NEW SYSTEMIC THERAPIES FOR METASTATIC MELANOMA – MAPK INHIBITORS AND IMMUNOTHERAPY

Alexander M Menzies
Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia.
Email: alexander.menzies@sydney.edu.au

Abstract

Metastatic melanoma has a poor prognosis and until recently systemic therapy was ineffective. Advances in the understanding of tumour biology and immune regulation have led to the development of targeted agents that have changed clinical practice. BRAF and MEK inhibitors target the constitutively active MAPK growth-signalling pathway in BRAF-mutant melanoma. They have a rapid mode of action, cause tumour regression in most patients, and offer improved survival compared with conventional chemotherapy. However, the near-universal and quite rapid development of acquired resistance is a major concern. Drugs targeting T cell regulation also show promise, with the anti-CTLA-4 antibody ipilimumab demonstrating a durable clinical benefit in a minority of patients but an overall survival advantage over conventional chemotherapy, while the emerging anti-PD-1 and anti-PD-L1 antibodies look likely to improve response rates with less toxicity. Trials of combinations of these therapies and new drugs targeting other molecular aberrations are under way, as are efforts to understand the mechanisms behind drug resistance.

Melanoma is increasing in incidence, and while it is curable in the majority of early stage cases, visceral metastatic disease carries an extremely poor prognosis. Until recently, systemic treatments were largely ineffective, with response rates of less than 10% and median overall survival times of only six to nine months.[1] The last few years have witnessed a revolution in systemic treatment, founded upon a rapidly evolving understanding of tumour biology and immune physiology, providing significant improvements in outcomes for patients with metastatic melanoma. Central to this process has been the discovery of specific driver oncogenes that exist in a large proportion of melanoma patients, as well as an improved understanding of the processes involved in immune regulation. Several targeted drugs have recently been shown to be more effective than previous systemic regimens, but while these have rapidly entered routine clinical practice, a large number of trials are under way, designed to build on the early success of these therapies.

Molecular pathways and therapeutic targets

Advances in the understanding of molecular biology have identified complex intracellular signalling pathways that control cell proliferation, survival, differentiation, motility and angiogenesis. One such pathway critical to most cancers is the mitogen-activated protein kinase (MAPK) pathway (figure 1). This pathway is dysregulated and overactive in melanoma as a result of molecular alterations in genes encoding key components of the pathway (eg. BRAF and NRAS mutations) or upstream alterations in cell-surface receptors (eg. KIT), resulting in uncontrolled tumour proliferation and survival.[2,3]

Mutations in BRAF occur in approximately 50% of melanomas.[4,5] Mutations generally occur at codon 600 in exon 15 of the BRAF gene, with 75% being V600E and 20% V600K.[5] Age is the best correlate of BRAF status, being inversely proportional to BRAF-mutant status.[5] While other clinical correlates exist such as tumour histological subtype, primary melanoma site and chronic sun damage,[6] BRAF-mutant melanoma is thought to carry a poor prognosis compared with BRAF wild-type disease once metastatic spread has occurred.[6]

