Melanoma

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Abstract | Melanoma is a common cancer in the Western world with an increasing incidence. Sun exposure is still considered to be the major risk factor for melanoma. The prognosis of patients with malignant (advanced-stage) melanoma differs widely between countries, but public campaigns advocating early detection have led to significant reductions in mortality rates. As well as sun exposure, distinct genetic alterations have been identified as associated with melanoma. For example, families with melanoma who have germline mutations in *CDKN2A* are well known, whereas the vast majority of sporadic melanomas have mutations in the mitogen-activated protein kinase cascade, which is the pathway with the highest oncogenic and therapeutic relevance for this disease. *BRAF* and *NRAS* mutations are typically found in cutaneous melanomas, whereas *KIT* mutations are predominantly observed in mucosal and acral melanomas. *GNAQ* and *GNA11* mutations prevail in uveal melanomas. Additionally, the PI3K–AKT–PTEN pathway and the immune checkpoint pathways are important. The finding that programmed cell death protein 1 ligand 1 (PDL1) and PDL2 are expressed by melanoma cells, T cells, B cells and natural killer cells led to the recent development of programmed cell death protein 1 (PD1)-specific antibodies (for example, nivolumab and pembrolizumab). Alongside other new drugs — namely, BRAF inhibitors (vemurafenib and dabrafenib) and MEK inhibitors (trametinib and cobimetinib) — these agents are very promising and have been shown to significantly improve prognosis for patients with advanced-stage metastatic disease. Early signs are apparent that these new treatment modalities are also improving long-term clinical benefit and the quality of life of patients. This Primer summarizes the current understanding of melanoma, from mechanistic insights to clinical progress. For an illustrated summary of this Primer, visit: http://go.nature.com/vX2N9s

Melanoma is a malignancy of melanocytes (BOX 1), which are pigment-producing cells of neuroectodermal origin that can be found throughout the body (including in the skin, iris and rectum). The cutaneous form of the disease is common in the Western world and causes the majority (75%) of deaths related to skin cancer; its global incidence is 15–25 per 100,000 individuals[1]. Sun (UV) exposure is the major risk factor for cutaneous melanoma and leads to a genetic signature that is characteristic of melanoma[2]. Indeed, characteristic genetic alterations underlying cutaneous melanoma have been described in recent years and these are significantly different to those associated with the uveal and mucosal forms of the disease, of which the latter is the most frequent form in Asia[3]. Survival rates in patients with melanoma (cumulative for all forms) have shown persistent differences between countries in Europe, ranging between <50% in Eastern Europe to >90% in northern and central Europe for 5-year survival after primary diagnosis[4]. Probable explanations for these differences in survival between countries include varying degrees of effectiveness of prevention and early diagnosis programmes, as well as accessibility to adequate healthcare systems, different diagnostic intensity and screening approaches, and differences in cancer biology[4].

The clinical diagnosis and surgical management of patients with melanoma have reached a constant and high level in western Europe, Australia and North America. In the same vein, the classification of melanoma has become more refined; evidence-based guidelines for these clinical aspects have been developed to reflect these advances[5]. Furthermore, patients with melanoma who have a high risk of relapse can be identified with good precision such that traditional concepts of adjuvant therapies in melanoma are being reconsidered. Despite advances, distant metastatic melanoma (American Joint Committee on Cancer (AJCC) stage IV) was still associated with a poor prognosis and a median survival of 6–12 months until recently. Until 2010, no randomized clinical trial had provided evidence for improved survival for those with advanced-stage metastatic melanoma. However, in the past 5 years, several prospective randomized Phase III

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trials have demonstrated improvements in progression-free survival (PFS) and overall survival in these patients, leading to prolonged clinical benefit, as well as increasing 2-year, 3-year and 5-year survival rates.

In this Primer article, we summarize all of the major facets of current melanoma research and clinical care, including medical and surgical management, and the molecular underpinnings of this disease.

Box 1 | **Types of melanoma**

Major histopathological subtypes

- Superficial spreading melanoma is characterized by a radial or horizontal growth phase with melanocytes arranged in nests or solitary units displayed in a pagetoid pattern
- Nodular melanoma usually occurs exclusively in the vertical growth phase (that is, no melanoma *in situ* or melanoma *in situ* confined to no more than three adjacent rete ridges beyond the margins of the tumour nodule)
- Lentigo maligna melanoma has cells that are characteristically singly dispersed along the dermal–epidermal junction and skin appendages; signs of chronic UV radiation are prominent
- Acral lentiginous melanoma has cells that are present as single units along the dermal–epidermal junction and as confluent foci; this type of melanoma most commonly arises at acral sites but occasionally occurs at mucosal sites

Other well-defined clinical or histopathological variants

- Naevoid melanoma shows histopathological features of a banal naevus (that is, 'small-cell melanoma')
- Spitzoid melanoma has histopathological features of a Spitz naevus
- Desmoplastic melanoma displays unique histopathological features, including 'spindle-shaped' melanoma cells that morphologically resemble fibroblasts found in scar tissue
- Ocular melanoma arises within the uvea of the eye
- Mucosal melanoma originates at a mucosal site (for example, mouth, nasopharynx, larynx, conjunctiva, vagina or anus)
- Acral melanoma forms on the palms of hands, soles of feet, and nails; the majority of acral melanomas, but not all, are of the acral lentiginous histopathological subtype
- Amelanotic melanoma lacks clinically evident pigment and often appears pink in colour; any of the major histopathologic subtypes or variants can be amelanotic

Epidemiology

Cutaneous melanoma occurs mainly in white populations with fair skin, whereas pigmented populations from Africa and Asia mainly develop acral and mucosal melanomas at low incidence rates[6]. Globally, cutaneous melanoma incidence rates vary up to 100-fold among different populations, with the highest rates worldwide being reported in Australia and New Zealand, where the incidence rate reaches ~60 cases per 100,000 inhabitants per year (FIG. 1). In Europe, the rate is ~20 cases per 100,000 per year, whereas in the United States, a rate of ~30 cases per 100,000 per year has been reported; by comparison, incidence rates in dark-skinned populations from Africa and Asia are approximately one case per 100,000 per year[7]. A dramatic increase in UV exposure with changing leisure-time habits (that is, prolonged periods in the sun) is thought to be the main cause of the dramatic increase in the incidence of melanoma and epithelial skin cancers since World War 2, with incidence rates now reaching epidemic levels. A typical UV damage-induced genetic signature — C to T (C>T) transition — is, therefore, frequently observed in melanoma tumours, leading to an extremely high mutation rate[2].

Between 1950 and 2007, incidence rates in the United States rose 17-fold in men and 9-fold in women[8]. Similar increases in incidence rates were observed in Australia, central Europe and Scandinavia[9,10]. There is still a continuing increase in incidence rates in spite of decades of public prevention campaigns in many countries. Interestingly, the highest incidence rates have been observed for individuals with high socioeconomic status, probably reflecting extended sun exposure in leisure time and holidays[11]. Screening campaigns, as well as insurance-paid systematic screening examinations (as in Germany), might contribute to an initially increased incidence that should then 'flatten out' if screening continues[12]. An apparent levelling-off of incidence rates in young birth cohorts, as reported in Australia, might be caused, at least in part, by immigration of young people from Asia who have a low risk for developing melanoma[13,14].

The most important prognostic factor for primary cutaneous melanoma is Breslow's tumour thickness, which is a measure of the invasion of the tumour into the dermis and subcutis. In the 1980s and 1990s, a significant decrease in tumour thickness of primary melanoma at diagnosis was reported in western Europe and in Australia, indicating that early detection by public campaigns and screening programmes was effective[15]. This development reflects the increase in the incidence of thin (<1 mm tumour thickness) melanomas (that is, reflecting earlier diagnosis). However, the incidence of thick melanomas (with a Breslow's thickness of ≥2 mm) in Europe, the United States and Australia did not decline, and incidence rates of thick melanomas have steadily increased. In the developed world, the majority of cutaneous melanoma is now diagnosed with a thickness of <1 mm and the proportion of all primary cutaneous melanoma that will later metastasize is 10–15%[4,16].

Intermittent sun exposure (holiday time) and sunburns are significant risk factors for melanoma development. Contrary to popular belief, sunburn is not required

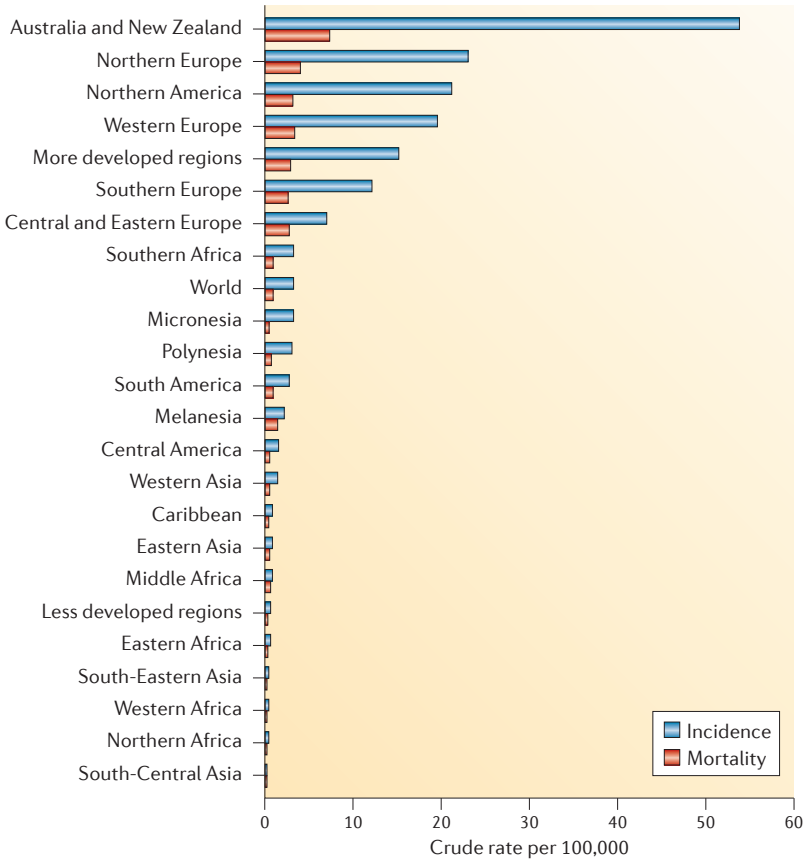

Figure 1 | **Incidence and mortality of cutaneous melanoma.** According to data from Globocan 2012, the crude rates of incidence and mortality from melanoma per 100,000 inhabitants per year show differences between countries. Reproduced with permission from Ferlay, J., Soerjomataram, I., Ervik, M., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D.M., Forman, D., Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 02/02/2015.

for melanoma development[17]. Sun exposure in genetically susceptible individuals — mainly during childhood and adolescence — induces melanocytic naevi, which are often also referred to as 'moles', high numbers of which are associated with increased risk for melanoma development. Individuals with ≥100 melanocytic naevi carry a sevenfold increased risk for lifelong melanoma development, according to one meta-analysis[18]. Furthermore, the presence of atypical melanocytic naevi that represent larger and more asymmetric and irregular forms of naevi are an additional risk factor. The use of sunbeds during youth significantly increases the relative risk for melanoma development[19,20]. Consequently, several countries have banned the use of artificial tanning devices by children and adolescents.

Clinically, cutaneous melanoma occurs most commonly in individuals who are between the ages of 40 years and 60 years, but it can affect those in adolescence and in late life (≥80 years). The median age at diagnosis is 57 years[6], which is almost one decade before most solid tumours — for example, breast, colon or lung tumours — typically arise. Cutaneous melanoma is one of the most common cancers in young adults aged 20–29 years. Consequently, the calculated loss of life in years is among the highest for this subtype of melanoma when considered alongside other subtypes[21]. The most frequent locations of melanoma are the back in males and the lower extremities in females. Women have an unexplained survival advantage compared with men for all tumour stages[22,23].

Mechanisms/pathophysiology

Transformation of melanocytes into melanoma requires a complex interplay of exogenous and endogenous events (FIG. 2). Tremendous progress has been made in unravelling the genetic basis of melanoma, which we are now beginning to understand[24]. The first genetic evidence came from germline alterations in families with two or more close relatives affected by melanoma. A familial background occurs in ~8% of all patients with melanoma and, of these, 40% carry high-risk, high-penetrance germline mutations in the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) locus[25,26]. The *CDKN2A* gene encodes two distinct tumour suppressors — $p16^{INK4A}$ and $p14^{ARF}$ — through the use of alternative promoters and through translation in different reading frames. Wild-type $p16^{INK4A}$ maintains cell-cycle control by inhibiting cyclin-dependent kinase 4 (CDK4)- or CDK6-mediated phosphorylation and inactivation of retinoblastoma-associated protein (RB), whereas functional $p14^{ARF}$ prevents ubiquitylation mediated by the E3 ubiquitin-protein ligase MDM2 and the subsequent degradation of cellular tumour antigen p53 (which is encoded by *TP53*)[27]. Thus, inactivating mutations in *CDKN2A* promote G1–S cell-cycle transition by loss of two important regulators of cellular homeostasis, RB and p53 (REF. 28). Germline mutations in *CDK4* have also been found in melanoma-prone families, further underscoring the relevance of defective cell-cycle control for melanoma transformation[29]. Other germline mutations — for example, in *BAP1*, which encodes a deubiquitylating enzyme involved in the DNA damage response and chromatin modification[30], or in the telomere shelterin gene *POT1* (REFS 31,32) — are also rare; thus, >50% of all familial melanomas have an unknown genetic basis[24].

Sporadic melanomas, which comprise ~90% of all melanomas, are frequently driven by low-risk or moderate-risk alleles that have high prevalence and low penetrance, pointing to a causative role of environmental factors for malignant transformation[33–35]. Several population studies have revealed that inactivating variants of the highly polymorphic melanocortin 1 receptor gene (*MC1R*; which has >100 allelic variants) are associated with red hair, poor tanning ability and increased melanoma risk[36,37]. *MC1R* encodes a G protein-coupled receptor that signals through adenylate cyclase to induce the master regulator of pigmentation *MITF* (which encodes micropthalmia-associated transcription factor) and, thereby, the production of melanin in response to binding of α-melanocyte stimulating hormone (α-MSH)[37]. *MITF* alone is amplified in 4–21% of all melanomas[38,39]. Additional germline polymorphisms have also been found in other pigmentation-related genes including *ASIP* (which encodes agouti signalling

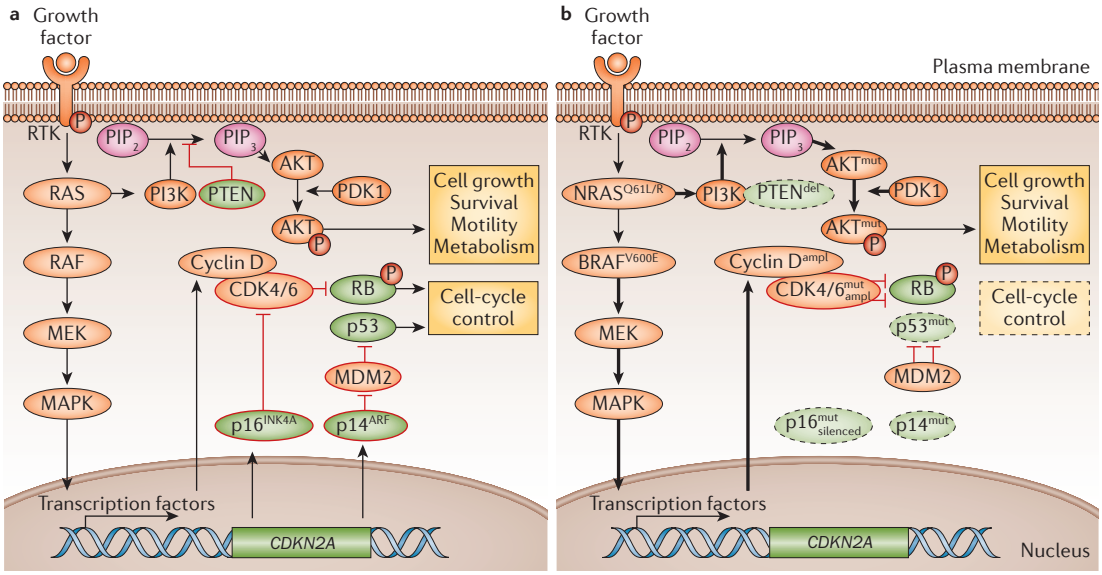

Figure 2 | **Signalling pathways in melanoma.** **a** | Under normal conditions, mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)–AKT signalling permit balanced control of basic cellular functions, including cell-cycle regulation, survival, motility and metabolism. **b** | In melanoma, the depicted genetic alterations are frequently observed, and lead to constitutive pathway activation (indicated by thick arrows) and loss of cellular homeostasis. Malignant transformation can require combinations of genetic defects. The functional consequences of genetic events determine whether mutations can coexist or remain mutually exclusive (for example, mutations in *NRAS* and *BRAF* occur very rarely in the same melanoma cell, whereas combined genetic alterations of *BRAF* and *PTEN* are common). CDK, cyclin-dependent kinase; MDM2, E3 ubiquitin-protein ligase MDM2; MEK, MAP/ERK kinase; P (in a red circle), phosphate; $p14^{ARF}$, splice variant encoded by the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) gene; $p16^{INK4A}$, splice variant encoded by the *CDKN2A* gene; PDK1, 3-phosphoinositide-dependent protein kinase 1; PIP_2, phosphatidylinositol-(4,5)-bisphosphate (also known as PtdIns(4,5)P_2); PIP_3, phosphatidylinositol-(3,4,5)-trisphosphate (also known as PtdIns(3,4,5)P_3); PTEN, phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase; RB, retinoblastoma-associated protein; RAF, serine/threonine-protein kinase RAF; RAS, GTPase RAS; RTK, receptor tyrosine kinase.

protein), *OCA2* (oculocutaneous albinism II), *PAX3* (paired box 3), *EDNRB* (endothelin receptor type B), *SLC45A2* (solute carrier family 45 member 2), *SOX10*, *TYRP1* (tyrosinase-related protein 1) and *TYR* (tyrosinase)[34,35]. Depending on the mutational activity of *MC1R* or downstream pigmentation genes, melanocytes produce different levels of highly UV-protective dark-brown eumelanin or less-protective yellow-red pheomelanin. Consequently, in the red hair phenotype, individual genetic susceptibility and exposure to additional mutagens, such as intermittent sunburns, increase the individual's risk of developing melanoma[34].

