipilimumab. It was also shown to be superior to chemotherapy in previously untreated patients whose melanoma did not have a *BRAF*^{V600} mutation. Nivolumab was shown

to increase 12 months' survival to 72.9% and had a 40% objective response rate in previously untreated metastatic melanoma patients [9].

In September 2015, the FDA approved the combination of nivolumab and ipilimumab for treatment of advanced melanoma after randomized Phase II and III clinical trials showed an increase in progression-free survival, compared with ipilimumab or nivolumab alone, albeit with a higher incidence of serious immune-related adverse events [10].

Immunotherapy by intralesional injection

In October 2015, the FDA approved a new immunotherapy for advanced melanoma, talimogene laherparepvec (T-VEC). T-VEC is herpes simplex virus type 1 that has been modified to reduce its pathogenicity in healthy cells and promote its replication in tumor cells. The virus is genetically modified to encode and express the gene for granulocyte macrophage-colony stimulating factor (GM-CSF), which when injected into the tumor, induces antigen presenting cell activation. With the *in situ* release of tumor antigens upon virus-induced tumor lysis, together with GM-CSF, an antitumor immune response is elicited. In an Phase III study of 436 patients with unresectable melanoma, patients who received T-VEC had a durable response of a minimum of 6 months of 16.3% compared with 2.1% in controls who had received GM-CSF. Median overall survival was improved to 23.3 months from 18.9 months in the T-VEC arm [11]. In this study, a higher durable response rate and longer median overall survival was seen particularly in untreated patients or those with stage IIIB, IIIC or IVM1a disease. T-VEC is the first oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma. Oncolytic viruses are a novel therapeutic class that is under continued investigation for many malignancies.

Radiotherapy in the multidisciplinary treatment of advanced stage melanoma

New data are also emerging regarding the role of radiotherapy in the treatment of melanoma. ANZMTG 1.02/TROG 02.01, a randomized controlled trial, enrolled patients with clinically palpable node-positive melanoma considered at high risk for relapse after lymphadenectomy and randomized them to either observation or regional nodal irradiation [12]. At final follow-up, radiotherapy yielded a reduction in regional nodal recurrences (HR: 0.52) without any impact on relapse-free survival or overall survival [13].

In the setting of advanced melanoma, radiotherapy can provide durable local control and/or palliation of symptoms. Stereotactic radiosurgery for intracranial metastases delivers high doses to targeted areas within the brain. Available data suggest high rates of local control for brain metastases treated with stereotactic radiosurgery [14]. Similarly, stereotactic body radiotherapy (SBRT) delivers a high dose under image guidance to an extracranial target in one to five doses. This precision delivery and dose escalation provide a significant improvement in therapeutic efficacy as compared with standard fractionated radiotherapy. Recent reports show local control upward of 88% in melanoma metastases treated with SBRT [15]. Radiotherapy is also quite effective in providing palliation for painful bony metastases from melanoma. Finally, there are tantalizing hints of synergy between SBRT and targeted systemic agents such as anti-CTLA-4 antibodies or PD-1 inhibitors [16]. Theoretical frameworks suggest that ablative radiotherapy may release tumor antigens and drive an immune response in conjunction with targeted systemic therapies. This is rapidly becoming an active area of study.

Intralesional, topical & other therapies for locoregional recurrence of melanoma

A multidisciplinary approach by a dedicated team such as the Northwestern Medicine Melanoma Group, is key to supporting and managing care for patients with locoregional recurrence of melanoma. The ideal approach is some combination of local injectables, topical agents or limb perfusion, combined with a systemic agent to try to elicit a potential additive or synergistic effect. T-VEC is only one of several recognized intralesional therapies for melanoma. Intralesional Bacille Calmette-Guerin (BCG) has been used in melanoma since 1974 [17]. Morton and colleagues demonstrated that 90% of injected cutaneous lesions showed regression and 17% of those patients had regression also of uninjected lesions. A 31% disease-free survival was achieved and sustained for up to 74 months after injection [17]. Two more recent series have shown complete regression of small series of patients with in-transit disease (five of nine patients and three of three patients, respectively) when intralesional BCG was used in combination with topical imiquimod 5% cream [18,19]. IL-2 is approved and also used as intralesional therapy for patients with locally recurrent and in-transit metastases.

“In this new era, the paradigm shifts to consider management of advanced melanoma as a chronic disease.”