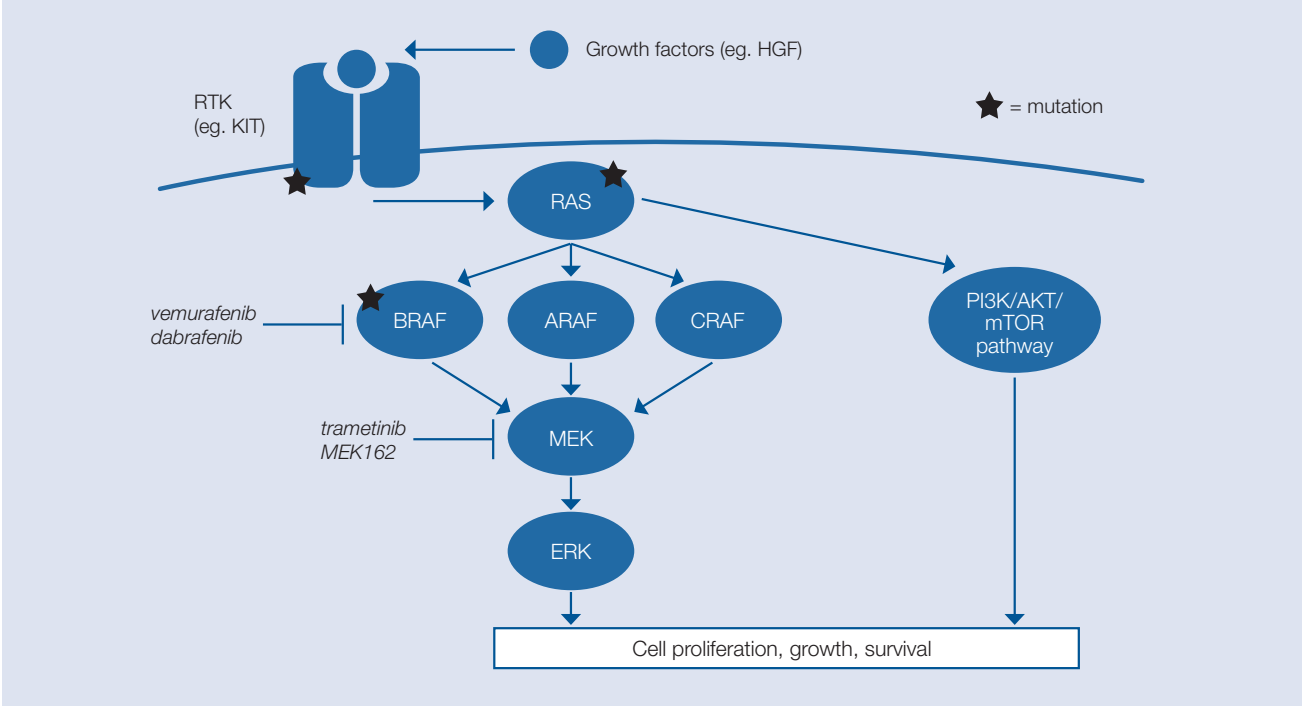
NRAS and KIT mutations are less common (20% and <5% respectively). No clinical correlates exist for NRAS-mutant melanoma, however KIT mutations occur more commonly in acral and mucosal melanomas, and NRAS-mutant melanoma may have a poorer survival after diagnosis of metastatic disease than BRAF-mutant or BRAF/NRAS wild-type disease.[4]

Several other pathways exist and are often abnormal in melanoma, such as the PI3K, Wnt and NF-κB pathways, however to date most interest has focused on the MAPK pathway.

BRAF inhibitors

Initial attempts to target mutant BRAF were unsuccessful. Sorafenib, a multi-kinase inhibitor, was trialled because of its known activity against RAF kinases. Phase 2 clinical trials failed to show significant efficacy, with pharmacodynamic analyses suggesting that only partial inhibition of BRAF signalling was achieved at maximum tolerated dose.[7,8] The selective BRAF inhibitors vemurafenib (PLX4032) and dabrafenib (GSK2118436) were designed to specifically inhibit mutant BRAF over other RAF kinases, enabling higher concentrations of drug to be administered without approaching the maximum tolerated dose, resulting in more complete inhibition of BRAF kinase activity.[9,10] The result of this has been an unprecedented improvement in clinical outcome for patients. However, specific toxicities have emerged, notably cutaneous squamous cell carcinoma.

Figure 1: *The MAPK pathway and BRAF and MEK inhibitors. In normal cells, growth factors bind to cell surface receptor tyrosine kinases (RTK), triggering signalling down various pathways, including the RAS-RAF-MEK-ERK (MAPK) and PI3K/AKT/mTOR pathways, resulting in cell proliferation, growth and survival. Specific aberrations in melanomas affecting the MAPK pathway include BRAF (50%), NRAS (20%) and KIT (<5%) mutations*



Vemurafenib, the first selective BRAF inhibitor, was developed with a companion PCR-based BRAF diagnostic test designed to detect the V600E BRAF mutation. Clinical trials in V600E BRAF-mutant patients demonstrated high activity, a rapid mode of action and a significant clinical benefit.[11,12] A small number of V600K patients were retrospectively identified and were also shown to have had benefit, and recent case reports suggest activity in all V600 BRAF-mutant melanomas. Initial results from a phase 3 trial were reported in 2011,[13] and recently more mature data have been presented.[14] When used as first line therapy in V600E BRAF-mutant metastatic melanoma, vemurafenib had a response rate of 53%, a median progression-free survival (PFS) of 6.9 months and a median overall survival of 13.6 months, much higher than conventional dacarbazine chemotherapy. Vemurafenib was approved by the Australian Therapeutic Goods Association in mid 2012. A phase 1 study in patients with brain metastases has shown intracranial activity,[15] and a phase 2 study in such patients is underway.