Contemporary advances in cancer genome deep sequencing have revealed that, with a median number of >10 mutations per megabase of DNA, melanomas carry the highest mutational load of all human tumours and harbour an overwhelming number of UV-signature mutations, such as C>T or G>T transitions, which are induced by UVB and UVA, respectively[39–41]. Current landscape genetic analyses provide compelling evidence for a direct mutagenic role of UVB and UVA light, not only in the mutational background noise of melanoma cells (so-called passenger mutations), but also in 46% of attested driver gene mutations; for example, in *RAC1*, *STK19* (which encodes serine/threonine kinase 19), *FBXW7* and *IDH1* (which encodes isocitrate dehydrogenase 1; the full list of driver genes has been published elsewhere[39,41,42]). Such analyses have enabled the direct linkage of UVB-mediated damage with a fitness advantage in melanoma cells. For example, the activating mutation $RAC1^{P29S}$ keeps its gene product (a small RHO GTPase) preferentially in the GTP-bound form, leading to downstream activation of p21-activated protein kinase (PAK) signalling[39]. *TP53*, one of the most prominent human cancer genes, showed the highest number of total putative UV-related mutations[39], challenging the dogma that emphasizes its characteristic wild-type status in melanoma[27,43]. Also, the cell-cycle regulators $p14^{ARF}$ and $p16^{INK4A}$ harbour presumed UV-induced loss-of-function mutations[39]. Thus, adding up all of the known germline and sporadic mutations, deletions and epigenetic silencing events in the $p16^{INK4A}$–CDK4/CDK6–RB pathway (which are found in 90% of all melanomas[28,44,45]), restoration of disabled cell-cycle control emerges as a prime therapeutic goal for the majority of patients with melanoma. Indeed, pharmacological targeting of the cell cycle — for example, by the dual CDK4 and CDK6 inhibitor palbociclib — is currently in clinical development[46].

Several observations complicate the hypothesis that melanoma is exclusively UV-dependent. For example, melanomas can develop in non-sun-exposed skin or in internal organs[24]. Moreover, most mutations in the

mitogen-activated protein kinase (MAPK) cascade — which is currently the pathway that has the highest oncogenic and therapeutic relevance for melanoma — are not attributable to direct UV damage[39]. Common mutations without typical UV signatures include *BRAF*^{V600E} (detectable in ~50% of all melanomas), *NRAS*^{Q61L} or *NRAS*^{Q61R} (*NRAS*$^{Q61L/R}$; ~15–20% of melanomas harbour *NRAS* mutations[47], 1–2% harbour *HRAS* and *KRAS* mutations[48]), *KIT*^{V559A} (~10–20% of mucosal and acral melanomas have a *KIT* mutation, <1% of melanomas overall harbour *KIT* mutations[48]) and *GNA11*^{Q209L} (mutations in *GNAQ* and *GNA11* (which encode the guanine nucleotide-binding proteins $G\alpha_q$ and $G\alpha_{11}$) occur in 85% of uveal melanomas[49]). The lack of typical UV signatures, however, does not completely exclude any causal role for UV radiation in the generation of these mutations. Free radicals resulting from the biochemical interaction of UVA with melanin[50] act as secondary mutagens and can indirectly cause genetic aberrations[24].

Dependence on genetic defects

Traditionally, the MAPK pathway is depicted as a canonical signalling cascade composed of the small GTPase RAS (HRAS, KRAS or NRAS) and the downstream activated kinases RAF (ARAF, BRAF or CRAF), MAP/ERK kinase (MEK1 and MEK2; also known as MAP2K1 or MAP2K2) and MAPK (MAPK1 or MAPK3; also known as ERK2 and ERK1). In uveal melanoma, members of the Gα family of G proteins, such as $G\alpha_q$ and $G\alpha_{11}$, alternatively activate RAS and RAF upon stimulation by membrane-bound G protein-coupled receptors[48]. The classic MAPK pathway in cutaneous melanoma transmits mitogenic signals from growth factors — such as hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) — via transmembrane receptor tyrosine kinases (RTKs) to the nucleus and transcriptional targets, such as cyclin D1 (which is encoded by *CCND1*)[51].

In patients carrying the *BRAF*^{V600E} mutation, the use of *BRAF*^{V600E}-targeting compounds (for example, vemurafenib or dabrafenib) or a combination of these with MEK inhibitors (for example, trametinib or cobimetinib) leads to dramatic growth arrest and death of melanoma cells[52–55]. The dependence of melanoma on functional MAPK signalling becomes fully apparent when melanoma cells overcome therapeutic MAPK blockade by exploiting their biological plasticity. Numerous resistance mechanisms have been identified and are categorized as genetic and phenotypic mechanisms or, when regarding the spatiotemporal evolution of resistance, they are categorized as intrinsic, adaptive and acquired mechanisms[56,57]. For example, melanoma cells maintain high levels of MAPK1 and MAPK3 phosphorylation despite BRAF inhibition through constitutively active mutant *MEK1*^{C121S} (REF. 37), or through expression of mutant *NRAS*$^{Q61K/R/L}$ (REFS 38–40), leading to dimerization of *BRAF*^{V600E} with other wild-type RAF isoforms[51]. At the level of RAF, pathway restoration can occur through amplification of *BRAF* copy numbers[58], expression of (resistant) alternative *BRAF* splice variants[59] or increased expression and subsequent dimerization of CRAF[60,61]. Pathway restoration upstream of RAF occurs via upregulation of RTKs such as epidermal growth factor receptor (EGFR), PDGF receptor-β (PDGFRB) and insulin-like growth factor 1 receptor (IGF1R)[62–64].

Co-operating genetic defects

Given that mutations in *BRAF*, *NRAS* and *GNA11* are frequently also observed in benign melanocytic neoplasms (indeed, >80% of acquired naevi harbour *BRAF*^{V600E})[45], it has been suggested that these mutations represent primary steps in the transformation of melanocytes that lead to oncogene-induced senescence[65]. That is, full development of melanoma might require secondary or tertiary genetic aberrations to overcome senescence — a perception that might eventually lead to a molecular-based taxonomy of melanoma subtypes[24]. The functional consequences of genetic events determine whether mutations can coexist or remain mutually exclusive (owing to lethal pathway overstimulation). For instance, coexistence of mutations in *BRAF*, *NRAS* or other MAPK effectors in untreated melanomas is mutually exclusive with only few exceptions. Also, aberrations in cell-cycle control genes — such as *CDKN2A*, *CDK4* and *CCND1* — coexist rarely[39,48], whereas combinations of mutations in MAPK signalling and cell-cycle control cooperate efficiently.

The genetically engineered *Hgf-Cdk4*^{R24C} mouse model has been used to show that overexpression of mitogenic *Hgf* in addition to the expression of a constitutively active CDK4 mutant successfully induces primary melanoma growth[66]. UV exposure in this model promotes metastatic progression of primary melanomas through modulation of the tumour microenvironment. This effect depends on the recruitment of neutrophils initiated by the release of high mobility group box 1 (HMGB1) from UV-damaged keratinocytes[67]. Another study reported that in mice expressing *Braf*^{V600E} in their melanocytes, a single dose of UV radiation induced clonal expansion, and repeated UV doses increased melanomagenesis via mutational inactivation of *Tp53* (REF. 68). In addition to their direct biological relevance, the latter two findings strongly support clinical recommendations for sunscreen use, particularly in individuals who already have naevi or melanomas. However, UV-independent secondary cofactors are also involved in melanoma development. For instance, pheomelanin by itself can act as a pro-oncogenic agent. Mice carrying a conditional melanocyte-targeted allele of *Braf*^{V600E} together with an inactivating mutation in *Mc1r* (resembling the red hair phenotype) develop invasive melanomas even without UV exposure[69]. When melanin synthesis was ablated in this model by introducing an albino allele, pheomelanin-mediated production of reactive oxygen species decreased and melanoma growth was dramatically prevented[69].

Genetic evidence in melanoma also supports cooperation between the MAPK pathway and the signalling pathway mediated by phosphatidylinositol 3-kinase (PI3K), AKT, PTEN (phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase) and mammalian target of rapamycin (mTOR) as a cancer trigger. PI3K can be activated by

multiple signals, including RTKs and RAS, and subsequently phosphorylates phosphatidylinositols in the plasma membrane, which attract the RAC serine/threonine-kinases AKT1, AKT2 and AKT3. The AKTs are then activated by phosphorylation through 3-phosphoinositide-dependent protein kinase 1 (PDK1) and mTOR complex 2 (mTORC2). Activated AKTs phosphorylate numerous downstream targets that regulate key cellular processes, such as growth, survival, motility and metabolism. The phosphatase PTEN antagonizes the activity of PI3K[46]. The combination of mutated *BRAF* and focal deletions or mutations of *PTEN* is observed in most melanoma cell lines and also in up to 40% of human melanomas[39,70,71], and this is associated with decreased therapeutic response to BRAF inhibitors[72]. The combination of *PTEN* loss with *NRAS* mutations is less frequent (~4%), most probably because *NRAS* can independently activate PI3K signalling[34,39]. Other activating mutations are point mutations in *PIK3CA* (which encodes the catalytic α-subunit of phosphatidylinositol-4,-5-bisphosphate 3-kinase; 2–6% of melanomas), *AKT1* (1–2%) and *AKT3* (1–2%)[46]. Accordingly, in a *Tyr::CreER; Braf*$^{CA/+}$*; Pten*$^{lox5/ox5}$ mouse model (mice expressing a conditional *Braf*^{V600E} allele and loss of *Pten* in cells expressing the Cre recombinase under the control of the tyrosinase promoter), *Braf*^{V600E} alone could only promote benign melanocytic hyperplasia, whereas concurrent deletion of *Pten* induced metastatic progression[70]. The functional role of PI3K–AKT–PTEN signalling has been validated in many cancer models, and a number of inhibitors of PI3K, AKT and mTOR are currently undergoing clinical evaluation[46].

Interaction with the tumour stroma

For successful tumour development, melanoma cells modulate the tissue environment and, in particular, the immune response through a myriad of mechanisms. For example, melanomas co-opt immune-checkpoint pathways that normally mediate self-tolerance. By expression of programmed cell death protein 1 ligand 1 (PDL1; also known as B7-H1 and CD274) and PDL2 — which are the ligands of the surface receptor programmed cell death protein 1 (PD1) — melanoma cells limit T cell effector activity in the tumour tissue[73]. Alongside T cells, B cells and natural killer (NK) cells also express PD1 and are, therefore, also affected. By contrast, cytotoxic T lymphocyte protein 4 (CTLA4) is expressed exclusively on T cells, where it primarily dampens the amplitude of the initial T cell activation that occurs after antigen presentation by dendritic cells in the lymph nodes[73]. Recent therapeutic approaches to block these immune checkpoints using CTLA4-specific or PD1-specific antibodies potently release this 'immune brake', and these approaches have achieved significant and durable clinical responses in a subset of patients with advanced-stage melanoma[74,75]. Additional mechanisms involved in immunosuppression are downregulation of tumour-associated antigens and MHC class I molecules, as well as immuno-editing and the secretion of inhibitory factors such as transforming growth factor-β (TGF-β), interleukin-10 (IL-10) or nitric oxide[76]. Multiple stromal cell types converge to support a tumorigenic niche. Fibroblasts and macrophages can be educated by tumour cells to acquire pro-tumorigenic functions, for example, through secretion of proteases, cytokines, and pro-angiogenic and growth factors. As tumours grow, immune-suppressor cells — including myeloid-derived suppressor cells (MDSCs) and regulatory T (T_{Reg}) cells — are mobilized into the bloodstream in response to tumour-derived cytokines — such as TGF-β or CXC-chemokine ligand 5 (CXCL5) — and infiltrate the tumour to disrupt the immune attack through multiple mechanisms[77].

Metastatic progression

Melanoma progression is typically depicted as a linear and stepwise process in which metastasis occurs as a late event. However, metastatic spread can also be initiated earlier, even during primary tumour formation, leading to the model of parallel metastatic progression[78–80]. Thus, even early genetic events, such as *BRAF*^{V600E} or *NRAS*$^{Q61K/R/L}$, can be functionally important for metastasis[81]. Parallel progression would predict the genetic and epigenetic signatures are distinct in metastases and the primary tumours of an individual patient. Recent DNA sequencing of matched metastatic and primary melanomas revealed both relative homogeneity and heterogeneity[82–84]. This finding suggests that, depending on the individual tumour, metastatic spread can occur early or late and may result from a continuous process in which the metastatic outgrowth is dependent on secondary factors — such as the survival of disseminating cells, host defence or microenvironmental factors — and the tumour-initiating capacity of the cell upon arrival at the pre-metastatic niche. The question of whether tumour initiation in melanoma follows a classic cancer stem cell hierarchy is still outstanding because of a lack of reliable markers and models. However, it seems that selected melanoma cell subpopulations possess a high potential to repopulate the tumour mass and to survive exogenous stress (such as hypoxia and drugs), pointing to considerable functional heterogeneity in melanoma[85–87].

Metastatic progression can also be guided by secondary genetic or phenotypic drivers. For instance, activation of telomerase progressively increases from benign naevi to primary and metastatic melanomas[88,89]. Accordingly, mutations in the promoter of *TERT* (which encodes telomerase reverse transcriptase) are more frequent in metastases than in primary melanomas and represent an independent prognostic factor[90–92]. The stage-dependent regulation of anti-apoptotic proteins in melanoma is an example of a mostly phenotypic driver of disease progression. For example, although B cell lymphoma 2 (BCL-2) expression progressively decreases from the radial tumour growth phase (which is typical for early, thin cutaneous melanoma) to the vertical tumour growth phase (typical for thick, highly invasive cutaneous melanoma), the expression levels of MCL1, BCL-X_L, survivin (also known as BIRC5) and XIAP increase. By contrast, expression of livin (also known as BIRC7) remains stage-independent[93]. The role of differentiation factors (such as MITF or WNT) in metastasis

remains unclear. Current findings suggest a dual role in which — depending on the microenvironmental context — these pathways can display either protumorigenic or antitumorigenic properties[78]. However, melanoma cells probably use developmental programmes such as Notch or WNT signalling during metastasis to actively maintain their high mesenchymal cell-like plasticity. New compounds targeting developmental pathways — for example, the γ-secretase inhibitor RO4929097 — are under clinical development[94].

Diagnosis, screening and prevention

The differing aetiologies, clinical presentations and genotypes[95] of melanoma emphasize that melanocyte-derived malignancies are heterogeneous by definition. The subsets of the disease (BOX 1) are closely but imperfectly associated with distinctive histopathological growth patterns and anatomical site predilections. Acral and mucosal melanomas are least associated with UV radiation and are among the most challenging to identify. By contrast, lentigo maligna melanoma occurs on chronically sun-exposed skin, is directly linked to cumulative UV radiation exposure and is often detected through simple visual inspection. Most melanomas are of the superficial spreading type and are associated with intermittent exposure to UV radiation. Early diagnosis of superficial spreading melanoma requires careful and thorough skin examination because of significant overlap in its clinical presentation with benign melanocytic naevi. Finally, nodular type melanoma exhibits rapid growth but often appears innocuous, which presents a significant barrier to early detection. Although these distinctions deserve considerable attention outside the scope of this Primer, this section focuses on the importance of protection from UV radiation exposure and the use of total-body skin examination as the foundation of melanoma prevention and screening, respectively, as these aspects are most applicable to the majority of cutaneous melanomas today.