One study of 24 patients achieved a complete response rate of 63% and partial response rate of 21% [20]. When intralesional IL-2 was combined with other agents (topical imiquimod and topical retinoids) to treat cutaneous metastatic melanoma, complete responses were achieved [21].

Another promising novel agent is rose bengal, a water-soluble xanthene dye, which has been developed as a 10% solution called PV-10 for use as intralesional therapy for melanoma. In an Phase II trial of 80 patients, an overall response rate of 51%, complete response rate of 26% and partial response rate of 25% was seen [22]. Patients treated with rose bengal have shown a possible systemic immune response, with one study showing 33% of 21 subjects with evaluable bystander lesions achieving complete response in these lesions [23].

Intralesional therapies are frequently time and labor intensive, requiring several treatments (sometimes multiple times per week, as is done for IL-2) until regression of tumor is achieved. Side effects vary with each agent, but include injection site reactions, fatigue, chills, pyrexia, myalgia, arthralgia and pain in extremities [11], in addition to seroconversion and systemic infection with BCG. Despite these drawbacks, intralesional therapies remain an important tool in the armamentarium of melanoma treatments, particularly for unresectable, recurrent and locoregional disease.

For locoregional disease and in-transit melanoma metastases, there is a role for topical agents, particularly when used in combination with other modalities. Imiquimod is a Toll-like receptor agonist that activates TLR7 and induces cytokine secretion and activation of Th1 lymphocytes and effector cells. There have been numerous reports of the use of imiquimod cream, as monotherapy or in combination with other agents, resulting in tumor regression rates of up to 90% for superficial lesions [24–26]. Diphencyprone cream is another topical agent that has been used as melanoma treatment. As a contact sensitizer that induces contact hypersensitivity, diphencyprone cream may be effective against melanoma via immunomodulation and activation of the thymus-derived TH17 lymphocytes [27]. In a series of 50 patients with

locally recurrent, in-transit or dermal metastatic melanoma, 46% of patients achieved a complete response and 38% patients had a partial response [28]. Patients with superficial dermal or epidermal disease had a better response, with 61% showing a complete response compared with 21% of patients with bulky disease [28]. In addition to intralesional and topical therapies, other modalities have also been used to treat in-transit or regional recurrence of melanoma. Cryotherapy, radiotherapy and various lasers may offer a significant benefit in patients with in-transit or regional recurrence [27]. Most series reporting results of these palliative treatments consist of less than 20 patients.

In the last 4 years alone, the landscape of treatment for advanced melanoma has changed dramatically. With the advent of advances in medical and radiation oncology and robust ongoing investigation of targeted therapies and immunotherapy, there is renewed hope for extended survival in patients with advanced unresectable disease. While patients are benefiting from these new therapies, a unique population of advanced melanoma survivors is developing. With increasing prevalence in the general population and more survivors, we anticipate higher numbers of patients who will be undergoing surveillance and treatment for prolonged periods of time. Dermatologists, medical oncologists, surgical oncologists, radiation oncologists and primary care physicians must be aware of this new subset of patients who will require close surveillance and follow-up. In this new era, the paradigm shifts to consider management of advanced melanoma as a chronic disease.

Financial & competing interests disclosure

The authors have no 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. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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

References

- 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).
- Menzies AM, Haydu LE, Visintin L *et al.* Distinguishing clinicopathologic features of patients with V600E and V600K *BRAF*-mutant metastatic melanoma. *Clin. Cancer Res.* 18(12), 3242–3249 (2012).
- 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).