Dabrafenib, the second BRAF inhibitor to be developed, underwent phase 1 trials in V600E/K/D and K601E BRAF-mutant melanoma,[10] and phase 2 trials in V600E/K melanoma.[16] As with vemurafenib, initial results were impressive. Dabrafenib was shown to be highly active, but more so in V600E than V600K patients, and no activity was seen in patients with non-V600 tumours. Early analysis of the first line phase 3 study in V600E patients reported a response rate of 53%, and median PFS of 5.1 months.[17] Overall survival data are not mature. A phase 2 study in patients with V600E/K melanoma with brain metastases has recently been completed, demonstrating unprecedented activity and benefit in patients with untreated, and previously treated but relapsed, brain metastases, with response rates of 30-40%, a median PFS of 16 weeks and a median overall survival of 33 weeks in V600E patients.[18]

At this stage it appears that vemurafenib and dabrafenib share similar efficacy, but have different toxicity profiles. Class-like cutaneous toxicities, including rash, hyperkeratosis, cutaneous squamous cell carcinoma and keratoacanthoma occur with both drugs, but to a lesser degree with dabrafenib. Of note, cutaneous squamous cell carcinomas occurred in 19% of patients treated with vemurafenib,[13] and in only 5% of those treated with dabrafenib.[17] Other class toxicities such as arthralgia and fatigue also appear to occur at a higher rate and grade with vemurafenib. Drug-specific toxicities include photosensitivity and hepatitis (10% grade 3) with vemurafenib,[13] and pyrexia (3% grade 3) with dabrafenib.[17] Despite these toxicities, both drugs are generally well tolerated, with mild and manageable side-effects that rarely lead to drug discontinuation. A small number of patients on either drug have developed new primary melanomas, with studies ongoing as to whether this is an iatrogenic phenomenon.[19]

Most patients treated with BRAF inhibitors receive only brief benefit (a few months) due to the rapid development of acquired resistance. Much attention is currently focused on the specific mechanisms behind this. Based upon biopsies of progressing lesions from patients, it appears that 'MAPK reactivation' occurs in the majority. This is due to amplification and splice variation,[20,21] of BRAF, RAF isoform switching,[22,23] as well as new mutations in NRAS,[24] MEK,[25] and overexpression of COT (a partner kinase).[26] A minority of cases do not demonstrate MAPK reactivation,

but show increased signalling through other pathways (such as the PI3K pathway), apparently as a result of increased expression of growth factor receptors such as IGF-1R and PDGFRB.[22,24] To date, it appears that no single mechanism predominates, but that changes to the drug-binding site in the BRAF protein do not occur, as is the common mechanism of acquired resistance with other targeted therapies.[27,28]

MEK inhibitors

MEK inhibitors began development prior to BRAF inhibitors, the objective being to inhibit MAPK signalling at a downstream level. They were initially trialed in melanoma patients without knowledge of their BRAF (or NRAS) status with limited effect. Recently, trials have been conducted in BRAF-mutant and NRAS-mutant melanoma patients with impressive results.

Trametinib is the most studied MEK inhibitor in melanoma. A phase I trial in all BRAF-mutant and wild-type patients demonstrated significant activity in BRAF-mutant melanoma, with little activity in BRAF wild-type disease.[29] A phase 2 study in patients with or without prior BRAF inhibitor therapy demonstrated no response when given after BRAF inhibitor failure.[30] Initial reports from a recent phase 3 trial showed a response rate of 22% and a median PFS of 4.8 months. Overall survival data were immature, but currently the hazard ratio for progression or death is 0.54 when compared with chemotherapy (dacarbazine or paclitaxel).[31] Toxicity included MEK inhibitor class-like effects such as rash (including acneiform rash), hypertension, diarrhoea, oedema, transient mild cardiac dysfunction, as well as rare ocular toxicity (chorioretinopathy) and creatine kinase elevation. Most toxicities were mild and did not require drug discontinuation.