Diagnosis

Melanoma is unique among cancers in that it can be readily detected in its earliest stages because most melanomas are pigmented and occur on the skin surface. Indeed, most melanomas are self-detected by patients[96,97] and a greater proportion of melanomas are being diagnosed at earlier stages in recent years[98]. Nonetheless, significant diagnostic hurdles persist. The ubiquity of naevi and other benign pigmented lesions that are potential precursors or mimics of melanoma limits the positive predictive value of lesions that are clinically selected by healthcare providers to undergo skin biopsies[99]. The pathological diagnosis of melanoma is sometimes challenging, and definitive molecular diagnostics and prognostic stratification factors are lacking, which contributes to a significant risk of overdiagnosis (that is, detection of true but biologically indolent melanoma that would not result in death).

Clinical diagnosis. To elicit a patient history and perform a total-body skin examination remain central to the clinical diagnosis of melanoma. Although the decision-making involved in melanoma detection is complex[100], diagnosis has been aided recently by several bedside technological advancements. Dermoscopy is a non-invasive imaging technique involving the use of a handheld device that permits the visualization of colours, structures and patterns in skin lesions that are imperceptible to the naked eye (FIG. 3). Dermoscopy has been criticized by some for not being associated clearly with improved patient outcomes and for requiring considerable training, which limit its universal acceptance, particularly in the United States. Nevertheless, the technique has been shown to improve diagnostic accuracy for primary cutaneous melanoma[101] and to decrease unnecessary biopsies of benign skin neoplasms[102,103], when compared with naked-eye examination alone. Furthermore, sequential digital dermoscopic images of indeterminate skin lesions can be captured over time, enabling 'mole monitoring'. This technique has been shown to reduce unnecessary excisions of benign lesions compared with dermoscopy alone[104], and it enables the detection of melanomas that lack diagnostic clinical or dermoscopic features at baseline[105,106].

Digital total-body photography is often obtained in patients with high numbers of naevi and/or atypical naevi. Photographs are used during follow-up examinations by healthcare providers to facilitate the

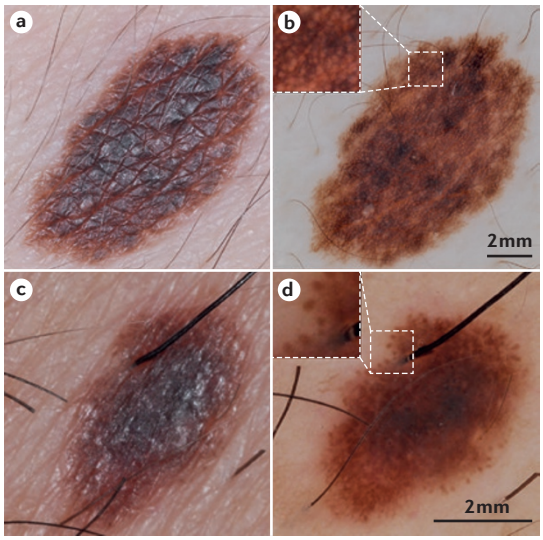

Figure 3 | **Dermoscopy enables visualization of subsurface features present in skin lesions that are not evident to the naked eye.** **a** | Clinical image of a 13 × 7 mm skin lesion with irregular borders and colour variegation. **b** | Dermoscopy shows a bland network-like appearance throughout the lesion, which is diagnostic of a banal melanocytic naevus. The inset highlights a regular network pattern consisting of intersecting pigmented lines and hypopigmented holes. **c** | Clinical image of a 5 × 3 mm symmetrical skin lesion with a dark centre. **d** | Dermoscopy reveals pseudopods present focally at the periphery, which is a melanoma-specific dermoscopic criterion. The inset highlights the pseudopods, which are bulbous projections from the tumour body. Histopathological examination confirmed melanoma *in situ* arising within a compound melanocytic naevus.

identification of new or changing lesions. Although the efficacy of this technique remains unproven through a randomized clinical trial, proponents of its use argue that total-body photography improves the sensitivity and specificity of skin examinations[107–110]. Dermoscopy, sequential digital dermoscopic imaging and total-body photography are often used together in a complementary fashion. Retrospective series of patients who are at particularly high risk for melanoma have shown that the combined use of these techniques enables the detection of melanoma at early stages with low rates of biopsy of benign skin lesions[111,112].

In vivo reflectance confocal laser microscopy is an evolving non-invasive bedside imaging modality that permits visualization of the epidermis and superficial dermis at a resolution approaching histological detail. The use of this technique as a second-level diagnostic test in combination with dermoscopy has been shown to improve diagnostic accuracy for melanoma and to reduce unnecessary biopsies of ultimately benign melanocytic neoplasms[113,114]. Further research is required to understand the limitations of *in vivo* reflectance confocal microscopy and how to best incorporate this bedside 'quasi-histological' tool into clinical practice.

Automated diagnostic systems for melanoma detection with high sensitivity and specificity are inherently appealing to patients and healthcare providers alike. Over the past decade, computer-aided multispectral digital analysis[115] and electrical impedance spectroscopy[116] have been commercially developed in the United States and Europe, respectively, for the diagnosis of melanoma. Although both systems have yielded promising initial results, the overall quality and quantity of evidence remains low, particularly with regard to the inclusion criteria that have been used in these pivotal studies and their applicability to standard practice.

An area of potential opportunity is the development of imaging devices to assist in the visualization and early diagnosis of amelanotic (non-pigmented) melanomas. Although this subtype represents a minority of cutaneous melanomas, it is clinically and dermoscopically difficult to recognize and is diagnosed at a more advanced stage than pigmented melanomas[117].

Pathological diagnosis. The gold standard for the diagnosis of melanoma remains the histopathological assessment of tissue sections stained with haematoxylin and eosin, combined with knowledge of the clinical context of the lesion and the patient. However, the absence of objective, highly reproducible criteria that apply to all melanomas, as well as a subset of lesions with contradictory or borderline findings, contributes to substantial discordance in the histopathological diagnosis of melanoma, even among experts[118–120]. The risk-adverse medico-legal environment in some countries might be a contributing factor leading to false-positive diagnoses[121]. Immunohistochemical staining is an important and frequently used adjunct to the histopathological diagnosis of melanoma. For example, immunohistochemistry using the S100 marker can more clearly delineate 'subtle' melanoma cells present in the epidermis or help to identify rare subtypes of disease, such as desmoplastic melanoma[122]. More recently, analytical genetic and genomic techniques have been developed to improve diagnostic accuracy, particularly for uncertain cases. For example, comparative genomic hybridization (CGH) analysis reveals that most melanomas have recurrent patterns of chromosomal aberrations — such as losses of 6q, 8p, 9p and 10q, and gains of 1q, 6p, 7, 8q, 17q and 20q — whereas naevi lack such changes[123]. CGH might be particularly useful in the interpretation of neoplasms with spitzoid features[124].

A commercially available fluorescence *in situ* hybridization (FISH) assay using four specific nucleic acid probes (Vysis Melanoma FISH Probe Kit, Abbott Molecular, USA) has been reported to have a sensitivity of 85% and specificity of 95% for the diagnosis of histopathologically straightforward benign and malignant lesions[125]. The application of this FISH test to diagnostically ambiguous melanocytic tumours has yielded mixed results; some studies have reported that FISH assay results correlate well with clinical outcome[126,127], whereas others have reported contrasting results[128,129]. Although FISH is intrinsically more limited in its cytogenetic analysis than CGH, it requires less tissue and can detect small populations of abnormal cells within a genomically heterogeneous tumour. Emerging FISH assays that assist the diagnosis of rare and diagnostically challenging melanomas (for example, spitzoid, nodular amelanotic and naevoid melanomas) are under investigation[130–134].

Mutational analysis of tissue specimens provides important information to guide the rational targeting of crucial melanoma signalling pathways. For example, BRAF inhibitors (such as vemurafenib or dabrafenib) or MEK inhibitors (such as trametinib or cobimetinib) can be used in melanomas with $BRAF^{V600}$ mutations. *NRAS* mutations are currently targeted using MEK inhibitors (for example, binimetinib) in clinical trials, and KIT inhibitors (for example, imatinib or nilotinib) are being studied, but have not been shown to be clinically efficacious[134].

Novel emerging molecular diagnostics include a commercially available assay (Myriad myPath™ Melanoma, Myriad Genetics, USA) of gene expression that has been reported to have a sensitivity of 90% and specificity of 91% in differentiating melanomas and naevi[135]. This assay analyses the expression of 23 genes that are principally involved in melanocyte differentiation, immune signalling and immune regulation. Further independent studies with large sample sizes are needed to determine the diagnostic accuracy and clinical utility of this technology. The difficulty of the multidimensionality in biomarker assessment in various tumours was recently outlined by van Kempen and Spatz[136], who emphasized the need for combining phenotypic, immunohistochemical and molecular variables for diagnostic taxonomy and prognostication.

Screening

The general — but not formal[137,138] — consensus is that individuals who are at significantly increased risk

for melanoma should undergo routine dermatological evaluation to promote early detection. However, to date, no study has formally shown that skin surveillance of such individuals can actually reduce the risk of death from melanoma. Furthermore, no consensus exists on the definition of a 'high-risk' population or an appropriate screening interval. In general, individuals with a personal history of melanoma, a strong family history of melanoma, and numerous or atypical naevi are recommended to undergo regular screening via total-body skin examination by a healthcare provider. Some authorities additionally identify fair-skinned men and women aged >65 years as a group that is at substantially increased risk for melanoma[137]. The role of genetic risk assessment in familial melanoma remains controversial[139,140].

Population-based screening for melanoma has received considerable recent attention. Total-body skin examinations are inherently rapid, inexpensive and non-invasive, and the potential benefits of early melanoma detection are considerable. Conversely, the potential harms of overdiagnosis and unnecessary biopsies, and the significant costs of treatment of non-melanoma skin cancers often detected during screening, raise important questions. Increased detection pressure for melanoma through screening is suggested to have led to substantial overdiagnosis of melanoma in the United States[141,142]. Consistent with this hypothesis, Welch *et al.*[143] found that melanoma incidence is associated with biopsy rates in a population-based ecological study using participants aged ≥65 years from the US Surveillance Epidemiology and End Results (SEER) registry. The authors of this study[143] and others (for example, REF. 144) have concluded that screening might be associated with the identification of 'histologically malignant' tumours that have little to no impact on survival. Nonetheless, melanomas detected by healthcare providers are thinner than those found by patients or other laypersons[145]; similarly, melanomas diagnosed during deliberate skin examinations are thinner than those found incidentally[96].

In the absence of randomized control trials demonstrating an impact of screening on mortality, authorities have been reluctant to recommend population-based screening. An ongoing German public health programme of population-based screening has yielded initial results of an almost 50% decrease in melanoma mortality[146]. However, this report has been criticized for some shortcomings. Namely, the study revealed a decrease in mortality that started before formal screening began (that is, no lag time was observed); the researchers did not report data on the incidence of advanced-stage melanoma; and no proportionality was evident between participation rates and mortality decreases. Nevertheless, if the final results definitively show an impact on mortality rates, a paradigm shift might occur with regard to national guidelines for population-based screening for melanoma. Until this occurs, skin cancer screening remains controversial. Indeed, in the United States, the Surgeon General (in 2014) and the US Preventive Services Task Force (in 2009) concluded that insufficient evidence exists to assess the balance of benefits and harms of skin cancer screening[147,148].

Prevention

The entire spectrum of UV radiation, including both UVA and UVB wavelengths, has been implicated in the pathogenesis of melanoma[39,41,149]. UV radiation exposure — from both solar radiation and indoor tanning devices — is recognized as carcinogenic to humans by the World Health Organzation[150] and is the only known preventable risk factor for cutaneous melanoma[17,19,151]. Furthermore, a 4-year prospective, community-based, randomized controlled trial in Queensland, Australia, showed that individuals ($n = 812$) instructed to apply daily sunscreen to the head, neck, arms and hands developed 73% fewer invasive melanomas on the entire body over the study period and 10 years of follow-up than participants ($n = 809$) assigned to discretionary sunscreen use ($P = 0.045$)[152]. Although valid concerns regarding the design, analysis and interpretation of this trial have been raised[153], this study provides the strongest evidence to date that sunscreen use may prevent melanoma[154].

These findings have formed the rationale behind UV radiation avoidance (for example, staying indoors, tanning bed abstinence and seeking shade when outdoors) and UV radiation protection (for example, wearing wide-brimmed hats, sunglasses, clothing and sunscreens) as the principal strategies for melanoma prevention in the general population. However, controversy exists regarding UV radiation avoidance and protection measures, especially given the role of UV radiation in cutaneous vitamin D synthesis, and the reported association between chronic sunscreen use and low serum 25-hydroxyvitamin D levels[155]. In both children and adults, adequate vitamin D levels are critical for calcium and bone homeostasis, and for the prevention of rickets, osteoporosis and fractures[156]. Furthermore, individuals with dark skin have a reduced capacity for vitamin D synthesis in the skin and are at significantly lower risk for the development of UV radiation-related melanomas[156]. Strategies of public education for melanoma prevention must consider that the major source of vitamin D for most humans worldwide is exposure to sunlight[156]. However, a randomized double-blind study in Australia showed that adults who regularly applied sunscreen to the head, neck and upper extremities ($n = 58$) had mean serum 25-hydroxyvitamin D levels that were not significantly different to those of adults assigned to use a placebo cream ($n = 55$) for a duration of 7 months[157]. These data, albeit controversial[158], suggest that application of sunscreen to limited anatomical sites enables adequate vitamin D production in light-skinned individuals living in areas with very high levels of UV irradiance. When available, oral vitamin D supplementation is an alternative and highly effective means by which to maintain or increase vitamin D levels[159].

Despite knowledge that UV radiation is a significant environmental risk factor for melanoma, tanning remains popular in Western societies. High-frequency UV radiation-seeking individuals have been suggested

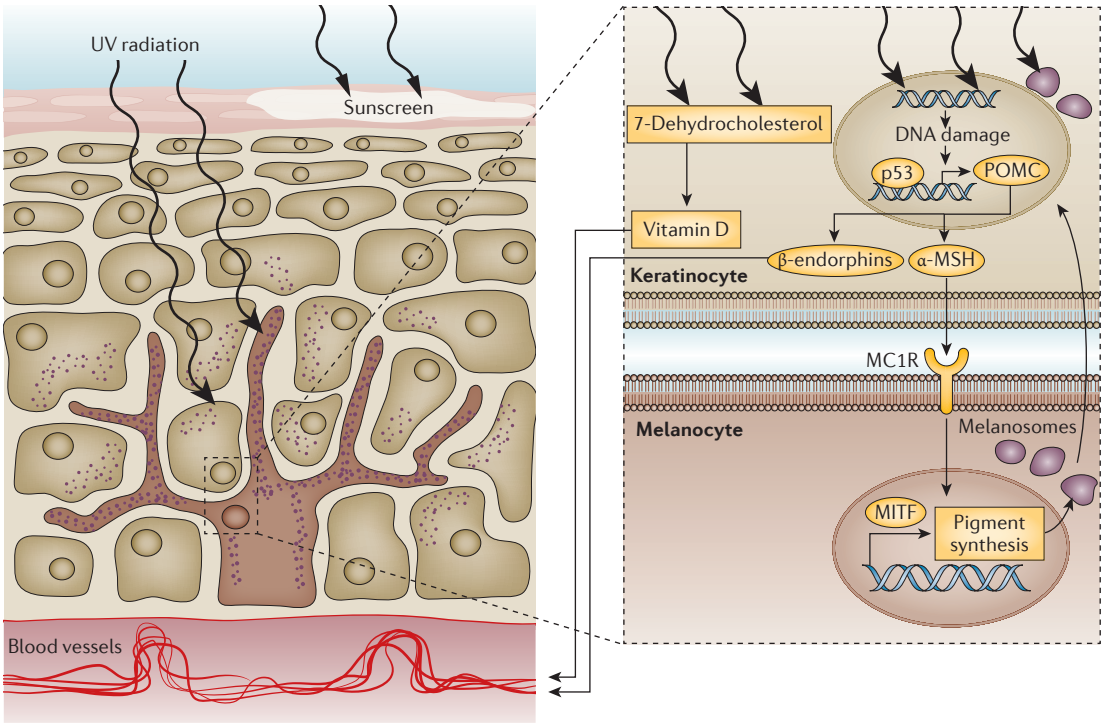

Figure 4 | **UV radiation: carcinogenesis, vitamin D, tanning and addiction behaviours.** UVB range (280–315 nm) radiation interacts with 7-dehydrocholesterol to produce vitamin D (right panel), which enters the bloodstream and is activated by hydroxylation in the liver and kidneys (not shown). Similar wavelengths produce direct DNA damage throughout the epidermis, as do UVA wavelengths (315–400 nm), which produce indirect DNA damage through oxidative chemical damage. In keratinocytes, DNA damage induces p53, which transcriptionally stimulates expression of pro-opiomelanocortin (*POMC*). POMC is post-translationally processed and secreted into the bioactive peptides α-melanocyte-stimulating hormone (α-MSH) and β-endorphin. α-MSH stimulates melanocortin 1 receptor (MC1R) on melanocytes, resulting in cyclic AMP-mediated signalling that stimulates microphthalmia-associated transcription factor (MITF) to induce pigment synthesis within melanosome organelles. In red-haired and/or fair-skinned people, the *MC1R* gene typically exists as non-functional polymorphic variants that fail to transduce the α-MSH signal. Melanosomes are trafficked from melanocytes to overlying keratinocytes where they become positioned in a polarized fashion on the 'sun-exposed' side of the nucleus, providing some protection against further DNA damage. Increases in the levels of β-endorphin in the blood have been found after UV exposure and lead to addiction-like behavioural consequences[162]. Sunscreen (left panel) and chemopreventive agents (not shown) can act via absorption of UV wavelengths or neutralization of oxidative damage, and can be applied topically or in theory via systemic routes.

to have a 'tanning addiction' and often meet diagnostic criteria for substance-related disorders[160,161]. Studies in mice have identified a biological basis for these clinical observations, with UV radiation exposure leading to elevated blood levels of β-endorphin, a systemic analgesia that is reversible with opioid receptor blockade, and dependency and addiction-like behaviours[162] (FIG. 4).