- 4 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).
- 5 Long GV, Stroyakovskiy D, Gogas H *et al.* Dabrafenib and trametinib versus dabrafenib and placebo for Val600 *BRAF*-mutant melanoma: a multicentre, double-blind, Phase 3 randomised controlled trial. *Lancet* 386(9992), 444–451 (2015).
- 6 Larkin J, Ascierto PA, Dreno B *et al.* Combined vemurafenib and cobimetinib in *BRAF*-mutated melanoma. *N. Engl. J. Med.* 371(20), 1867–1876 (2014).
- 7 Long GV, Weber JS, Infante JR *et al.* Overall survival and durable responses in patients with *BRAF*V600-mutant metastatic melanoma receiving dabrafenib combined with trametinib. *J. Clin. Oncol.* 34(8), 871–878 (2016).
- 8 Robert C, Schachter J, Long GV *et al.* Pembrolizumab versus ipilimumab in advanced melanoma. *N. Engl. J. Med.* 372(26), 2521–2532 (2015).
- 9 Robert C, Long GV, Brady B *et al.* Nivolumab in previously untreated melanoma without *BRAF* mutation. *N. Engl. J. Med.* 372(4), 320–330 (2015).
- 10 Larkin J, Chiarion-Sileni V, Gonzalez R *et al.* Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N. Engl. J. Med.* 373(1), 23–34 (2015).
- 11 Andrtbacka RH, Kaufman HL, Collichio F *et al.* Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J. Clin. Oncol.* 33(25), 2780–2788 (2015).
- 12 Burmeister BH, Henderson MA, Ainslie J *et al.* Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. *Lancet Oncol.* 13(6), 589–597 (2012).
- 13 Henderson MA, Burmeister BH, Ainslie J *et al.* Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk of further lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a Phase 3, randomised controlled trial. *Lancet Oncol.* 16(9), 1049–1060 (2015).
- 14 Liew DN, Kano H, Kondziolka D *et al.* Outcome predictors of gamma knife surgery for melanoma brain metastases. Clinical article. *J. Neurosurg.* 114(3), 769–779 (2011).
- 15 Stinauer MA, Kavanagh BD, Schefter TE *et al.* Stereotactic body radiation therapy for melanoma and renal cell carcinoma: impact of single fraction equivalent dose on local control. *Radiation Oncol.* 6, 34 (2011).
- 16 Postow MA, Callahan MK, Barker CA *et al.* Immunologic correlates of the abscopal effect in a patient with melanoma. *N. Engl. J. Med.* 366(10), 925–931 (2012).
- 17 Morton DL, Eilber FR, Holmes EC *et al.* BCG immunotherapy of malignant melanoma: summary of a seven-year experience. *Annals Surg.* 180(4), 635–643 (1974).
- 18 Kidner TB, Morton DL, Lee DJ *et al.* Combined intralesional Bacille Calmette-Guerin (BCG) and topical imiquimod for in-transit melanoma. *J. Immunother.* 35(9), 716–720 (2012).
- 19 Kibbi N, Ariyan S, Faries M, Choi JN. Treatment of in-transit melanoma with intralesional Bacillus Calmette-Guerin (BCG) and topical imiquimod 5% cream: a report of 3 cases. *J. Immunother.* 38(9), 371–375 (2015).
- 20 Radny P, Caroli UM, Bauer J *et al.* Phase II trial of intralesional therapy with interleukin-2 in soft-tissue melanoma metastases. *Br. J. Cancer.* 89(9), 1620–1626 (2003).
- 21 Shi VY, Tran K, Patel F *et al.* 100% complete response rate in patients with cutaneous metastatic melanoma treated with intralesional interleukin (IL)-2, imiquimod, and topical retinoid combination therapy: results of a case series. *J. Am. Acad. Dermatol.* 73(4), 645–654 (2015).
- 22 Argwala S. Locoregional disease control in metastatic melanoma: exploratory analysis from Phase 2 testing of intralesional rose bengal. Presented at: *ECCO-ESMO-ESTRO Congress*. Amsterdam, The Netherlands, 27 September–1 October 2013.
- 23 Argwala S. Chemoablation of metastatic melanoma with rose bengal (PV-10). Presented at: *ASCO Annual Meeting*. Chicago, IL, USA, 4–8 June 2010.
- 24 Florin V, Desmedt E, Vercambre-Darras S, Mortier L. Topical treatment of cutaneous metastases of malignant melanoma using combined imiquimod and 5-fluorouracil. *Invest. New Drugs* 30(4), 1641–1645 (2012).
- 25 Rivas-Tolosa N, Ortiz-Brugues A, Toledo-Pastrana T *et al.* Local cryosurgery and imiquimod: a successful combination for the treatment of locoregional cutaneous metastasis of melanoma: a case series. *J. Dermatol.* 43(5), 553–556 (2016).
- 26 Heber G, Helbig D, Ponitzsch I, Wetzig T, Harth W, Simon JC. Complete remission of cutaneous and subcutaneous melanoma metastases of the scalp with imiquimod therapy. *J. Dtsch Dermatol. Ges.* 7(6), 534–536 (2009).
- 27 Abbott AM, Zager JS. Locoregional therapies in melanoma. *Surg. Clin. North Am.* 94(5), 1003–1015, viii (2014).
- 28 Damian DL, Saw RP, Thompson JF. Topical immunotherapy with diphencyprone for in transit and cutaneously metastatic melanoma. *J. Surg. Oncol.* 109(4), 308–313 (2014).