FROM THE ANALYST'S COUCH

The malignant melanoma landscape

Rachel M. Webster and Samuel E. Mentzer

Image from Nikola Spasenoski/Alamy

In 2014 an estimated 112,200 patients will be diagnosed with malignant melanoma in the United States and five major European markets. More than 90% will be diagnosed early when the disease is resectable[1]. However, when discovered late, the prognosis is poor.

Current treatment options

Prior to 2011, the mainstay of treatment for unresectable malignant melanoma was cytotoxic therapy, notably dacarbazine, which is characterized by low response rates (10%) and poor survival (12-month overall survival is 36%). In 2011, two important drugs were approved. Ipilimumab (Yervoy; Bristol-Myers Squibb), a first-in-class monoclonal antibody that targets cytotoxic T lymphocyte antigen 4 (CTLA4) — a negative regulator of cytotoxic T cell activation — is associated with low response rates (11%), but responses are frequently durable, extending to several years. Vemurafenib, a small-molecule inhibitor (Zelboraf; Roche/Genentech/Daiichi Sankyo/Chugai) is another first-in-class drug that is marketed with a companion diagnostic (Cobas 4800 BRAF V600 Mutation Test; Roche). It targets the V600E mutation in the BRAF enzyme, which is found in 40–50% of patients. It shows a 3.9-month median overall survival benefit over dacarbazine. Although response rates to vemurafenib are high (57%) and rapid, resistance to treatment usually develops within 6 months. Ipilimumab is currently used to treat up to 30% of $BRAF^{V600E}$-positive patients with low tumour burden, owing to the potential for durable responses[1].

In May 2013, two additional targeted therapies, dabrafenib (Tafinlar; GlaxoSmithKline) and trametinib (Mekinist; GlaxoSmithKline), as well as the ThxID-BRAF (BioMérieux) companion diagnostic test, were approved. Dabrafenib also inhibits $BRAF^{V600E}$, whereas trametinib is a first-to-market MAPK/ERK (MEK) inhibitor that is approved for use in $BRAF^{V600E}$ and the less common $BRAF^{V600K}$-mutated malignant melanoma. Both drugs achieved statistically significant improvements in progression-free survival in Phase III studies. Trametinib had response rates of 22% compared with 52% for dabrafenib. A combination of dabrafenib and trametinib was granted accelerated approval by the US Food and Drug Administration (FDA) for unresectable or metastatic $BRAF^{V600E}$ or $BRAF^{V600K}$ malignant melanoma, based on Phase I/II trials. These findings were replicated in the Phase III COMBI-d trial, achieving a median progression-free survival of 9.3 months (compared with 8.8 months for dabrafenib monotherapy), and a 67% response rate. Moreover, the combination was associated with a reduction in the incidence of cutaneous hyperproliferative events (2%) compared with dabrafenib alone (9%). Although the combination of BRAF and MEK inhibitors prolongs response to therapy, acquired resistance is inevitable; and although immunotherapy offers the potential for durable responses, few patients will benefit. ▸

Table 1 | **Select therapies in Phase III development for malignant melanoma**

Products	Developers	Target or mechanism	Notes on trials
BRAF–MEK–ERK pathway inhibitors			
Dabrafenib (Tafinlar), trametinib (Mekinist)	GlaxoSmithKline	BRAF or MEK	Tested as adjuvant combination treatment for $BRAF^{V600E}$ or $BRAF^{V600K}$ malignant melanoma
Cobimetinib	Roche/Genentech/ Exelixis	MEK	Tested in combination with vemurafenib in $BRAF^{V600E}$ or $BRAF^{V600K}$ malignant melanoma
Encorafenib (LGX818)	Novartis	BRAF	Tested alone or in combination with binimetinib in $BRAF^{V600E}$ or $BRAF^{V600K}$ malignant melanoma
Binimetinib (MEK162)	Novartis/Array	MEK	Tested in *NRAS*-mutated melanoma and in combination with encorafenib in $BRAF^{V600E}$ or $BRAF^{V600K}$ malignant melanoma
Immune checkpoint inhibitors			
Nivolumab	Bristol-Myers Squibb	PD1	Tested alone or in combination with ipilimumab in treatment-naive patients with malignant melanoma and in patients who have progressed on prior ipilimumab
Pembrolizumab (MK-3475)	Merck & Co.	PD1	Tested as single-agent in ipilimumab-naive patients with malignant melanoma
Other immunotherapies and therapeutic vaccines			
Talimogene laherparepvec (T-Vec)	Amgen	Viral vector vaccine	Tested in unresectable stage IIIb/IIIc or IV malignant melanoma

ERK, extracellular signal-regulated kinase; MEK, MAPK/ERK kinase; PD1, programmed cell death protein 1.

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Late-stage drug pipeline

Several BRAF and MEK inhibitors are in late-stage clinical development[1,2] (TABLE 1). The MEK inhibitor cobimetinib (Roche/Genentech/Exelixis) is being evaluated in a Phase III study in combination with vemurafenib. In a Phase Ib study, cobimetinib/vemurafenib achieved a response rate of 87% in BRAF-inhibitor-naive patients. The MEK inhibitor binimetinib (MEK162; Novartis/Array) has potential for the treatment of *NRAS*-mutated malignant melanoma (accounting for approximately 15–25% of patients), but response rates are low (20% in both *NRAS*- and *BRAF*-mutated patients). Binimetinib is also being evaluated in a three-armed Phase III study in combination with the BRAF inhibitor encorafenib (LGX818; Novartis) versus encorafenib and vemurafenib monotherapies.