Although improvements in our understanding of UV radiation-induced carcinogenesis and the dominant molecular pathways that are active in melanoma initiation, promotion and progression provide the foundation for developing effective chemoprevention, the field remains in its infancy. Any intervention for disease prevention in the general population should not only have proven clinical efficacy, but should be without adverse effects and be of low cost. Chemoprevention trials in lung cancer and colorectal cancer serve as a reminder that agents with early initial promise or actual efficacy might ultimately prove harmful[163,164]. Randomized clinical trials and case–control studies have found no efficacy for statins or fibrates[165,166], and non-steroidal anti-inflammatory drugs (NSAIDs)[167–169], respectively, in the prevention of melanoma. Agents that are currently under investigation include calcitriol, retinoids, flavonoids, sulforaphane, catechins, resveratrol and curcumin, among others[170,171].

Management

Localized and locoregional disease

Surgery and adjuvant treatment. Surgical removal is the prevailing gold standard treatment option for patients with primary cutaneous melanoma who have clinically negative regional lymph nodes (that is, localized disease; patients with positive regional lymph nodes are said to have locoregional disease). Two aspects need consideration when planning the surgery: the excision margin around the melanoma and the approach to the regional nodal basin. Before surgery, other cutaneous lesions that might be additional primary melanomas, regional adenopathy (swollen lymph nodes), satellite and/or in-transit metastases, and signs and symptoms indicative of distant metastasis must also be identified — any such findings can alter treatment plans.

Table 1 | **Recommendations for primary cutaneous melanoma excision margins**

Tumour thickness	Excision margin
In situ	0.5 (– 1) cm
≤1.00 mm	1 cm
1.01–2.00 mm	1 (–2) cm
2.01–4.00 mm	2 cm
>4.00 mm	2 cm

Wide excision margins are based on Breslow's thickness and are measured from the edges of the biopsy site or residual pigment. Wide excision should include subcutaneous tissue down to the level of, but generally not including, the underlying muscular fascia. Recommended margins of excision are summarized in TABLE 1.

The approach to the regional nodal basin for patients with clinically negative regional lymph nodes is informed by tumour thickness as well as other factors. Overall, the risk of occult regional lymph node metastasis ranges from <5% among patients with primary melanomas that are <0.75 mm thick to >50% for patients with thick (>4 mm), ulcerated, primary melanomas. Given that finite regions of skin drain via afferent lymphatic vessels to lymph nodes — so-called sentinel nodes — and that these nodes are the most likely to contain metastatic disease, lymphatic mapping and sentinel lymph node biopsy (SNB) are advocated for some patients[172,173]. This multidisciplinary approach requires collaboration across nuclear medicine, surgical and pathology teams. Preoperative lymphoscintigraphy is performed to identify at-risk regional nodal basins and to localize the sentinel nodes. Histological analysis is performed, usually as a combination of step sectioning and immunohistochemical analysis. SNB is usually recommended for patients with primary cutaneous melanomas that are ≥1 mm thick[174]. By contrast, owing to the overall low risk of microscopic regional metastasis among patients with thin melanomas, a very selective approach to SNB is typically used in this cohort. Although indications for this procedure among these patients continue to evolve, one rational approach is to discuss and to consider SNB for a patient whose primary tumour is ≥0.75 mm thick[175]. According to the National Comprehensive Cancer Network (NCCN) melanoma guidelines[176], apart from primary tumour thickness in patients with thin melanomas (≤1.0 mm), what should be considered 'high-risk features' for a positive sentinel node is not precisely defined. Conventional risk factors for a positive sentinal lymph node — such as ulceration, high mitotic rate and lymphovascular invasion — are very uncommon in melanomas that are ≤0.75 mm thick; when present, SNB can be considered on an individual basis.

Sentinel node histological status is a critically important independent predictor of survival[177,178]. Although completion lymphadenectomy (CLND) has been the standard of care for patients with a positive SNB for more than two decades, its role in these patients continues to evolve. Indeed, its use has been called into question; the recently completed MSLT-I randomized clinical trial did not demonstrate an overall survival benefit for patients undergoing SNB[178]. However, subset analyses among all node-positive patients revealed a survival advantage in SNB-positive patients with intermediate-thickness primary melanomas (1.20–3.50 mm) who underwent immediate CLND, compared with those patients who had nodal observation and CLND only upon biopsy-confirmed nodal recurrence[178]. Although promising, more data must accumulate before a change in practice can be advocated; two clinical trials are currently addressing the role of CLND in the SNB-positive population: the randomized international MSLT-II clinical trial (ClinicalTrials.gov identifier NCT00297895) and the European Organization for Research and Treatment of Cancer (EORTC) registry-based MINITUB study (ClinicalTrials.gov identifier NCT01942603).

In patients with SNB-negative primary melanomas of AJCC stages IIA–IIIC, 25 years of trials with adjuvant interferon-α (IFNα) have consistently shown a modest relative risk reduction that is estimated in meta-analyses to be as high as 17% for disease-free survival (DFS) and 9% overall survival[179] compared with undertreated control groups (observation alone). These results were obtained independently of the dose, pharmacokinetics (pegylated IFN or conventional IFN)[180] and regimens. Nevertheless, it is important to keep in mind that several of the studies were performed in the era before SNB staging was widely accepted and numerous clinically 'tumour-free' patients without SNB staging were included who would nowadays have sentinel node positivity ranges of up to 25% after SNB staging). No IFN-based regimen has found universal acceptance, as all regimens tested so far have had modest effects on DFS and overall survival; accordingly, an untreated control arm in clinical trials is still acceptable[181], and IFN is not offered to patients as an adjuvant treatment option in several countries. Notably, the clinical benefit of adjuvant IFN is hardly detectable in patients with clinically evident (palpable) nodes[182], suggesting that such nodal characteristics represent a more-advanced biological phase of disease. Furthermore, the role of ulceration in primary melanomas as a predictive biomarker for immunotherapies such as IFN or ipilimumab (a fully human monoclonal CTLA4-specific immunoglobulin G1 (IgG1) antibody) is also currently debated[182]. Patients with AJCC stage IIC–IIIC melanoma are at high risk of death from metastatic disease, and an effective adjuvant therapy is needed urgently. However, providing adjuvant therapy only to these high-risk patients would neglect potentially lethal cases within the intermediate- and low-risk cohorts. Given that patient numbers with AJCC stage IIA–IIB are much lower, patients at risk will require better and more precise identification, as well as low toxicity regimens and/or more reliable response predictors, to obtain an acceptable risk-benefit ratio. In the United States, for example, 30% of deaths from melanoma are caused by melanomas that are thin at first presentation[183]. Low-dose IFN is so far

Table 2 | **Findings from large clinical trials of ipilimumab, nivolumab, vemurafenib, dabrafenib and trametinib**

Study	Trial acronym	Agent	*n*	Response rate (%)	Median PFS (months)	HR PFS	Median OS (months)	HR OS	1-year survival (%)	2-year survival (%)	3-year survival (%)
Hodi *et al.* (2010)[188]*	MDX010-20	Ipilimumab	137	11	2.9	0.64	10.1	0.66	46	24	21‡
		gp100	136	1.50	2.8		6.4		24	14	NA
Robert *et al.* (2015)[213]§	Checkmate 066	Nivolumab	210	40	5.1	0.43	NR	0.42	73	NR	NR
		Dacarbazine	208	14	2.2		10.8		43	NR	NR
Chapman *et al.* (2011)[193]‖	BRIM-3	Vemurafenib	337	48	5.3	0.26	13.6¶	0.37	56	39 (18 months)	NA
		Dacarbazine	338	5	1.6		9.7¶		NA	NA	NA
Hauschild *et al.* (2012)[53]‖	BREAK-3	Dabrafenib	187	50	5.1	0.3	NA	0.61	70#	45#	31#
		Dacarbazine	63	6	2.7		NA		63#**	32#**	28#**
Flaherty *et al.* (2012)[202]‡‡	METRIC	Trametinib	214	22	4.8	0.45	16.1§§	0.72¶	61§§	31§§	NA
		Dacarbazine or paclitaxel	108	8	1.5		11.1§§		50§§**	28§§**	NA
Robert *et al.* (2011)[189]‖‖	CA184-024	Ipilimumab + dacarbazine	250	15	2.8	0.76	11.2	0.72	47¶¶	28¶¶	21¶¶
		Dacarbazine	252	10	2.6		9.1		36¶¶	18¶¶	12¶¶

HR, hazard ratio; NA, not available in the publication; NR, not reached; OS, overall survival; PFS, progression-free survival. *Enrolled previously treated patients with advanced-stage melanoma with no BRAF restriction. ‡Data from REF. 250. §Enrolled previously untreated patients with advanced-stage melanoma without *BRAF* mutation. ‖Enrolled patients with BRAF mutant advanced-stage melanoma who had not been previously treated with a systemic therapy. ¶Data from follow-up manuscript. #Data from REF. 194. **Results confounded by cross over. ‡‡Enrolled patients with BRAF mutant advanced-stage melanoma who were either previously treated with a systemic therapy or had received one line of chemotherapy. §§Data from REF. 251. ‖‖Enrolled untreated patients with advanced-stage melanoma with no BRAF restriction[52]. ¶¶Data from REF. 252.

the only treatment modality that has gained some acceptance in this patient group in some, but not all, parts of the world. Although adjuvant vaccines are well-tolerated, clinical benefit in melanoma has not been definitively shown and their use remains experimental.

Aside from IFN-based adjuvant regimens, targeted therapies against tumour angiogenesis, such as bevacizumab, also have a limited impact on metastatic spread. Bevacizumab has demonstrated a small DFS benefit and no overall survival improvement in a recent adjuvant trial[184]. Furthermore, drugs with proven efficacy in advanced-stage metastatic disease are good candidates for adjuvant treatment. Their specific toxicity profile and the low conceptual risk of the induction of resistance towards targeted therapies justify their use primarily in high-risk patients (AJCC stage IIIA–IIIC). In this vein, trials of vemurafenib and a combination of dabrafenib and trametinib in patients with $BRAF^{V600}$ mutations are ongoing. As another example, high-dose ipilimumab (10 mg kg^{-1}) for 3 years has shown to substantially reduce the risk of disease recurrence (25%), but overall survival data are not yet available[185]. The high rate of severe toxicities of this regimen combined with a maintenance schedule of up to 3 years makes this treatment difficult to accept unless a significant overall survival improvement in a mature data set is demonstrated. Other immune-checkpoint inhibitors, such as antibodies against PD1, are likely to be tested in adjuvant trials in 2015.

As there is currently no internationally accepted standard of care that has a significant overall survival benefit for patients with melanoma at high risk of recurrence, these patients should be referred to clinical trials if possible. DFS is an accepted clinical trial end point, but clear benefits in overall survival would be superior. However, more effective therapies for the metastatic stage — that provide an overall survival benefit for AJCC stage IV melanoma — will affect the current outcome parameters. An adjuvant treatment with a prolongation of DFS could, therefore, be considered as a 'bridge' to the availability of innovations for advanced-stage melanoma.

Distant metastatic disease

Patients who are found to have distant metastases in visceral and non-visceral organs should undergo histological confirmation and full staging studies. The restaging examinations usually include MRI of the brain (or a CT scan of the brain with intravenous contrast) and either total-body PET–CT scan or CT scans of the chest, abdomen and pelvis, thus providing imaging data from the most common sites for melanoma metastasis. The histological sample should be analysed for at least the presence or absence of $BRAF^{V600}$ mutations. Mutation panels for other mutations are increasingly being used to detect *NRAS* or *KIT* mutations; next-generation sequencing of tens to hundreds of genes that are commonly associated with cancer can also provide broad information on potentially actionable mutations in melanoma[186].

Local therapy for distant metastases. Unlike in localized disease, surgery is not usually a curative option in patients with advanced-stage metastatic melanoma. Nevertheless, in cases of limited spread to soft tissues or to (single) visceral organs, a multidisciplinary treatment team should discuss whether a complete surgical resection of the metastasis is achievable based on previously identified tumour characteristics (for example, tumour dynamics). For the majority of patients, however, the benefit from surgery for distant metastases

Table 3 | **Findings from large clinical trials in patients with *BRAF*^{V600}-mutated metastatic melanoma***

Study	Trial acronym	Agent	*n*	Grade 3–4 adverse events (%)	Response rate (%)	Median PFS (months)	HR PFS	Median OS (months)	HR OS
Flaherty *et al.* (2012)[54]	None	Dabrafenib	54	43	54	5.8	0.39	NA	NA
		Dabrafenib + trametinib	54	58	76	9.4		25.0‡	
Long *et al.* (2014)[205]	COMBI-d	Dabrafenib	212	37	51	8.8	0.75	NA	0.63
		Dabrafenib + trametinib	211	35	67	9.3		NA	
Larkin *et al.* (2014)[206]	coBRIM	Vemurafenib	248	59	45	6.2	0.51	NA	0.65
		Vemurafenib + cobimetinib	247	65	68	9.9		NA	
Robert *et al.* (2015)[207]	COMBI-v	Vemurafenib	352	64	51	7.3	0.56	17.2	0.69
		Dabrafenib + trametinib	352	53	64	11.4		NR	

HR, hazard ratio; NA, not available in the publication; NR, not reached; OS, overall survival; PFS, progression-free survival.
*Comparing single-agent BRAF inhibitor with or without a MEK inhibitor. ‡Data from REF. 253.

is palliative, and it is only curative in rare cases. Common indications for palliative surgery or radiotherapy are brain metastases, bleeding or obstruction from small bowel metastases, and symptomatic cutaneous, subcutaneous, nodal or bone lesions that become a local problem. Occasionally, patients with isolated metastases, even in the brain, might derive long-term control with surgery alone[187].

Systemic treatments. Until the approval of ipilimumab in 2011, the chemotherapeutic agents dacarbazine, temozolomide and fotemustine were commonly used for the palliative treatment of patients with metastatic melanoma. However, none of these agents had been approved based on a randomized trial demonstrating an improvement in overall survival. These agents have been mostly supplanted by the use of the conclusive data from randomized trials with immune-checkpoint inhibitors, and BRAF and MEK inhibitors (TABLES 2,3).

Two randomized clinical trials of ipilimumab demonstrated improvement in overall survival, leading to its broad regulatory approval in North America, Europe and Australia for the treatment of unresectable or metastatic melanoma at a dose of 3 mg kg^{-1} administered at 3-week intervals for four doses. One clinical trial compared ipilimumab to a gp100 peptide vaccine in HLA-A*0201-positive patients with previously treated unresectable AJCC stage III–IV melanoma[188]. The primary end point of overall survival favoured the ipilimumab arm (hazard ratio, 0.66; $P = 0.003$; TABLE 2). Grade 3–4 immune-related adverse events (that is, the most severe adverse events) occurred in 10–15% of patients treated with ipilimumab, the most common being colitis, skin rash and endocrinopathies[188].

The second randomized clinical trial compared ipilimumab (10 mg kg^{-1}) plus dacarbazine (850 mg m^{-2}) or dacarbazine (850 mg m^{-2}) plus placebo. This study also showed that overall survival was significantly improved in the group receiving ipilimumab. However, the combination of ipilimumab and dacarbazine is not widely used owing to a high rate of grade 3–4 adverse events (56%), including, in particular, increases in transaminases that denote liver toxicity[189]. Indeed, the FDA approval of ipilimumab comes with a black box warning to the potential for severe and occasionally fatal immune-mediated adverse reactions[190]. The most common amongst these are enterocolitis, hepatitis, dermatitis, neuropathy and endocrinopathies (such as hypophysitis and thyroiditis). In the case of such adverse reactions, the recommendation in the package insert is to permanently discontinue ipilimumab infusions and to initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

Two oral BRAF inhibitors — vemurafenib and dabrafenib — have been widely approved in North America, Europe and Australia for the treatment of patients with *BRAF*^{V600}-mutant metastatic melanoma[191,192]. Two Phase III trials were performed comparing vemurafenib (960 mg twice daily)[193] or dabrafenib (150 mg twice daily)[53] with dacarbazine. Both BRAF inhibitors showed similar response rates and improvements in PFS. Both reduced the risk of progression by >70% and the trial of vemurafenib, which did not allow cross over, reduced the risk of death by 63% (TABLE 2). An update of these trials showed a median overall survival of 20.0 months (dabrafenib) versus 15.6 months (dacarbazine), and 13.6 months (vemurafenib) versus 9.7 months (dacarbazine), respectively[52,194,195]. Common adverse events associated with both agents were skin-related toxic effects, arthralgia and fatigue. Comparing the major clinically relevant toxicities between both agents, the incidence of photosensitivity is higher with vemurafenib, and the incidence of fever is higher with dabrafenib. Other adverse events with BRAF-inhibitor treatment include secondary cutaneous squamous cell carcinomas and keratoacanthomas, which occur in ~20% of patients and usually appear in the first 2–3 months of therapy[196]. Also, second primary melanomas are observed in 2–5% of BRAF-inhibitor-treated patients[197]. Pre-existing *RAS* mutations and concomitant RAS-GTP signalling drive the formation of BRAF–CRAF dimers, and blocking wild-type BRAF in a

heterodimer with CRAF transactivates *CRAF* and drives tumour formation. This interaction results in increased MAPK signalling through the paradoxical transactivation of *CRAF*[198,199]. These skin cancers are usually treated with local excision and do not require a change in the dose of the BRAF inhibitor.