MEK162 has recently completed a phase 2 trial, examining activity in both BRAF-mutant and NRAS-mutant melanoma.[32] In BRAF-mutant melanoma patients (N=25), including 20% with prior BRAF inhibitor therapy, a response rate of 23% and median PFS of 3.5 months were seen. Among NRAS-mutant melanoma patients (N=28), a response rate of 21% and median PFS of 3.6 months were reported. Adverse events were similar to those associated with trametinib, but higher rates of grade 3 creatine kinase elevation and diarrhoea were seen, and less hypertension and cardiac dysfunction occurred.

Combination BRAF and MEK inhibitors

BRAF, and to a lesser extent MEK inhibitors, provide high initial efficacy, but the near-universal development of acquired resistance is often rapid. In order to further improve response rates and delay resistance, new approaches have been explored, such as combining therapies. The first attempt to do this was with the combination of dabrafenib and trametinib. The rationale behind this approach was based upon the individual activity and different toxicity profile of the two drugs. Furthermore, since both drugs target the MAPK pathway, and because BRAF inhibitor resistance generally results in reactivation of the pathway, it was postulated that combined blockade might suppress resistance. Finally, it was thought that combining the two drugs might reduce the toxicities of each drug when given individually (especially cutaneous toxicity from BRAF inhibitors).

Table 1: *Summary of BRAF and MEK Inhibitors.*

	vemurafenib[13,14] %	**dabrafenib[17] %**	**trametinib[31] %**	**dabrafenib + trametinib[35] %**
Outcome				
RR	57	53	22	63
DCR	97	95	78	100
PFS	6.9 mo	5.1 mo	4.8 mo	10.8 mo
OS	13.6 mo	-	-	-
Toxicity (G3/4)				
cutaneous squamous cell carcinoma	19	5	-	3
keratoacanthoma	10	2	-	-
hyperkeratosis	1	3	-	-
rash	9	-	9	2
other	hepatitis 10	fever 3	HTN 12 cardiac 7 ocular 1	fever 8

Outcome measures and grade 3/4 toxicities with BRAF and MEK inhibitors. RR, response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; HTN, hypertension.

NB. Only vemurafenib has mature outcome data at this stage.

An early analysis of data from the phase 1/2 trial of combination therapy was presented in 2011. A higher response rate was reported than that achieved with BRAF inhibitor monotherapy,[33] and an impressive 19% response rate was seen in those who had failed prior BRAF inhibitor therapy.[34] In BRAF inhibitor naïve patients a response rate of 63% and a median PFS of 10.8 months were recently reported.[35] Toxicities with this combination were mild. Notably, cutaneous toxicities such as hyperkeratosis, cutaneous squamous cell carcinoma, and keratoacanthoma seen with dabrafenib, and rash, hypertension, cardiac dysfunction seen with trametinib were greatly reduced (table 1). The most common toxicity was fever (8% grade 3), significantly more frequent than with dabrafenib monotherapy. The process behind this is incompletely understood, but it generally occurs early, is rarely repetitive, can be managed with brief dose interruption and corticosteroid prophylaxis (in recurrent cases), and does not necessitate dose reduction.[36] Furthermore, it does not appear to be related to disease burden or treatment response.[36] A phase 3 trial of the combination dabrafenib and trametinib versus dabrafenib monotherapy is underway (NCT01584648).