Programmed cell death protein 1 (PD1)-directed monoclonal antibodies, a novel class of immune checkpoint inhibitors, are also in Phase III clinical development. In December 2013, nivolumab (Bristol-Myers Squibb/Ono) was filed for regulatory approval in Japan based on Phase II data; this is the first global filing of an anti-PD1 agent. Nivolumab is in three Phase III studies in the United States and Europe. Phase Ib data for nivolumab are remarkable, with high response rates (41%) and durable responses (median overall survival is 20 months). Nivolumab combined with ipilimumab achieved an even higher response rate (53%). Responses were also rapid and durable (82% of responses were ongoing at analysis), with an unprecedented median overall survival of 40 months. However, the higher incidence of adverse events and the likely high cost that the immunotherapy combination will command could constrain its uptake. Pembrolizumab (MK-3475; Merck), another anti-PD1 therapy, is also in Phase III development. It was awarded FDA breakthrough designation and has been undergoing a rolling review for patients with unresectable or metastatic malignant melanoma who have previously received ipilimumab. It remains to be determined which PD1-directed therapy will demonstrate the highest and most durable response rates[1,2].

Other immunotherapeutic approaches are also being explored. The oncolytic immunotherapy talimogene laherparepvec (T-Vec; Amgen) is a modified version of herpes simplex virus type 1 (HSV1) that is modified to selectively replicate in tumour cells and activate a systemic immune response. In a Phase III study it achieved a durable response rate of 16% compared with 2% for patients treated with granulocyte–macrophage colony-stimulating factor (GM-CSF). However, its median overall survival was not met with statistical significance (23.3 months versus 18.9 months with GM-CSF). Interestingly, talimogene laherparepvec is being evaluated in combination with ipilimumab in a Phase I/II study. Preliminary data show that the combination achieved an overall response rate of 41%, with an impressive complete response rate of 24%.

Ipilimumab is also being tested as adjuvant treatment after resection of stage III melanoma. Initial results reported from a Phase III trial show a recurrence-free survival of 26.1 months (compared with 17.1 months for placebo). However, the frequency of grade 3/4 immune-related adverse events was high with ipilimumab (42%) and there were treatment-related deaths (1.1%). The rate of discontinuation owing to adverse events was also higher with ipilimumab (48.8%) than with placebo (1.7%).

Market indicators

In 2013, ipilimumab and vemurafenib achieved US sales of $577 million and $127 million, respecively. Dabrafenib and trametinib achieved early strong uptake in the United States (US$30 million). Ipilimumab has had a considerable impact on the malignant melanoma market, and in 2013 it accounted for nearly two-thirds of total malignant melanoma therapy US sales[1] (FIG. 1). Additional immune checkpoint inhibitors, namely nivolumab and pembrolizumab, are expected to enter the malignant melanoma market before the end of 2014. These agents will compete with ipilimumab, driving a growth in sales of the immune checkpoint inhibitor drug class.

Vemurafenib dominated BRAF and MEK inhibitor sales in 2013, but despite nearly half of malignant melanoma tumours harbouring *BRAF* mutations, this drug class contributed just one-fifth of total US sales in this year[1]. We anticipate that the $BRAF^{V600}$-mutated segment will become more competitive as several large companies vie to secure maximum market share for their products. Considering that the immune checkpoint inhibitors can be used to treat patients regardless of mutational status and have the potential to induce rapid and durable responses and considerably prolong survival, BRAF and MEK inhibitors may be relegated to the smaller, and thus less lucrative, later-stage disease settings. We also expect that later-to-market BRAF plus MEK combination therapies will face challenges in gaining traction in what will be a crowded and competitive market.

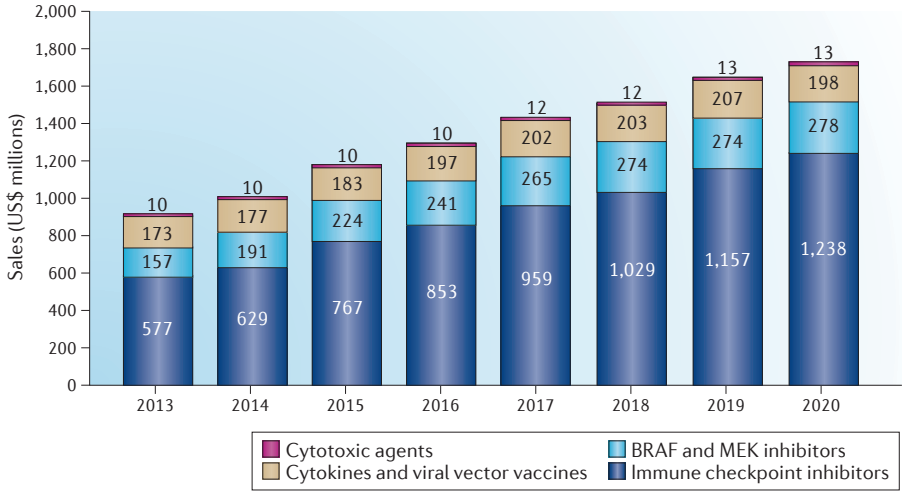

Figure 1 | **US sales of therapies for malignant melanoma, by drug class (estimated).** MEK, MAPK/ERK kinase.

1. Decision Resources Group. *Malignant Melanoma* (Pharmacor; 2013–2014).
2. Decision Resources Group. *Immunotherapies* (Pharmacor; 2014).

Rachel M. Webster and Samuel E. Mentzer are at 6th Floor Aldermary House, 10–15 Queen Street, London EC4N 1TX, UK. Correspondence to R.M.W.
e-mail: rwebster@dresourcesgroup.com

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Competing interests statement
The authors declare no competing interests.