MEK inhibitors reduce cellular proliferation in $BRAF^{V600}$-mutant melanoma and can also have some activity in *NRAS*-mutant disease[200,201]. For example, trametinib improved PFS and overall survival in a Phase III trial compared with dacarbazine or paclitaxel in patients with $BRAF^{V600}$-mutant metastatic melanoma[202] (TABLE 2). The most common toxicities were rash, diarrhoea and peripheral oedema. As single agents, MEK inhibitors have a higher incidence of adverse effects and a lower efficacy compared with BRAF inhibitors, which are preferred over MEK inhibitors for the treatment of patients with *BRAF*-mutated advanced-stage melanoma. Nevertheless, the most common mechanism of resistance to single-agent BRAF-inhibitor therapy is mediated by the reactivation of the MAPK pathway through MEK[203,204]. Thus, combined therapy with a BRAF inhibitor and MEK inhibitor can result in a greater initial tumour response and prevent MAPK-driven acquired resistance mechanisms. Furthermore, adding a MEK inhibitor to a BRAF inhibitor would block the paradoxical MAPK activation that leads to secondary squamous cell carcinomas and other toxicities from single-agent treatment with BRAF inhibitors[199]. The superiority of combined BRAF inhibitor and MEK inhibitor therapy over BRAF inhibitors alone has been demonstrated in three Phase III clinical trials (COMBI-d, COMBI-v and coBRIM; TABLE 3). In aggregate, these studies show a consistent improvement in PFS, with hazard ratios between 0.39 and 0.75; the COMBI-v study demonstrated an improvement in overall survival with a hazard ratio of 0.69. The combination of dabrafenib and trametinib was approved in the United States in 2014 for the treatment of *BRAF*-mutated advanced-stage melanoma, and the recent confirmatory data[205–207] should lead to similar approvals of BRAF inhibitor plus MEK inhibitor combinations by regulatory bodies around the world.

Although mutations in *KIT* are, overall, infrequent in melanoma (~1%), they are more prevalent in mucosal and acral melanomas. KIT inhibitors — such as imatinib, dasatinib and sunitinib — have modest activity in *KIT*-mutant melanoma, with response rates in the range of 15–20%[208].

Finally, antibodies against PD1 or PDL1 have demonstrated a high rate of durable tumour responses[209–211]. Nivolumab is a fully human PD1-specific antibody that has been tested in several cancers, including melanoma[210]. The response rate was 31% in patients with advanced-stage melanoma who received nivolumab at different doses administered every 2 weeks for up to 96 weeks; 1-year and 2-year survival rates were 62% and 43%, respectively[210]. The activity in patients pretreated with ipilimumab led to accelerated FDA approval of nivolumab in December 2014. Treatment-related grade 3–4 adverse events were observed in only 14% of patients. Rare adverse events of special interest included pneumonitis, vitiligo, colitis, hepatitis, hypophysitis and thyroiditis[74]. Response rates for pembrolizumab (which also targets PD1) were between 26% and 51% in patients with advanced-stage melanoma[211]; following evaluation of different doses and schedules, a dose of 2 mg kg^{-1} every 3 weeks was recommended[212]. The activity in ipilimumab-pretreated advanced-stage melanoma led to the accelerated FDA approval of pembrolizumab in September 2014. In general, response rates to the PD1-specific antibodies are higher in patients whose tumours also express the ligand PDL1. However, the available methods for PDL1 detection are not robust enough (in terms of antibody selection, staining platforms and cut-off values), nor is PDL1 expression sufficiently predictive, to use PDL1 expression as a means to select patients for therapy[74,210,212–214]. Despite the impressive durability of response, resistance has occurred with both PD1-specific antibodies, although the mechanisms of resistance remain poorly defined.

Cell-based therapy. Infusing large numbers of autologous tumour-specific T cells into patients with melanoma has been an exploratory treatment approach for more than 20 years. Adoptive cell transfer (ACT) therapy involves the infusion of T cells specific for cancer antigens, usually in conjunction with conditioning chemotherapy to partially deplete endogenous lymphocytes after IL-2 infusion. The approaches include the harvesting of T cells from tumours and their reinfusion to patients after a period of *ex vivo* expansion, known as tumour-infiltrating lymphocyte (TIL) ACT, or the genetic modification of blood T lymphocytes with viral vectors to express transgenic T cell receptors (TCRs), known as TCR-engineered ACT. ACT has shown reproducible antitumour activity in patients with advanced-stage melanoma[215,216]. The most advanced ACT-based approach is TIL, with responses in excess of 50% in patients with previously treated advanced-stage melanoma[216]. This mode of personalized cell therapy continues its development as an experimental approach mainly in academic centres.

Other therapies. The role of disease burden and/or biologic aggressiveness will still remain of considerable importance in therapy selection for patients with metastatic melanoma, even with all of the new agents available. Discussion on treatment algorithms in the advanced-stage settings will continue based on clinical trial results. Currently, treatment approaches have been relegated to the use of chemotherapy agents when other (targeted) therapies have not worked. The only chemotherapy agent that has improved PFS (but not overall survival) compared with the 'old' standard of care (dacarbazine) in a large randomized trial has been nab-paclitaxel, which is an additional option in this setting[217]. There is also reported activity with carboplatin and paclitaxel[218]. IL-2 was approved in 1998 and is infrequently used in the United States on the basis of its ability to induce long-term remissions in approximately 6% of patients[219]. Patients with in-transit metastases have additional options, including the intratumoural injection of the oncolytic virus talimogene laherparepvec, which was shown in a randomized trial to be superior

to granulocyte–macrophage colony-stimulating factor in terms of durable tumour responses[220].

Quality of life

Quality of life can be defined in many ways, making its measurement and incorporation into scientific study difficult. As illness and its treatment affect the psychological, social and economic wellbeing, as well as the biological integrity, of individuals, any definition should be all encompassing while allowing individual components to be delineated. In most cases, the evaluation of individuals with cancer and other chronic illnesses uses standardized, structured questionnaires. Such questionnaires can independently assess single dimensions, such as pain (covered, for example, by the brief pain inventory[221,222]) or anxiety (the Spielberger state–trait anxiety inventory[223,224]), but can also be part of multidimensional instruments for measuring health-related quality of life (HR-QOL). These questionnaires assess the burden of a disease in an individual patient, and whether any intervention can alleviate or worsen it as perceived by the individual patient. HR-QOL instruments are questionnaires that incorporate multi-item functional scales (such as physical, role, cognitive, emotional and social functioning), symptom scales (measuring fatigue, pain and nausea or vomiting) and a global health status scale, as well as single items, such as dyspnoea, loss of appetite, constipation, diarrhoea, sleep disturbance and/or financial impact. For each scale or item, a linear transformation is applied to standardize the raw score for a range from 0–100, with 100 representing best possible function or quality of life for functional scales, and highest burden of symptoms for symptom scales and symptom items.

Although reducing the burden of disease is the goal of any medical intervention from the human and societal perspectives, transforming this concept in to a reliable, sensitive and robust measure is challenging. HR-QOL instruments can be generic, such as the SF-36 (REF. 225), and can accordingly be used in any disorder. By contrast, serum tumour markers are typical examples of disease-specific instruments, such as the EORTC QLQ-C30 (REF. 226). It is important to underscore that HR-QOL assessment summarizes the combined impact of the disease and treatments, whereas usual medical assessment separately assesses only clinical benefits and adverse events. Clear-cut clinical improvements such as measuring tumour response or DFS can produce little, if any, noticeable benefit for the patient or can even be associated with a decline in quality of life if the adverse-effect profile of a given treatment is high. Conversely, when the outcome of clinical trials reveals only modest differences between treatments by doctor-defined outcomes, quality of life indicators can provide helpful additional information to assess the benefit from the patient perspective.

As with the diagnosis of other cancers, the diagnosis of melanoma leads to anxiety, depression and other distress related to uncertainty, especially if the patient must undergo several years of surveillance. However, HR-QOL instruments do not usually detect differences from normal population[227]. It is interesting to note that patients who have undergone nodal surgery, including SNB and lymphadenectomy tend to score well on HR-QOL instruments[228], probably because they have changed their expectations according to the new context (locally advanced disease), which is a well-known phenomenon referred to as 'response shift' (REF. 229).

Several studies have documented the obvious dose-dependent impairment of HR-QOL in patients receiving adjuvant therapy with IFNs[230–232]. By contrast, recent data suggest that, despite high toxicity, a clinically significant decrease in HR-QOL is not apparent when ipilimumab is given in the adjuvant setting, except in the first few weeks of treatment[185]. Measuring HR-QOL in tumour-free patients with melanoma who are at high risk of metastasis in the adjuvant setting is certainly different from analysing it in advanced-stage disease in a palliative situation. Specifically, in those with advanced-stage metastatic disease, performance status (measured using either the Eastern Cooperative Oncology Group[233] or Karnofsky metrics[234]) is initially often preserved. However, a single metastasis — particularly in the brain — can severely affect a patient's daily life. Careful monitoring of the patient's symptoms and their palliative care (including surgery, radiotherapy and analgesics) can influence some of the scales; preservation of patient performance and mental status is a key treatment goal.

The immediate demand for patients with advanced-stage metastatic melanoma is survival. Once a given therapy or therapies can substantially increase survival, the quality of survival becomes important for the patient, but also for the payers who will use metrics such as quality-adjusted life years (QALYs) or disability-adjusted life years[235] (DALYs; BOX 2) to assess the real benefit of costly drugs. The survival benefit obtained with targeted therapies and immune-checkpoint inhibitors comes at the cost of new adverse events, many of which affect everyday life (such as skin lesions, arthralgia, diarrhoea and fever). The frequent disconnect between the doctor's 'objective' assessment of the tumour response and adverse events, and the patient's 'subjective' perception of the overall 'disease-treatment package' makes it crucial to understand what the actual benefit is from the patient's point of view. Only a few trials of new immune and targeted therapies have reported HR-QOL data[236–238]. However, even in these studies, only the EORTC QLQ questionnaires were used and evaluations are still limited. From these reports, BRAF

Box 2 | **Assessing quality of life**

Quality-adjusted life years (QALYs)
The arithmetic product of the number of years of life that would be added by the intervention and a measure of the quality of the gained life years, each year in perfect health being assigned the value of 1.0 down to a value of 0.0 for death.

Disability-adjusted life years (DALYs)
The sum of the years of life lost owing to premature mortality in the population and the years lost due to disability for people living with the health condition or its consequences. One DALY can be thought of as one lost year of 'healthy' life.

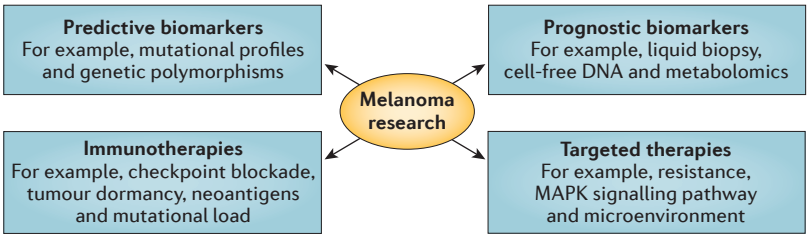

Figure 5 | **The future of melanoma research.** Over the next 5–10 years, the focus will be on understanding how resistance to targeted therapies develops and how to overcome potential crosstalk with other signalling pathways, leading to optimized patient selection and enhanced synergy of combination regimens. Similarly, antibodies targeting additional immune-checkpoint molecules will be tested, and strategies to sequence or combine these treatments will be based on a better understanding of exact mechanisms of action. Mutational profiles or mutational loads might become relevant for patient selection, treatment algorithms and research. Validated predictive and prognostic biomarkers will be of critical importance for treatment optimization in clinical trials, and the clinical relevance of such biomarkers will increase if the underlying technologies are ready for routine use. MAPK, mitogen-activated protein kinase.

inhibitors and MEK inhibitors, and a combination of both, have been shown to preserve HR-QOL better than chemotherapy[236–238], suggesting that the highly significant improvements in response rate or PFS contribute to improvements in at least some of the quality of life scales measured over the clinical course.

Measurements of patient-reported outcomes are needed to evaluate all new strategies in melanoma, even if methodological issues influence the quantification of the benefit and, therefore, the resulting health-economic assessment. Furthermore, it has to be kept in mind that, whatever the results, each patient will estimate his or her benefit on their own 'subjective' scale.

Outlook

Having acquired the status of a 'graveyard of pharmaceutical development' (REFS 239, 240), advanced-stage cutaneous melanoma has drawn interest from only a very small subset of the oncology community. However, a well-functioning global clinical trial network is in place that has revitalized the community, promoting new biological advances and championing the innovation of new drugs. These agents build on an improved understanding of the biology of melanoma and its interactions with the immune system, resulting in unprecedented benefits to patients. Consequently, the management of metastatic melanoma of cutaneous and mucosal origin has significantly improved in the past 5 years, with the introduction of immune-checkpoint inhibitors that reactivate immune responses against cancer and the use of targeted BRAF inhibitors and MEK inhibitors for patients with *BRAF*^{V600}-mutated advanced-stage melanoma. For the first time, long-term clinical benefit with increasing 2-year, 3-year and 5-year survival rates are apparent.

The field continues to advance (FIG. 5) and it is hoped that an improved understanding of the mechanisms of drug response and resistance will enable further optimization of patient care. This requires in-depth systematic analysis of all major biological mechanisms that affect clinical efficacy of drugs and drug combinations, including tumour–microenvironment interactions, epigenetic modifications, tumour heterogeneity and tumour plasticity. Only a fully comprehensive view of melanoma biology in its natural context — the human host — will enable us to develop new rationales for drug combinations and sequential drug regimens. In parallel, novel predictive and prognostic markers need to be identified for further therapeutic guidance. Regarding the rapidly improving insights into the complex and multifactorial regulation of melanoma, it is difficult to make reliable predictions about the most promising therapeutic targets in the near future. Currently, there is much interest in blocking all oncogenic signalling pathways to prevent cell survival via signalling bypasses. However, whether such blockade should be made simultaneously or in a sequential fashion is unclear. Most probably, the next step in this development is the integration of inhibitors of the PI3K–AKT–PTEN–mTOR pathway — which is currently targeted in other cancer types — into routine clinical practice for melanoma. However, it is not possible to predict whether this approach will succeed in terms of providing a tolerable adverse-effects profile, especially in combination with other signalling inhibitors or immunotherapies. The class of immuno-oncologic drugs is a rapidly expanding field of research by itself and will soon include the use of new immune-checkpoint inhibitors (for example, lymphocyte activation gene 3 protein (LAG3) and GITR (also known as TNFRSF18)) alone and in combination with immune-checkpoint inhibitors. Although it is not possible to predict exactly how melanoma therapy will look in 5 years from now, it is commonly anticipated that metastatic melanoma will no longer be a near-certain death sentence but rather a chronic condition with increased long-term benefit and improved survival for a growing percentage of patients.

Although treatments are available that undoubtedly extend the lives of patients with advanced-stage disease, the accepted trial end point of overall survival is difficult to define. The major challenge for future drug development in metastatic melanoma will be clinically effective and approved drugs that confound — because of their use in subsequent lines of therapy over the clinical course of treatment — the overall survival end point; consequently, attributing the overall survival benefit to the one tested drug will be increasingly difficult. Accordingly, the identification of robust and reliable surrogate markers of overall survival is of immense importance to keep up the momentum in melanoma drug development, including drug sequencing studies and combinations of already-registered drugs.

Despite this progress in the cutaneous disease, very limited progress has been made in the management of metastatic melanoma of uveal origin, for which new knowledge about the driver mutations has not led to the specific development of targeted therapies; immunotherapies have either not been tested or they have shown limited efficacy[241]. Although genetic and genomic studies have opened the possibility of accurately predicting which patients have favourable or poor prognoses, effective therapies are still lacking. Targeting of the downstream events of the activating mutations *GNAQ* and *GNA11* is currently being attempted. The combination of protein

kinase C inhibitors and MEK inhibitors showed activity in a mouse xenograft model that has mutations in *Gnaq* and *Gna11* (REF. 242), and such inhibitor combinations are now being tested in clinical trials (ClinicalTrials.gov identifier NCT01801358). New reports have also identified *GNAQ* and *GNA11* mutations that lead to activation of a Yes-associated protein (YAP) component of the Hippo signalling pathway[243,244], which is involved in the regulation of cell proliferation and apoptosis. The YAP inhibitor verteporfin could inhibit growth and present a novel potential therapy for uveal melanomas.