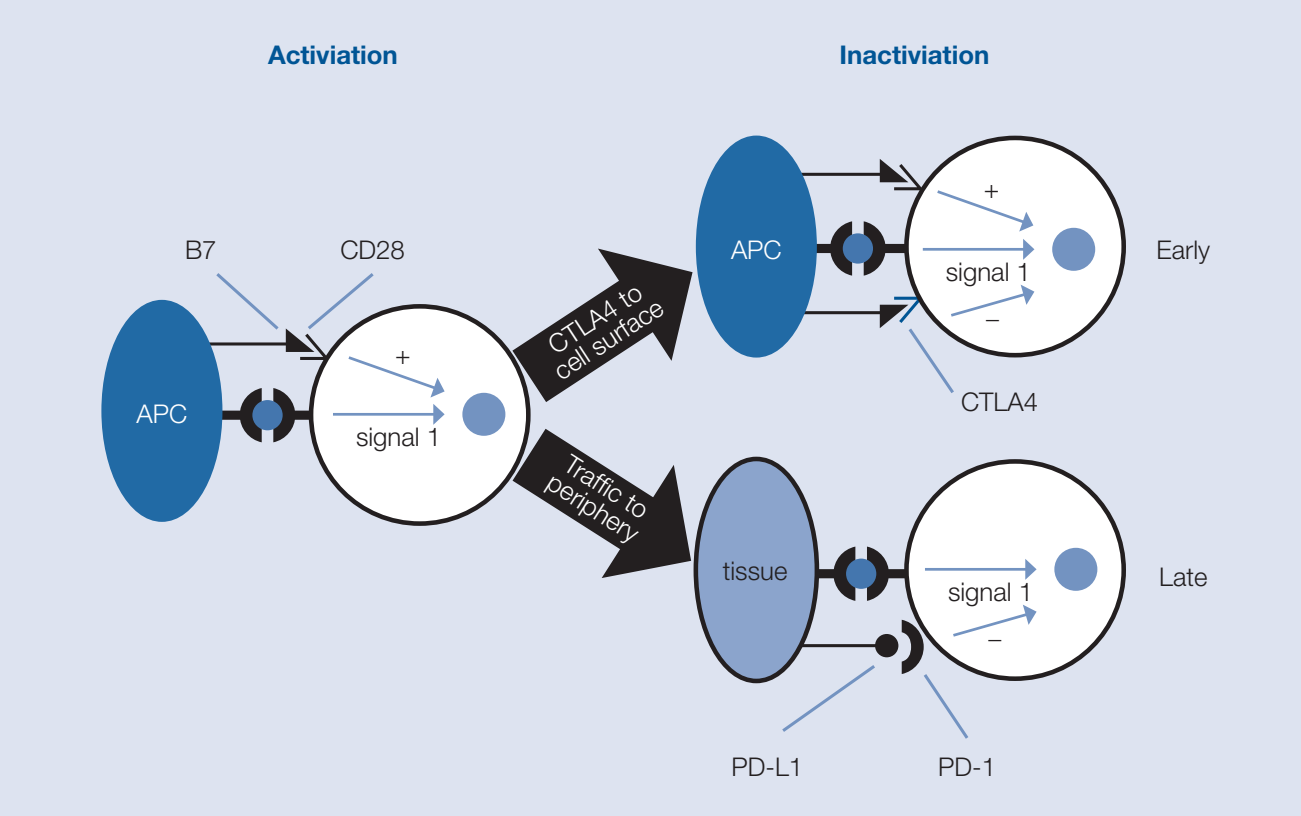
Immune regulation and drug targets

Immunotherapy has a long and generally disappointing history in melanoma, but no doubt remains a critical component of treatment. To date, immunotherapy for metastatic disease has been largely limited to a few centres worldwide. IL-2 and adoptive T cell therapy provide durable responses in a small subset of patients, but these therapies are highly toxic and not feasible for the wider melanoma population. Recent advances in the understanding of T cell regulation and the development of specific agents that target critical components of this have proven successful.

Regulation of the immune system is highly complex. T cells express numerous receptors on their surface that interact with antigen presenting cells (APCs), leading to T cell activation and inactivation. T cell activation occurs via two steps: 1) APCs present antigens (eg. tumour antigens) to the T cell receptor; 2) APCs express B7 which interacts with the T cell CD28 receptor. This co-stimulation is required for T cell activation (figure 2).[37]

Once activated, T cells are inactivated in a number of ways in order to prevent widespread autoimmunity. One process of inactivation that occurs early involves expression of the CTLA-4 receptor on the T cell surface, which binds to B7 on APCs and results in an inhibitory signal to the T cell. In peripheral tissues (such as tumours) at sites of inflammation, T cells express PD-1, which binds to PD-L1 expressed by tissue leading to inactivation and protection of tissues from collateral damage. CTLA-4 is therefore important early in the immune response and interacts with APCs, whereas PD-1 is more specific for peripheral tissues and can interact with tissue directly. Inhibition of CTLA-4 or PD-1 can therefore promote anti-tumour immunity.[37]