Finally, mutations in *SF3B1* (which encodes subunit 1 of splicing factor 3b) and *EIF1AX* (which encodes X-linked eukaryotic translation intiation factor 1A) have been identified in uveal melanoma, but their role is still poorly understood. However, as these mutations are associated with a good prognosis (that is, the absence of metastases), their therapeutic relevance in uveal melanoma is not clear[245]. By contrast, *BAP1* loss is a marker of poor prognosis[246,247]. *BAP1* is implicated in chromosome modification and cell reprograming, which potentially lead to a de-differentiated cell phenotype[248]. Therapeutically targeting such gene alterations could prove challenging; however, promising initial experimental results with histone deacetylase inhibitors have been reported[249]. Overall, these developments are encouraging and will hopefully soon translate into effective therapies for patients with uveal melanoma.

1. Schadendorf, D. & Hauschild, A. Melanoma in 2013: Melanoma—the run of success continues. *Nat. Rev. Clin. Oncol.* **11**, 75–76 (2014).
2. Lawrence, M. S. *et al.* Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature* **499**, 214–218 (2013).
3. Si, L., Wang, X. & Guo, J. Genotyping of mucosal melanoma. *Chin. Clin. Oncol.* **3**, 27 (2014).
4. De Angelis, R. *et al.* Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE—5-a population-based study. *Lancet Oncol.* **15**, 23–34 (2014).
5. Pflugfelder, A. *et al.* Malignant melanoma S3-guideline "diagnosis, therapy and follow-up of melanoma". *J. Dtsch. Dermatol. Ges.* **11** (Suppl. 6), 1–116, 1–126 (2013).
6. Garbe, C. & Bauer, J. in *Dermatology* 3rd edn (eds Bolognia, J. L., Jorizzo, J. L. & Schaffer, J. V.) 1885–1914 (Elsevier, 2012).
7. Erdmann, F. *et al.* International trends in the incidence of malignant melanoma 1953-2008—are recent generations at higher or lower risk? *Int. J. Cancer* **132**, 385–400 (2013).
A paper describing the incidence rates of melanoma across the world.
8. Geller, A. C. *et al.* Melanoma epidemic: an analysis of six decades of data from the Connecticut Tumor Registry. *J. Clin. Oncol.* **31**, 4172–4178 (2013).
9. Garbe, C. & Leiter, U. Melanoma epidemiology and trends. *Clin. Dermatol.* **27**, 3–9 (2009).
10. MacKie, R. M., Hauschild, A. & Eggermont, A. M. Epidemiology of invasive cutaneous melanoma. *Ann. Oncol.* **20** (Suppl. 6), vi1–vi7 (2009).
11. Hausauer, A. K., Swetter, S. M., Cockburn, M. G. & Clarke, C. A. Increases in melanoma among adolescent girls and young women in California: trends by socioeconomic status and UV radiation exposure. *Arch. Dermatol.* **147**, 783–789 (2011).
12. Breitbart, E. W. *et al.* Systematic skin cancer screening in Northern Germany. *J. Am. Acad. Dermatol.* **66**, 201–211 (2012).
13. Iannacone, M. R., Youlden, D. R., Baade, P. D., Aitken, J. F. & Green, A. C. Melanoma incidence trends and survival in adolescents and young adults in Queensland, Australia. *Int. J. Cancer* **136**, 603–609 (2014).
14. Czarnecki, D. The incidence of melanoma is increasing in the susceptible young Australian population. *Acta Derm. Venereol.* **94**, 539–541 (2014).
15. Downing, A., Yu, X. Q., Newton-Bishop, J. & Forman, D. Trends in prognostic factors and survival from cutaneous melanoma in Yorkshire, UK and New South Wales, Australia between 1993 and 2003. *Int. J. Cancer* **123**, 861–866 (2008).
16. Livingstone, E. *et al.* A first prospective population-based analysis investigating the actual practice of melanoma diagnosis, treatment and follow-up. *Eur. J. Cancer* **47**, 1977–1989 (2011).
17. Gandini, S. *et al.* Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur. J. Cancer* **41**, 45–60 (2005).
18. Gandini, S. *et al.* Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur. J. Cancer* **41**, 28–44 (2005).
A paper that describes the association of UV exposure, melanocytic naevus count and melanoma development.
19. Boniol, M., Autier, P., Boyle, P. & Gandini, S. Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. *BMJ* **345**, e4757 (2012).
A systematic review and meta-analysis that links usage of sunbeds to the development of cutaneous melanoma.
20. Gandini, S. *et al.* Melanoma attributable to sunbed use and tan seeking behaviours: an Italian survey. *Eur. J. Dermatol.* **24**, 35–40 (2014).
21. Burnet, N. G., Jefferies, S. J., Benson, R. J., Hunt, D. P. & Treasure, F. P. Years of life lost (YLL) from cancer is an important measure of population burden—and should be considered when allocating research funds. *Br. J. Cancer* **92**, 241–245 (2005).
22. Joosse, A. *et al.* Superior outcome of women with stage I/II cutaneous melanoma: pooled analysis of four European Organisation for Research and Treatment of Cancer phase III trials. *J. Clin. Oncol.* **30**, 2240–2247 (2012).
23. Joosse, A. *et al.* Sex is an independent prognostic indicator for survival and relapse/progression-free survival in metastasized stage III to IV melanoma: a pooled analysis of five European organisation for research and treatment of cancer randomized controlled trials. *J. Clin. Oncol.* **31**, 2337–2346 (2013).
24. Bastian, B. C. The molecular pathology of melanoma: an integrated taxonomy of melanocytic neoplasia. *Annu. Rev. Pathol.* **9**, 239–271 (2014).
25. FitzGerald, M. G. *et al.* Prevalence of germ-line mutations in p16, 19ARF, and CDK4 in familial melanoma: analysis of a clinic-based population. *Proc. Natl Acad. Sci. USA* **93**, 8541–8545 (1996).
26. Goldstein, A. M. *et al.* High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. *Cancer Res.* **66**, 9818–9828 (2006).
27. Chin, L., Garraway, L. A. & Fisher, D. E. Malignant melanoma: genetics and therapeutics in the genomic era. *Genes Dev.* **20**, 2149–2182 (2006).
28. Sheppard, K. E. & McArthur, G. A. The cell-cycle regulator CDK4: an emerging therapeutic target in melanoma. *Clin. Cancer Res.* **19**, 5320–5328 (2013).
29. Zuo, L. *et al.* Germline mutations in the p16INK4a binding domain of CDK4 in familial melanoma. *Nat. Genet.* **12**, 97–99 (1996).
30. Wiesner, T. *et al.* Germline mutations in *BAP1* predispose to melanocytic tumors. *Nat. Genet.* **43**, 1018–1021 (2011).
31. Robles-Espinoza, C. D. *et al. POT1* loss-of-function variants predispose to familial melanoma. *Nat. Genet.* **46**, 478–481 (2014).
32. Shi, J. *et al.* Rare missense variants in *POT1* predispose to familial cutaneous malignant melanoma. *Nat. Genet.* **46**, 482–486 (2014).
33. Eggermont, A. M. M., Spatz, A. & Robert, C. Cutaneous melanoma. *Lancet* **383**, 816–827 (2014).
34. Hawryluk, E. B. & Tsao, H. Melanoma: clinical features and genomic insights. *Cold Spring Harb. Perspect. Med.* **4**, a015388 (2014).
35. Ward, K. A., Lazovich, D. & Hordinsky, M. K. Germline melanoma susceptibility and prognostic genes: a review of the literature. *J. Am. Acad. Dermatol.* **67**, 1055–1067 (2012).
36. Raimondi, S. *et al.* MC1R variants, melanoma and red hair color phenotype: a meta-analysis. *Int. J. Cancer* **122**, 2753–2760 (2008).
37. García-Borrón, J. C., Sánchez-Laorden, B. L. & Jiménez-Cervantes, C. Melanocortin-1 receptor structure and functional regulation. *Pigment Cell Res.* **18**, 393–410 (2005).
38. Garraway, L. A. *et al.* Integrative genomic analyses identify *MITF* as a lineage survival oncogene amplified in malignant melanoma. *Nature* **436**, 117–122 (2005).
39. Hodis, E. *et al.* A landscape of driver mutations in melanoma. *Cell* **150**, 251–263 (2012).
40. Alexandrov, L. B. *et al.* Signatures of mutational processes in human cancer. *Nature* **500**, 415–421 (2013).
41. Berger, M. F. *et al.* Melanoma genome sequencing reveals frequent *PREX2* mutations. *Nature* **485**, 502–506 (2012).
42. Krauthammer, M. *et al.* Exome sequencing identifies recurrent somatic *RAC1* mutations in melanoma. *Nat. Genet.* **44**, 1006–1014 (2012).
References 39, 41 and 42 are landmark papers describing the mutational landscape of melanoma.
43. Flaherty, K. T., Hodi, F. S. & Fisher, D. E. From genes to drugs: targeted strategies for melanoma. *Nat. Rev. Cancer* **12**, 349–361 (2012).
44. Kamb, A. Role of a cell cycle regulator in hereditary and sporadic cancer. *Cold Spring Harb. Symp. Quant. Biol.* **59**, 39–47 (1994).
45. Hussussian, C. J. *et al.* Germline p16 mutations in familial melanoma. *Nat. Genet.* **8**, 15–21 (1994).
46. Kwong, L. N. *et al.* Oncogenic NRAS signaling differentially regulates survival and proliferation in melanoma. *Nat. Med.* **18**, 1503–1510 (2012).
47. Jakob, J. A. *et al. NRAS* mutation status is an independent prognostic factor in metastatic melanoma. *Cancer* **118**, 4014–4023 (2012).
48. Griewank, K. G. *et al.* Genetic alterations and personalized medicine in melanoma: progress and future prospects. *J. Natl. Cancer Inst.* **106**, djt435 (2014).
49. Van Raamsdonk, C. D. *et al.* Mutations in *GNA11* in uveal melanoma. *N. Engl. J. Med.* **363**, 2191–2199 (2010).
50. Noonan, F. P. *et al.* Melanoma induction by ultraviolet A but not ultraviolet B radiation requires melanin pigment. *Nat. Commun.* **3**, 884 (2012).
51. Lito, P., Rosen, N. & Solit, D. B. Tumor adaptation and resistance to RAF inhibitors. *Nat. Med.* **19**, 1401–1409 (2013).
52. McArthur, G. A. *et al.* Safety and efficacy of vemurafenib in $BRAF^{V600E}$ and $BRAF^{V600K}$ mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. *Lancet. Oncol.* **15**, 323–332 (2014).
53. Hauschild, A. *et al.* Dabrafenib in *BRAF*-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* **380**, 358–365 (2012).
54. Flaherty, K. T. *et al.* Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N. Engl. J. Med.* **367**, 1694–1703 (2012).
55. Ribas, A. *et al.* Combination of vemurafenib and cobimetinib in patients with advanced *BRAF*V600-mutated melanoma: a phase 1b study. *Lancet. Oncol.* **15**, 954–965 (2014).
56. Hartsough, E., Shao, Y. & Aplin, A. E. Resistance to RAF inhibitors revisited. *J. Invest. Dermatol.* **134**, 319–325 (2014).

57. Roesch, A. Tumor heterogeneity and plasticity as elusive drivers for resistance to MAPK pathway inhibition in melanoma. *Oncogene* http://dx.doi.org/10.1038/onc.2014.249 (2014).
58. Shi, H. *et al.* Melanoma whole-exome sequencing identifies ^{V600E}*B-RAF* amplification-mediated acquired B-RAF inhibitor resistance. *Nat. Commun.* **3**, 724 (2012).
59. Poulikakos, P. I. *et al.* RAF inhibitor resistance is mediated by dimerization of aberrantly spliced BRAF(V600E). *Nature* **480**, 387–390 (2011).
60. Johannessen, C. M. *et al.* COT drives resistance to RAF inhibition through MAP kinase pathway reactivation. *Nature* **468**, 968–972 (2010).
61. Montagut, C. *et al.* Elevated CRAF as a potential mechanism of acquired resistance to BRAF inhibition in melanoma. *Cancer Res.* **68**, 4853–4861 (2008).
62. Nazarian, R. *et al.* Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. *Nature* **468**, 973–977 (2010).
63. Sun, C. *et al.* Reversible and adaptive resistance to BRAF(V600E) inhibition in melanoma. *Nature* **508**, 118–122 (2014).
64. Villanueva, J. *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* **18**, 683–695 (2010).
65. Michaloglou, C. *et al.* $BRAF^{E600}$-associated senescence-like cell cycle arrest of human naevi. *Nature* **436**, 720–724 (2005).
66. Gaffal, E. *et al.* Neonatal UVB exposure accelerates melanoma growth and enhances distant metastases in Hgf-$Cdk4^{R24C}$ C57BL/6 mice. *Int. J. Cancer* **129**, 285–294 (2011).
67. Bald, T. *et al.* Ultraviolet-radiation-induced inflammation promotes angiotropism and metastasis in melanoma. *Nature* **507**, 109–113 (2014).
68. Viros, A. *et al.* Ultraviolet radiation accelerates BRAF-driven melanomagenesis by targeting TP53. *Nature* **511**, 478–482 (2014).
69. Mitra, D. *et al.* An ultraviolet-radiation-independent pathway to melanoma carcinogenesis in the red hair fair skin background. *Nature* **491**, 449–453 (2012).
70. Dankort, D. *et al.* $Braf^{V600E}$ cooperates with Pten loss to induce metastatic melanoma. *Nat. Genet.* **41**, 544–552 (2009).
71. Tsao, H., Goel, V., Wu, H., Yang, G. & Haluska, F. G. Genetic interaction between *NRAS* and *BRAF* mutations and *PTEN/MMAC1* inactivation in melanoma. *J. Invest. Dermatol.* **122**, 337–341 (2004).
72. Nathanson, K. L. *et al.* Tumor genetic analyses of patients with metastatic melanoma treated with the BRAF inhibitor dabrafenib (GSK2118436). *Clin. Cancer Res.* **19**, 4868–4878 (2013).
73. Pardoll, D. M. The blockade of immune checkpoints in cancer immunotherapy. *Nat. Rev. Cancer* **12**, 252–264 (2012).
74. Topalian, S. L. *et al.* Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J. Clin. Oncol.* **32**, 1020–1030 (2014).
75. Wolchok, J. D. *et al.* Nivolumab plus ipilimumab in advanced melanoma. *N. Engl. J. Med.* **369**, 122–133 (2013).
76. Umansky, V. & Sevko, A. Melanoma-induced immunosuppression and its neutralization. *Semin. Cancer Biol.* **22**, 319–326 (2012).
77. Quail, D. F. & Joyce, J. A. Microenvironmental regulation of tumor progression and metastasis. *Nat. Med.* **19**, 1423–1437 (2013).
78. Damsky, W. E., Theodosakis, N. & Bosenberg, M. Melanoma metastasis: new concepts and evolving paradigms. *Oncogene* **33**, 2413–2422 (2014).
79. Hüsemann, Y. *et al.* Systemic spread is an early step in breast cancer. *Cancer Cell* **13**, 58–68 (2008).
80. Klein, C. A. Parallel progression of primary tumours and metastases. *Nat. Rev. Cancer* **9**, 302–312 (2009).
81. Bernards, R. & Weinberg, R. A. A progression puzzle. *Nature* **418**, 823 (2002).
82. Gartner, J. J. *et al.* Comparative exome sequencing of metastatic lesions provides insights into the mutational progression of melanoma. *BMC Genomics* **13**, 505 (2012).
83. Pleasance, E. D. *et al.* A comprehensive catalogue of somatic mutations from a human cancer genome. *Nature* **463**, 191–196 (2010).
84. Turajlic, S. *et al.* Whole genome sequencing of matched primary and metastatic acral melanomas. *Genome Res.* **22**, 196–207 (2012).
85. Meacham, C. E. & Morrison, S. J. Tumour heterogeneity and cancer cell plasticity. *Nature* **501**, 328–337 (2013).
86. Roesch, A. *et al.* A temporarily distinct subpopulation of slow-cycling melanoma cells is required for continuous tumor growth. *Cell* **141**, 583–594 (2010).
87. Roesch, A. *et al.* Overcoming intrinsic multidrug resistance in melanoma by blocking the mitochondrial respiratory chain of slow-cycling $JARID1B^{high}$ cells. *Cancer Cell* **23**, 811–825 (2013).
88. Ramirez, R. D. *et al.* Progressive increase in telomerase activity from benign melanocytic conditions to malignant melanoma. *Neoplasia* **1**, 42–49 (1999).
89. Rudolph, P. *et al.* Telomerase activity in melanocytic lesions: A potential marker of tumor biology. *Am. J. Pathol.* **156**, 1425–1432 (2000).
90. Horn, S. *et al.* TERT promoter mutations in familial and sporadic melanoma. *Science* **339**, 959–961 (2013).
91. Huang, F. W. *et al.* Highly recurrent TERT promoter mutations in human melanoma. *Science* **339**, 957–959 (2013).
92. Griewank, K. G. *et al. TERT* promoter mutation status as an independent prognostic factor in cutaneous melanoma. *J. Natl. Cancer Inst.* **106**, dju246 (2014).
93. Hartman, M. L. & Czyz, M. Anti-apoptotic proteins on guard of melanoma cell survival. *Cancer Lett.* **331**, 24–34 (2013).
94. Liu, J., Fukunaga-Kalabis, M., Li, L. & Herlyn, M. Developmental pathways activated in melanocytes and melanoma. *Arch. Biochem. Biophys.* **563C**, 13–21 (2014).
95. Curtin, J. A. *et al.* Distinct sets of genetic alterations in melanoma. *N. Engl. J. Med.* **353**, 2135–2147 (2005).
96. McPherson, M. *et al.* Presentation and detection of invasive melanoma in a high-risk population. *J. Am. Acad. Dermatol.* **54**, 783–792 (2006).
97. Brady, M. S. *et al.* Patterns of detection in patients with cutaneous melanoma. *Cancer* **89**, 342–347 (2000).
98. Criscione, V. D. & Weinstock, M. A. Melanoma thickness trends in the United States, 1988–2006. *J. Invest. Dermatol.* **130**, 793–797 (2010).
99. Argenziano, G. *et al.* Accuracy in melanoma detection: a 10-year multicenter survey. *J. Am. Acad. Dermatol.* **67**, 54–59 (2012).
100. Marghoob, A. A. & Scope, A. The complexity of diagnosing melanoma. *J. Invest. Dermatol.* **129**, 11–13 (2009).
101. Vestergaard, M. E., Macaskill, P., Holt, P. E. & Menzies, S. W. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. *Br. J. Dermatol.* **159**, 669–676 (2008). **After excluding two outlier studies, this meta-analysis of seven prospective studies with consecutively recruited patients showed that dermoscopy has a relative diagnostic odds ratio of 9.0 (95%CI 1.5–54.6; *P* = 0.03) for primary melanoma detection compared with naked-eye examination alone.**
102. Carli, P. *et al.* Addition of dermoscopy to conventional naked-eye examination in melanoma screening: a randomized study. *J. Am. Acad. Dermatol.* **50**, 683–689 (2004).
103. Carli, P. *et al.* Improvement of malignant/benign ratio in excised melanocytic lesions in the "dermoscopy era": a retrospective study 1997–2001. *Br. J. Dermatol.* **150**, 687–692 (2004).
104. Tromme, I. *et al.* Availability of digital dermoscopy in daily practice dramatically reduces the number of excised melanocytic lesions: results from an observational study. *Br. J. Dermatol.* **167**, 778–786 (2012).
105. Kittler, H. *et al.* Identification of clinically featureless incipient melanoma using sequential dermoscopy imaging. *Arch. Dermatol.* **142**, 1113–1119 (2006).
106. Haenssle, H. A. *et al.* Results from an observational trial: digital epiluminescence microscopy follow-up of atypical nevi increases the sensitivity and the chance of success of conventional dermoscopy in detecting melanoma. *J. Invest. Dermatol.* **126**, 980–985 (2006).
107. Kelly, J. W., Yeatman, J. M., Regalia, C., Mason, G. & Henham, A. P. A high incidence of melanoma found in patients with multiple dysplastic naevi by photographic surveillance. *Med. J. Aust.* **167**, 191–194 (1997).
108. Feit, N. E., Dusza, S. W. & Marghoob, A. A. Melanomas detected with the aid of total cutaneous photography. *Br. J. Dermatol.* **150**, 706–714 (2004).
109. Goodson, A. G., Florell, S. R., Hyde, M., Bowen, G. M. & Grossman, D. Comparative analysis of total body and dermatoscopic photographic monitoring of nevi in similar patient populations at risk for cutaneous melanoma. *Dermatol. Surg.* **36**, 1087–1098 (2010).
110. Rhodes, A. R. Intervention strategy to prevent lethal cutaneous melanoma: use of dermatologic photography to aid surveillance of high-risk persons. *J. Am. Acad. Dermatol.* **39**, 262–267 (1998).
111. Moloney, F. J. *et al.* Detection of primary melanoma in individuals at extreme high risk: a prospective 5-year follow-up study. *JAMA Dermatol.* **150**, 819–827 (2014).
112. Salerni, G. *et al.* Benefits of total body photography and digital dermatoscopy ("two-step method of digital follow-up") in the early diagnosis of melanoma in patients at high risk for melanoma. *J. Am. Acad. Dermatol.* **67**, e17–e27 (2012).
113. Guitera, P. *et al. In vivo* reflectance confocal microscopy enhances secondary evaluation of melanocytic lesions. *J. Invest. Dermatol.* **129**, 131–138 (2009).
114. Pellacani, G., Pepe, P., Casari, A. & Longo, C. Reflectance confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excisions: a longitudinal prospective study. *Br. J. Dermatol.* http://dx.doi.org/10.1111/bjd.13148 (2014).
115. Monheit, G. *et al.* The performance of MelaFind: a prospective multicenter study. *Arch. Dermatol.* **147**, 188–194 (2011).
116. Malvehy, J. *et al.* Clinical performance of the Nevisense system in cutaneous melanoma detection: an international, multicentre, prospective and blinded clinical trial on efficacy and safety. *Br. J. Dermatol.* **171**, 1099–1107 (2014).
117. Thomas, N. E. *et al.* Comparison of clinicopathologic features and survival of histopathologically amelanotic and pigmented melanomas: a population-based study. *JAMA Dermatol.* **150**, 12 (2014).
118. Lodha, S., Saggar, S., Celebi, J. T. & Silvers, D. N. Discordance in the histopathologic diagnosis of difficult melanocytic neoplasms in the clinical setting. *J. Cutan. Pathol.* **35**, 349–352 (2008).
119. Shoo, B. A., Sagebiel, R. W. & Kashani-Sabet, M. Discordance in the histopathologic diagnosis of melanoma at a melanoma referral center. *J. Am. Acad. Dermatol.* **62**, 751–756 (2010).
120. Cerroni, L. *et al.* Melanocytic tumors of uncertain malignant potential: results of a tutorial held at the XXIX Symposium of the International Society of Dermatopathology in Graz, October 2008. *Am. J. Surg. Pathol.* **34**, 314–326 (2010).
121. Levell, N. J., Beattie, C. C., Shuster, S. & Greenberg, D. C. Melanoma epidemic: a midsummer night's dream? *Br. J. Dermatol.* **161**, 630–634 (2009).
122. Ohsie, S. J., Sarantopoulos, G. P., Cochran, A. J. & Binder, S. W. Immunohistochemical characteristics of melanoma. *J. Cutan. Pathol.* **35**, 433–444 (2008).
123. Bauer, J. & Bastian, B. C. Distinguishing melanocytic nevi from melanoma by DNA copy number changes: comparative genomic hybridization as a research and diagnostic tool. *Dermatol. Ther.* **19**, 40–49.
124. Luo, S., Sepehr, A. & Tsao, H. Spitz nevi and other Spitzoid lesions part I. Background and diagnoses. *J. Am. Acad. Dermatol.* **65**, 1073–1084 (2011).
125. Gerami, P. *et al.* Fluorescence *in situ* hybridization (FISH) as an ancillary diagnostic tool in the diagnosis of melanoma. *Am. J. Surg. Pathol.* **33**, 1146–1156 (2009).
126. Massi, D. *et al.* Atypical Spitzoid melanocytic tumors: a morphological, mutational, and FISH analysis. *J. Am. Acad. Dermatol.* **64**, 919–935 (2011).
127. Vergier, B. *et al.* Fluorescence *in situ* hybridization, a diagnostic aid in ambiguous melanocytic tumors: European study of 113 cases. *Mod. Pathol.* **24**, 613–623 (2011).
128. Raskin, L. *et al.* Copy number variations and clinical outcome in atypical spitz tumors. *Am. J. Surg. Pathol.* **35**, 243–252 (2011).
129. Gaiser, T. *et al.* Classifying ambiguous melanocytic lesions with FISH and correlation with clinical long-term follow up. *Mod. Pathol.* **23**, 413–419 (2010).
130. Gerami, P. *et al.* Sensitivity of fluorescence *in situ* hybridization for melanoma diagnosis using RREB1, MYB, Cep6, and 11q13 probes in melanoma subtypes. *Arch. Dermatol.* **146**, 273–278 (2010).

131. Pouryazdanparast, P. *et al.* Distinctive clinical and histologic features in cutaneous melanoma with copy number gains in 8q24. *Am. J. Surg. Pathol.* **36**, 253–264 (2012).
132. Gammon, B., Beilfuss, B., Guitart, J. & Gerami, P. Enhanced detection of spitzoid melanomas using fluorescence *in situ* hybridization with 9p21 as an adjunctive probe. *Am. J. Surg. Pathol.* **36**, 81–88 (2012).
133. Gerami, P. *et al.* Fluorescence *in situ* hybridization for distinguishing nevoid melanomas from mitotically active nevi. *Am. J. Surg. Pathol.* **33**, 1783–1788 (2009).
134. Busam, K. J. Molecular pathology of melanocytic tumors. *Semin. Diagn. Pathol.* **30**, 362–374 (2013).
135. Rock, C. *et al.* Development and validation of a gene expression signature to distinguish malignant melanoma from benign nevi. *ASCO Meet. Abstr.* **32**, 9021 (2014).
136. Van Kempen, L. C. & Spatz, A. From biomarker development towards implementation of multidimensional biomarker panels in a clinical setting. *Mol. Oncol.* **8**, 781–782 (2014).
137. U.S. Preventive Services Task Force. Screening for skin cancer. U.S. Preventive Services Task Force recommendation statement. *Ann. Intern. Med.* **150**, 188–193 (2009).
138. Ferrini, R. L., Perlman, M. & Hill, L. American College of Preventive Medicine policy statement: screening for skin cancer. *Am. J. Prev. Med.* **14**, 80–82 (1998).
139. Kefford, R. *et al.* Genetic testing for melanoma. *Lancet. Oncol.* **3**, 653–654 (2002).
140. Hansen, C. B., Wadge, L. M., Lowstuter, K., Boucher, K. & Leachman, S. A. Clinical germline genetic testing for melanoma. *Lancet. Oncol.* **5**, 314–319 (2004).
141. Welch, H. G. & Black, W. C. Overdiagnosis in cancer. *J. Natl Cancer Inst.* **102**, 605–613 (2010).
142. Beddingfield, F. C. The melanoma epidemic: res ipsa loquitur. *Oncologist* **8**, 459–465 (2003).
143. Welch, H. G., Woloshin, S. & Schwartz, L. M. Skin biopsy rates and incidence of melanoma: population based ecological study. *BMJ* **331**, 481 (2005).
144. Swerlick, R. A. & Chen, S. The melanoma epidemic: more apparent than real? *Mayo Clin. Proc.* **72**, 559–564 (1997).
145. Epstein, D. S., Lange, J. R., Gruber, S. B., Mofid, M. & Koch, S. E. Is physician detection associated with thinner melanomas? *JAMA* **281**, 640–643 (1999).
146. Katalinic, A. *et al.* Does skin cancer screening save lives?: an observational study comparing trends in melanoma mortality in regions with and without screening. *Cancer* **118**, 5395–5402 (2012).
This paper reports that melanoma-specific mortality decreased by 47% in the years after a population-based skin cancer screening programme was conducted in the German state of Schleswig-Holstein from July 2003 to June 2004.
147. U.S. Preventive Services Task Force. Skin cancer: screening. Summary of recommendations and evidence. [online], http://www.uspreventiveservicestaskforce.org/uspstf09/skincancer/skincanrs.htm (2009).
148. U.S. Department of Health and Human Services. The Surgeon General's call to action to prevent skin cancer. [online], http://www.surgeongeneral.gov/library/calls/prevent-skin-cancer/call-to-action-prevent-skin-cancer.pdf (2014).
149. Lu, C. *et al.* The genomic landscape of childhood and adolescent melanoma. *J. Invest. Dermatol.* **135**, 816–823 (2014).
150. El Ghissassi, F. *et al.* A review of human carcinogens —part D: radiation. *Lancet Oncol.* **10**, 751–752 (2009).
151. Colantonio, S., Bracken, M. B. & Beecker, J. The association of indoor tanning and melanoma in adults: systematic review and meta-analysis. *J. Am. Acad. Dermatol.* **70**, 847–857.e1–18 (2014).
152. Green, A. C., Williams, G. M., Logan, V. & Strutton, G. M. Reduced melanoma after regular sunscreen use: randomized trial follow-up. *J. Clin. Oncol.* **29**, 257–263 (2011).
In this prospective randomized controlled trial conducted in Queensland, Australia, daily sunscreen application to the head and arms reduced the risk of all melanomas by 50% ($P = 0.051$) and invasive melanomas by 73% ($P = 0.045$) compared with discretionary sunscreen application.
153. Goldenhersh, M. A. & Koslowsky, M. Increased melanoma after regular sunscreen use? *J. Clin. Oncol.* **29**, e557–e558 (2011).
154. Bigby, M. & Kim, C. C. A prospective randomized controlled trial indicates that sunscreen use reduced the risk of developing melanoma. *Arch. Dermatol.* **147**, 853–854 (2011).
155. Matsuoka, L. Y., Wortsman, J., Hanifan, N. & Holick, M. F. Chronic sunscreen use decreases circulating concentrations of 25-hydroxyvitamin D. A preliminary study. *Arch. Dermatol.* **124**, 1802–1804 (1988).
156. Holick, M. F. & Chen, T. C. Vitamin D deficiency: a worldwide problem with health consequences. *Am. J. Clin. Nutr.* **87**, 1080S–1086S (2008).
157. Marks, R. *et al.* The effect of regular sunscreen use on vitamin D levels in an Australian population. Results of a randomized controlled trial. *Arch. Dermatol.* **131**, 415–421 (1995).
158. Holick, M. F., Matsuoka, L. Y. & Wortsman, J. Regular use of sunscreen on vitamin D levels. *Arch. Dermatol.* **131**, 1337–1339 (1995).
159. Vieth, R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am. J. Clin. Nutr.* **69**, 842–856 (1999).
160. Mosher, C. E. & Danoff-Burg, S. Addiction to indoor tanning: relation to anxiety, depression, and substance use. *Arch. Dermatol.* **146**, 412–417 (2010).
161. Harrington, C. R. *et al.* Addictive-like behaviours to ultraviolet light among frequent indoor tanners. *Clin. Exp. Dermatol.* **36**, 33–38 (2011).
162. Fell, G. L., Robinson, K. C., Mao, J., Woolf, C. J. & Fisher, D. E. Skin β-endorphin mediates addiction to UV light. *Cell* **157**, 1527–1534 (2014).
163. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N. Engl. J. Med.* **330**, 1029–1035 (1994).
164. Solomon, S. D. *et al.* Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N. Engl. J. Med.* **352**, 1071–1080 (2005).
165. Bonovas, S. *et al.* Can statin therapy reduce the risk of melanoma? A meta-analysis of randomized controlled trials. *Eur. J. Epidemiol.* **25**, 29–35 (2010).
166. Freeman, S. R. *et al.* Statins, fibrates, and melanoma risk: a systematic review and meta-analysis. *J. Natl Cancer Inst.* **98**, 1538–1546 (2006).
167. Cook, N. R. *et al.* Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA* **294**, 47–55 (2005).
168. Jacobs, E. J. *et al.* A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. *J. Natl Cancer Inst.* **99**, 608–615 (2007).
169. Asgari, M. M., Maruti, S. S. & White, E. A large cohort study of nonsteroidal anti-inflammatory drug use and melanoma incidence. *J. Natl Cancer Inst.* **100**, 967–971 (2008).
170. Francis, S. O., Mahlberg, M. J., Johnson, K. R., Ming, M. E. & Dellavalle, R. P. Melanoma chemoprevention. *J. Am. Acad. Dermatol.* **55**, 849–861 (2006).
171. Uzarska, M. *et al.* Chemoprevention of skin melanoma: facts and myths. *Melanoma Res.* **23**, 426–433 (2013).
172. Gershenwald, J. E. & Ross, M. I. Sentinel-lymph-node biopsy for cutaneous melanoma. *N. Engl. J. Med.* **364**, 1738–1745 (2011).
A review of current practice of SNB.
173. Morton, D. L. *et al.* Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch. Surg.* **127**, 392–399 (1992).
174. Wong, S. L. *et al.* Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Society of Surgical Oncology joint clinical practice guideline. *Ann. Surg. Oncol.* **19**, 3313–3324 (2012).
175. Gershenwald, J. E., Coit, D. G., Sondak, V. K. & Thompson, J. F. The challenge of defining guidelines for sentinel lymph node biopsy in patients with thin primary cutaneous melanomas. *Ann. Surg. Oncol.* **19**, 3301–3303 (2012).
176. NCCN Clinical Practice Guidelines in Oncology: Melanoma. *National Comprehensive Cancer Network* [online], http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf (2012).
177. Gershenwald, J. E. *et al.* Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J. Clin. Oncol.* **17**, 976–983 (1999).
178. Morton, D. L. *et al.* Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N. Engl. J. Med.* **370**, 599–609 (2014).
179. Mocellin, S., Lens, M. B., Pasquali, S., Pilati, P. & Chiarion Sileni, V. Interferon alpha for the adjuvant treatment of cutaneous melanoma. *Cochrane Database Syst. Rev.* **6**, CD008955 (2013).
A meta-analysis of IFNα use in adjuvant trials.
180. Grob, J. J. *et al.* Adjuvant therapy with pegylated interferon alfa-2b (36 months) versus low-dose interferon alfa-2b (18 months) in melanoma patients without macrometastatic nodes: an open-label, randomised, phase 3 European Association for Dermato-Oncology (EADO) study. *Eur. J. Cancer* **49**, 166–174 (2013).
181. Ascierto, P. A. *et al.* Adjuvant interferon alfa in malignant melanoma: an interdisciplinary and multinational expert review. *Crit. Rev. Oncol. Hematol.* **85**, 149–161 (2013).
182. Eggermont, A. M. M. *et al.* Ulceration and stage are predictive of interferon efficacy in melanoma: results of the phase III adjuvant trials EORTC 18952 and EORTC 18991. *Eur. J. Cancer* **48**, 218–225 (2012).
This study describes ulceration as an important biomarker for IFN treatment and clinical benefit.
183. Jemal, A. *et al.* Recent trends in cutaneous melanoma incidence and death rates in the United States, 1992–2006. *J. Am. Acad. Dermatol.* **65**, S17–S25. e1–e3 (2011).
184. Corrie, P. G. *et al.* Adjuvant bevacizumab in patients with melanoma at high risk of recurrence (AVAST-M): preplanned interim results from a multicentre, open-label, randomised controlled phase 3 study. *Lancet Oncol.* **15**, 620–630 (2014).
185. Eggermont, A. M. *et al.* Ipilimumab versus placebo after complete resection of stage III melanoma: Initial efficacy and safety results from the EORTC 18071 phase III trial. *ASCO Meet. Abstr.* **32**, LBA9008 (2014).
186. Garraway, L. A. & Baselga, J. Whole-genome sequencing and cancer therapy: is too much ever enough? *Cancer Discov.* **2**, 766–768 (2012).
187. Hsueh, E. C., Famatiga, E., Gupta, R. K., Qi, K. & Morton, D. L. Enhancement of complement-dependent cytotoxicity by polyvalent melanoma cell vaccine (CancerVax): correlation with survival. *Ann. Surg. Oncol.* **5**, 595–602.
188. Hodi, F. S. *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* **363**, 711–723 (2010).
189. Robert, C. *et al.* Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N. Engl. J. Med.* **364**, 2517–2526 (2011).
190. Bristol-Myers Squibb. YERVOY® (ipilimumab). [online], http://packageinserts.bms.com/pi/pi_yervoy.pdf (2013).
191. Ribas, A. & Flaherty, K. T. BRAF targeted therapy changes the treatment paradigm in melanoma. *Nat. Rev. Clin. Oncol.* **8**, 426–433 (2011).
192. McArthur, G. A. & Ribas, A. Targeting oncogenic drivers and the immune system in melanoma. *J. Clin. Oncol.* **31**, 499–506 (2013).
193. Chapman, P. B. *et al.* Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N. Engl. J. Med.* **364**, 2507–2516 (2011).
The first paper to describe an overall survival benefit using targeted therapy (the selective BRAF inhibitor vemurafenib) compared with chemotherapy in untreated metastatic melanoma.
194. Hauschild, A. 1092PD: an update on overall survival (OS) and follow-on therapies in BREAK-3, a phase III, randomized trial: dabrafenib (D) versus dacarbazine (DTIC) in patients (pts) with BRAF V600E mutation-positive metastatic melanoma (MM). *Ann. Oncol.* **25** (Suppl. 4), iv374–iv393 (2014).
195. Hauschild, A. *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). *ASCO Meet. Abstr.* **31**, 9013 (2013).
196. Sosman, J. A. *et al.* Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N. Engl. J. Med.* **366**, 707–714 (2012).
197. Zimmer, L. *et al.* Atypical melanocytic proliferations and new primary melanomas in patients with advanced melanoma undergoing selective BRAF inhibition. *J. Clin. Oncol.* **30**, 2375–2383 (2012).
198. Oberholzer, P. A. *et al.* RAS mutations are associated with the development of cutaneous squamous cell tumors in patients treated with RAF inhibitors. *J. Clin. Oncol.* **30**, 316–321 (2012).
199. Su, F. *et al.* RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. *N. Engl. J. Med.* **366**, 207–215 (2012).