Figure 2: *T cell regulation. CTLA-4 modulates the early phase of T cell activation. PD-1 is expressed on T cells in the periphery, serving to limit the activity of T cells during an inflammatory response, thereby protecting normal tissues from collateral destruction. APC, antigen presenting cell. Adapted from Topalian Current Opin Immonol. 2012*



Ipilimumab

Ipilimumab is the first immune therapy shown to improve overall survival in a large group of metastatic melanoma patients. It is an anti CTLA-4 antibody that binds to and inhibits the CTLA-4 T cell receptor, resulting in sustained but non-specific T cell activation. Two phase 3 clinical trials have now been completed. The response rate in the first line combination trial (with dacarbazine v dacarbazine alone),[38] and the second line trial (Ipilimumab v Ipilimumab + gp100 vaccine v gp100 alone),[39] was approximately 11-15%, with median PFS 2.8 months, and median overall survival 10-11 months. One and two year survival was 47% and 26%, approximately a 10% increase over the control arms. Results from these trials suggest that ipilimumab has a slow onset but durable response and survival advantage in a subset of patients, but as yet a biomarker of response has not been identified. Activity has also been demonstrated in patients with small asymptomatic brain metastases.[40] Ipilimumab received TGA approval in Australia as second line treatment in mid-2011.

Toxicities from ipilimumab, as expected, are immune related and include cutaneous gastrointestinal, and endocrine toxicities. Early detection and intervention of toxicities is essential as some are potentially life threatening, and early intervention is necessary. Most, however, respond to corticosteroids and may not preclude further dosing.

Anti-PD-1 and anti-PD-L1 antibodies

This new class of immune agents aims to augment the anti-tumour T cell response at a more tumour-specific level, by blocking the interaction of PD-1 and PD-L1, preventing T cell inactivation at a tumoural level. Multiple anti-PD-1 antibodies are in development, and two phase I trials have reported activity in melanoma thus far. The first-in-class phase I trial of BMS-936558, including 94 melanoma patients, reported a 28% response rate, with 20 of 31 patients having an ongoing response for over one year.[41] The phase 1 trial of MK-3475 included two patients with melanoma, one of whom achieved a partial response.[42] In the BMS-396558 study, no responses were seen in those whose tumours did not express PD-L1, suggesting that this may be a predictive biomarker. Toxicity with both agents was immunological, affecting skin, gastrointestinal and endocrine systems, but appeared to be less frequent and severe than that with ipilimumab, possibly indicating the more tumour-specific nature of this therapy.

Anti-PD-L1 antibodies are also in development, again designed to block PD-1/PD-L1 interaction, thus preventing T cell inactivation. The first-in-class phase 1 trial of BMS-936559 including 52 patients with melanoma demonstrated a response rate of 17%, with 8 of 16 patients having an ongoing response for over one year.[43] Again, toxicity was generally mild and manageable.

Next steps

While MAPK inhibitors and new immunotherapies appear vastly superior to previous chemotherapy regimens, they all have limitations. BRAF and MEK inhibitors provide responses in the majority of patients, but their benefit is often brief. Immune therapies provide slower, more durable responses but in a largely unidentifiable minority of patients. Based on this fact alone, it appears logical to combine MAPK and immune therapies (such as vemurafenib and ipilimumab). Translational evidence for this approach is robust, with evidence that BRAF inhibition leads to increased expression of melanoma differentiation antigens, and an influx of tumour infiltrating lymphocytes.[44,45] Such trials (eg. of vemurafenib and ipilimumab) have commenced and results are eagerly anticipated. Trials of other combinations have also begun, shaped by research into BRAF inhibitor resistance mechanisms, targeting other cell signalling pathways (eg. BRAF and PI3K inhibitors).

Perhaps the greatest role for these new treatments will be in the adjuvant setting. Currently the risk of distant relapse and death in patients with high-risk early stage melanoma (IIC/III) is approximately 50%.[46] Adjuvant trials of vemurafenib (NCT01667419) and the combination dabrafenib and trametinib (NCT01682083) will commence shortly, while the results from an adjuvant ipilimumab trial (NCT00636168) are expected in 2013.