200. Solit, D. B. *et al.* BRAF mutation predicts sensitivity to MEK inhibition. *Nature* **439**, 358–362 (2006).
201. Von Euw, E. *et al.* Antitumor effects of the investigational selective MEK inhibitor TAK733 against cutaneous and uveal melanoma cell lines. *Mol. Cancer* **11**, 22 (2012).
202. Flaherty, K. T. *et al.* Improved survival with MEK inhibition in BRAF-mutated melanoma. *N. Engl. J. Med.* **367**, 107–114 (2012).
203. Van Allen, E. M. *et al.* The genetic landscape of clinical resistance to RAF inhibition in metastatic melanoma. *Cancer Discov.* **4**, 94–109 (2014).
204. Shi, H. *et al.* Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy. *Cancer Discov.* **4**, 80–93 (2014).
205. Long, G. V. *et al.* Combined BRAF and MEK Inhibition versus BRAF Inhibition Alone in Melanoma. *N. Engl. J. Med.* **371**, 1877–1888 (2014).
206. Larkin, J. *et al.* Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N. Engl. J. Med.* **371**, 1867–1876 (2014).
207. Robert, C. *et al.* Improved overall survival in melanoma with combined dabrafenib and trametinib. *N. Eng. J. Med.* **372**, 30–39 (2015).
The first study to demonstrate an overall survival benefit in patients with *BRAF*^{V600}-mutant melanoma using a combined BRAF inhibitor plus MEK inhibitor compared with BRAF-inhibitor monotherapy.
208. Carvajal, R. D. *et al.* KIT as a therapeutic target in metastatic melanoma. *JAMA* **305**, 2327–2334 (2011).
209. Brahmer, J. R. *et al.* Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N. Engl. J. Med.* **366**, 2455–2465 (2012).
210. Topalian, S. L. *et al.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N. Engl. J. Med.* **366**, 2443–2454 (2012).
211. Hamid, O. *et al.* Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N. Engl. J. Med.* **369**, 134–144 (2013).
212. Robert, C. *et al.* Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet* **384**, 1109–1117 (2014).
213. Robert, C. *et al.* Nivolumab in previously untreated melanoma without BRAF mutation. *N. Eng. J. Med.* **372**, 320–330 (2015).
The first clinical study to demonstrate a clinically meaningful benefit using a PD1-specific antibody in untreated patients with no *BRAF* mutation compared with dacarbazine chemotherapy, leading to an increase in 1-year survival rate from 43% to 73%.
214. Tumeh, P. C. *et al.* PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* **515**, 568–571 (2014).
215. Rosenberg, S. A. Cell transfer immunotherapy for metastatic solid cancer—what clinicians need to know. *Nat. Rev. Clin. Oncol.* **8**, 577–585 (2011).
216. Rosenberg, S. A. *et al.* Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. *Clin. Cancer Res.* **17**, 4550–4557 (2011).
217. Hersh, E. M. *et al.* A phase 2 clinical trial of nab-paclitaxel in previously treated and chemotherapy-naive patients with metastatic melanoma. *Cancer* **116**, 155–163 (2010).
218. Hauschild, A. *et al.* Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. *J. Clin. Oncol.* **27**, 2823–2830 (2009).
219. Atkins, M. B. *et al.* High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J. Clin. Oncol.* **17**, 2105–2116 (1999).
220. Andtbacka, R. H. I. *et al.* OPTiM: A randomized phase III trial of talimogene laherparepvec (T-VEC) versus subcutaneous (SC) granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment (tx) of unresected stage IIIB/C & IV melanoma. *ASCO Meet. Abstr.* **31**, LBA9008 (2013).
221. Burton, A. W., Chai, T. & Smith, L. S. Cancer pain assessment. *Curr. Opin. Support. Palliat. Care* **8**, 112–116 (2014).
222. Cleeland, C. S. & Ryan, K. M. Pain assessment: global use of the Brief Pain Inventory. *Ann. Acad. Med. Singapore* **23**, 129–138 (1994).
223. Kvaal, K., Ulstein, I., Nordhus, I. H. & Engedal, K. The Spielberger State-Trait Anxiety Inventory (STAI): the state scale in detecting mental disorders in geriatric patients. *Int. J. Geriatr. Psychiatry* **20**, 629–634 (2005).
224. Spielberger, C. D., Gorsuch, R. L. & Lushene, R. E. *Manual for the State–Trait Anxiety Inventory*. (Palo Alto, CA: Consulting Psychologists Press, 1970).
225. Manocchia, M. *et al. SF-36 Health Survey Annotated Bibliography: Second Edition (1988–1996)*. (The Health Assessment Lab, New England Medical Center, 1998).
226. Aaronson, N. K. *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J. Natl Cancer Inst.* **85**, 365–376 (1993).
227. Holterhues, C. *et al.* Impact of melanoma on patients' lives among 562 survivors: a Dutch population-based study. *Arch. Dermatol.* **147**, 177–185 (2011).
228. De Vries, M., Hoekstra, H. J. & Hoekstra-Weebers, J. E. H. M. Quality of life after axillary or groin sentinel lymph node biopsy, with or without completion lymph node dissection, in patients with cutaneous melanoma. *Ann. Surg. Oncol.* **16**, 2840–2847 (2009).
229. Hamidou, Z., Dabakuyo, T. S. & Bonnetain, F. Impact of response shift on longitudinal quality-of-life assessment in cancer clinical trials. *Expert Rev. Pharmacoecon. Outcomes Res.* **11**, 549–559 (2011).
230. Brandberg, Y. *et al.* Health-related quality of life in patients with high-risk melanoma randomised in the Nordic phase 3 trial with adjuvant intermediate-dose interferon alfa-2b. *Eur. J. Cancer* **48**, 2012–2019 (2012).
231. Mohr, P., Hauschild, A., Trefzer, U. & Weichenthal, M. Quality of life in patients receiving high-dose interferon alfa-2b after resected high-risk melanoma. *J. Clin. Oncol.* **27**, e70; author reply e71 (2009).
232. Bottomley, A. *et al.* Adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma: a phase III randomized controlled trial of health-related quality of life and symptoms by the European Organisation for Research and Treatment of Cancer. *J. Clin. Oncol.* **27**, 2916–2923 (2009).
233. De Kock, I. *et al.* Conversion of Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group Performance Status (ECOG) to Palliative Performance Scale (PPS), and the interchangeability of PPS and KPS in prognostic tools. *J. Palliat. Care* **29**, 163–169 (2013).
234. Mor, V., Laliberte, L., Morris, J. N. & Wiemann, M. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. *Cancer* **53**, 2002–2007 (1984). 235. Hatswell, A. J. *et al.* Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death. *Health Qual. Life Outcomes* **12**, 140 (2014).
236. Schadendorf, D. *et al.* 1091PD COMBI-D: quality of life (QOL) impact of the combination of dabrafenib and trametinib (D + T) versus dabrafenib monotherapy (D) in patients with BRAF V600E/K unresectable or metastatic melanoma in a Phase III trial. *Ann. Onc.* **25** (Suppl. 4), iv377–iv393 (2014).
237. Grob, J.-J. *et al.* Patient perception of the benefit of a BRAF inhibitor in metastatic melanoma: quality-of-life analyses of the BREAK-3 study comparing dabrafenib with dacarbazine. *Ann. Oncol.* **25**, 1428–1436 (2014).
238. Schadendorf, D. *et al.* Functional and symptom impact of trametinib versus chemotherapy in BRAF V600E advanced or metastatic melanoma: quality-of-life analyses of the METRIC study. *Ann. Oncol.* **25**, 700–706 (2014).
239. Flaherty, K. T. *et al.* Surrogate endpoints for overall survival in metastatic melanoma: a meta-analysis of randomised controlled trials. *Lancet. Oncol.* **15**, 297–304 (2014).
240. Ives, N. J., Stowe, R. L., Lorigan, P. & Wheatley, K. Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2,621 patients. *J. Clin. Oncol.* **25**, 5426–5434 (2007).
241. Zimmer, L. *et al.* Phase II DeCOG-study of ipilimumab in pretreated and treatment-naïve patients with metastatic uveal melanoma. *PLoS ONE* (in the press).
242. Chen, X. *et al.* Combined PKC and MEK inhibition in uveal melanoma with GNAQ and GNA11 mutations. *Oncogene* **33**, 4724–4734 (2014).
243. Feng, X. *et al.* Hippo-independent activation of YAP by the GNAQ uveal melanoma oncogene through a trio-regulated rho GTPase signaling circuitry. *Cancer Cell* **25**, 831–845 (2014).
244. Yu, F.-X. *et al.* Mutant Gq/11 promote uveal melanoma tumorigenesis by activating YAP. *Cancer Cell* **25**, 822–830 (2014).
245. Martin, M. *et al.* Exome sequencing identifies recurrent somatic mutations in EIF1AX and SF3B1 in uveal melanoma with disomy 3. *Nat. Genet.* **45**, 933–936 (2013).
246. Harbour, J. W. *et al.* Frequent mutation of BAP1 in metastasizing uveal melanomas. *Science* **330**, 1410–1413 (2010).
247. Prescher, G. *et al.* Prognostic implications of monosomy 3 in uveal melanoma. *Lancet* **347**, 1222–1225 (1996).
248. Matatall, K. A. *et al.* BAP1 deficiency causes loss of melanocytic cell identity in uveal melanoma. *BMC Cancer* **13**, 371 (2013).
249. Landreville, S. *et al.* Histone deacetylase inhibitors induce growth arrest and differentiation in uveal melanoma. *Clin. Cancer Res.* **18**, 408–416 (2012).
250. Schadendorf, D. *et al.* Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. *J. Clin. Oncol.* http://dx.doi.org/10.1200/JCO.2014.59.5041 (2015).
An analysis of almost 5,000 patients with advanced-stage melanoma treated with ipilimumab, showing for the first time a long-term clinical benefit of a treatment and a 5-year survival rate of 20%.
251. Schadendorf, D. *et al.* Overall survival (OS) update on METRIC (NCT01245062), a randomized phase 3 study to assess efficacy of trametinib (T) compared with chemotherapy (C) in patients (pts) with BRAFV600E/K mutation-positive (+) advanced or metastatic melanoma (MM). *Pigment Cell Melanoma Res*, **26**, 997 (2013).
252. Maio, M. *et al.* Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a Phase III trial. *J. Clin. Oncol.* http://dx.doi.org/10.0.4.176/JCO.2014.56.6018 (2015).
253. Daud, A. *et al.* Overall survival update for BRF113220 Part C, a Phase II three-arm randomized study of dabrafenib alone (D) versus a combination of dabrafenib and trametinib (D + T) in pts with BRAF V600 mutation-positive metastatic melanoma. *Society for Melanoma Research 2013 International Congress* (17–20 Nov 2013).

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Introduction (D.S. and A. Hauschild); Epidemiology (C.G.); Mechanisms/pathophysiology (M.H. and A. Roesch); Diagnosis, screening and prevention (D.F., A. Halpern and M.A.M.); Management (J.E.G., J.-J.G., G.M. and A. Ribas); Quality of life (J.-J.G. and D.S.); Outlook (D.S. and A. Hauschild); and overview of Primer (D.S.).

Competing interests statement
D.S. and A. Hauschild declare an association with the following companies: Amgen, Bristol–Myers Squibb, Genentech, GlaxoSmithKline, Merck/MSD, Novartis, Pfizer, Boehringer Ingelheim and Roche. C.G. declares personal fees from Amgen, Merck/MSD and Novartis, and declares grants and personal fees from Bristol–Myers Squibb, GlaxoSmithKline and Roche outside of the submitted work. A. Roesch has received travel grants and honoraria from Roche and TEVA, and research grants from Novartis. M.A.M. has received honoraria from Next Meeting Generation for speaking on the topic of dermoscopy at the American Dermoscopy Meeting. A. Halpern serves as a consultant to Caliber Imaging and Diagnostics, Canfield Scientific, DermTech and SciBase AB, and serves on the data safety and monitoring board of Quintiles and Janssen Research and Development LLC. J.-J.G. has received fees for advisory boards and lectures from Amgen, GlaxoSmithKline, MSD, Novartis and Roche, and has received research grants from Bristol–Myers Squibb and Roche. J.E.G. serves on the global advisory board for Merck. A. Ribas has served as consultant for Amgen, Astellas, Genentech-Roche, GlaxoSmithKline, Merck, Novartis and Pierre Fabre, and serves on the scientific advisory board and has stock options for Compugen, Flexus Biosciences and Kite Pharma. G.M. has received consulting income from Provectus, and has received research support from Celgene and Pfizer. M.H. and D.E.F. declare no competing interests.