Conclusion

While results of recent clinical trials of MAPK and immunotherapy agents have been impressive, resulting in a seismic shift in the management of patients with metastatic melanoma, improvements are required to build upon the early success of these therapies. Adjuvant trials of many of these drugs are under way with the hope of improving cure rates for early melanoma, and as more molecular targets are identified and trials of combinations of targeted drugs commence, improvements in patient outcomes can be expected. The systemic management of metastatic melanoma has come a long way in a short time, but there is still a long way to go.

References

1. Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma in the era of molecular profiling. Lancet. 2009;374(9687):362-5.
2. McCubrey JA, Steelman LS, Chappell WH, et al. Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. Biochim Biophys Acta. 2007;1773(8):1263-84.
3. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature. 2002;417(6892):949-54.
4. Jakob JA, Bassett RL, Jr., Ng CS, et al. NRAS mutation status is an independent prognostic factor in metastatic melanoma. Cancer. 2012;118(16):4014-23.
5. Menzies AM, Haydu LE, Visintin L, et al. Distinguishing clinicopathologic features of patients with V600E and V600K BRAF-mutant metastatic melanoma. Clin Cancer Res. 2012;18(12):3242-9.
6. Long GV, Menzies AM, Nagrial AM, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. J Clin Oncol. 2011;29(10):1239-46.
7. Eisen T, Ahmad T, Flaherty KT, et al. Sorafenib in advanced melanoma: a Phase II randomised discontinuation trial analysis. Br J Cancer. 2006;95(5):581-6.
8. Flaherty KT, Redlinger M, Schuchter LM, Lathia CD, Weber BL, O'Dwyer PJ. Phase I/II, pharmacokinetic and pharmacodynamic trial of BAY 43-9006 alone in patients with metastatic melanoma. J Clin Oncol 2005;23(Suppl 16):(abstract 3037).
9. Bollag G, Hirth P, Tsai J, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature. 2010;467(7315):596-9.
10. Falchook GS, Long GV, Kurzrock R, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. Lancet. 2012;379(9829):1893-901.
11. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010;363(9):809-19.

12. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med. 2012;366(8):707-14.
13. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507-16.
14. 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 BRAFV600E-mutated melanoma. J Clin Oncol 2012;30(Suppl 15):(abstract 8502).
15. Dummer R, Rinderknecht J, Goldinger SM, et al. An open-label pilot study of vemurafenib in previously treated metastatic melanoma patients with brain metastases. J Clin Oncol 2011;29(Suppl 15):(abstract 8548).
16. Trefzer U, Minor DR, Ribas A, et al. BREAK-2: a phase IIA trial of the selective BRAF kinase inhibitor GSK2118436 in patients with BRAF mutation-positive (V600E/K) metastatic melanoma. Pigment Cell Melanoma Res 2011;24:1020 (abstract LBA1-1).
17. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380(9839):358-65.
18. Long GV, Trefzer U, Davies MA, et al. Efficacy of dabrafenib for the treatment of patients with BRAFV600E/K mutation-positive melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label phase 2 study. Lancet Oncol. 2012 (in press)
19. Zimmer L, Hillen U, Livingstone E, et al. Atypical Melanocytic Proliferations and New Primary Melanomas in Patients With Advanced Melanoma Undergoing Selective BRAF Inhibition. J Clin Oncol. 2012;30(19):2375-83.
20. Shi H, Moriceau G, Kong X, et al. Melanoma whole-exome sequencing identifies (V600E)B-RAF amplification-mediated acquired B-RAF inhibitor resistance. Nat Commun. 2012;3(724.
21. Poulikakos PI, Persaud Y, Janakiraman M, et al. RAF inhibitor resistance is mediated by dimerization of aberrantly spliced BRAF(V600E). Nature. 2011;480(7377):387-90.
22. Villanueva J, Vultur A, Lee JT, et al. Acquired resistance to BRAF inhibitors mediated by a RAF kinase switch in melanoma can be overcome by cotargeting MEK and IGF-1R/PI3K. Cancer Cell. 2010;18(6):683-95.
23. Montagut C, Sharma SV, Shioda T, et al. Elevated CRAF as a potential mechanism of acquired resistance to BRAF inhibition in melanoma. Cancer Res. 2008;68(12):4853-61.
24. Nazarian R, Shi H, Wang Q, et al. Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. Nature. 2010;468(7326):973-7.
25. Wagle N, Emery C, Berger MF, et al. Dissecting therapeutic resistance to RAF inhibition in melanoma by tumor genomic profiling. J Clin Oncol. 2011;29(22):3085-96.
26. Johannessen CM, Boehm JS, Kim SY, et al. COT drives resistance to RAF inhibition through MAP kinase pathway reactivation. Nature. 2010;468(7326):968-72.
27. Nguyen KS, Kobayashi S, Costa DB. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancers dependent on the epidermal growth factor receptor pathway. Clin Lung Cancer. 2009;10(4):281-9.
28. Gramza AW, Corless CL, Heinrich MC. Resistance to Tyrosine Kinase Inhibitors in Gastrointestinal Stromal Tumors. Clin Cancer Res. 2009;15(24):7510-8.
29. Falchook GS, Lewis KD, Infante JR, et al. Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: a phase 1 dose-escalation trial. Lancet Oncol. 2012;13(8):782-9.
30. Kim KB, Lewis K, Pavlick A, et al. A phase II study of the MEK1/MEK2 inhibitor GSK1120212 in metastatic BRAF-V600E or K mutant cutaneous melanoma patients previously treated with or without a BRAF inhibitor. Pigment Cell Melanoma Res 2011;24:1021 (abstract LBA1-3).
31. Flaherty KT, Robert C, Hersey P, et al. Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma. N Engl J Med. 2012
32. Ascierto PA, Berking C, Agarwala SS, et al. Efficacy and safety of oral MEK162 in patients with locally advanced and unresectable or metastatic cutaneous melanoma harboring BRAFV600 or NRAS mutations. J Clin Oncol 2012;30(Suppl 15):(abstract 8511).
33. Infante JR, Falchook GS, Lawrence DP, et al. Phase I/II study to assess safety, pharmacokinetics, and efficacy of the oral MEK 1/2 inhibitor GSK1120212 (GSK212) dosed in combination with the oral BRAF inhibitor GSK2118436 (GSK436). J Clin Oncol 2011;29(Suppl 15):(abstract CRA8503).
34. Flaherty K, Infante JR, Falchook GS, et al. Phase I/II expansion cohort of BRAF inhibitor GSK2118436 + MEK inhibitor GSK1120212 in patients with BRAF mutant metastatic melanoma who progressed on a prior BRAF inhibitor. Pigment Cell Melanoma Res 2011;24:1022 (abstract LBA1-4).
35. Weber JS, Flaherty KT, Infante JR, et al. Updated safety and efficacy results from a phase I/II study of the oral BRAF inhibitor dabrafenib (GSK2118436) combined with the oral MEK 1/2 inhibitor trametinib (GSK1120212) in patients with BRAFi-naive metastatic melanoma. J Clin Oncol 2012;30(Suppl 15):(abstract 8510).
36. Lee CI, Menzies AM, Haydu L, Clements A, Kefford R, Long GV. Correlates of fever in patients (pts) receiving combined dabrafenib (GSK2118436) plus trametinib (GSK1120212) for V600 BRAF-mutant metastatic melanoma (MM). J Clin Oncol 2012;30(Suppl 15):(abstract e19011).
37. Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. Curr Opin Immunol. 2012;24(2):207-12.
38. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma. N Engl J Med. 2011
39. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711-23.
40. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol. 2012;13(5):459-65.
41. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443-54.
42. Patnaik A, Kang SP, Tolcher AW, et al. Phase I study of MK-3475 (anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. J Clin Oncol. 2012;30(Suppl 15):(abstract 2512).
43. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366(26):2455-65.
44. Boni A, Cogdill AP, Dang P, et al. Selective BRAFV600E inhibition enhances T-cell recognition of melanoma without affecting lymphocyte function. Cancer Res. 2010;70(13):5213-9.
45. Wilmott JS, Long GV, Howle JR, et al. Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. Clin Cancer Res. 2012;18(5):1386-94.
46. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27(36):6199-206.