Melanoma

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Cutaneous melanoma causes 55 500 deaths annually. The incidence and mortality rates of the disease differ widely across the globe depending on access to early detection and primary care. Once melanoma has spread, this type of cancer rapidly becomes life-threatening. For more than 40 years, few treatment options were available, and clinical trials during that time were all unsuccessful. Over the past 10 years, increased biological understanding and access to innovative therapeutic substances have transformed advanced melanoma into a new oncological model for treating solid cancers. Treatments that target B-Raf proto-oncogene serine/threonine-kinase (*BRAF*)^{V600} (Val600) mutations using selected BRAF inhibitors combined with mitogen-activated protein kinase inhibitors have significantly improved response and overall survival. Furthermore, advanced cutaneous melanoma has developed into a prototype for testing checkpoint-modulating agents, which has increased hope for long-term tumour containment and a potential cure. These expectations have been sustained by clinical success with targeted agents and antibodies that block programmed cell-death protein 1 in locoregional disease, which induces prolongation of relapse-free, distant-metastasis-free, and overall survival times.

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Epidemiology

Incidence, mortality, and survival

Worldwide, about 232 100 (1·7%) cases of all newly diagnosed primary malignant cancers (excluding non-melanoma skin cancer) are cases of cutaneous melanoma, and about 55 500 cancer deaths (0·7% of all cancer deaths) are due to cutaneous melanoma annually. The incidence and mortality rates of cutaneous melanoma differ widely by country. In 2012, the age-standardised (world standard population) incidence of cutaneous melanoma ranged from 0·2 per 100 000 person-years in southeast Asia to 7·7 per 100 000 person-years in the Americas. Incidences were highest in New Zealand (35·8 per 100 000 person-years) and Australia (34·9 per 100 000 person-years). The incidence was 10·2 per 100 000 person-years in the EU and 13·8 per 100 000 person-years in North America (figure 1).[1] The incidence of cutaneous melanoma has increased since the early 1970s in predominantly fair-skinned populations (figure 2).[2]

Age-cohort period analyses of melanoma incidence in Australia, New Zealand, Norway, Sweden, the UK, and the white population of the USA from 1982 to 2011 revealed that the incidence increased about 3% annually, and will further increase at least until 2022 in Norway, Sweden, the UK, and the USA. Although melanoma incidence in New Zealand is still increasing, this incidence is projected to decline in the next 5 years. In Australia, the incidence has been decreasing since 2005. This decline might reflect improved primary prevention and changing lifestyles, with people having a greater tendency to stay indoors nowadays than in the past.[3] Of the ten leading cancer types (excluding basal-cell and squamous-cell carcinoma of the skin), cutaneous melanoma was the fifth most common malignancy in men and the sixth most common in women in the USA in 2017.[4]

In 2012, the estimated age-standardised mortality rates of cutaneous melanoma ranged from 0·1 per 100 000 person-years in South-East Asia to 1·5 per 100 000 person-years in the EU. The highest mortality rates were observed in New Zealand (4·7 per 100 000 person-years) and Australia (4·0 per 100 000 person-years).[1] In 2017, the estimated percentage of deaths due to cutaneous melanoma among all skin-cancer deaths (excluding basal-cell and squamous-cell carcinoma of the skin) in the USA was 72%.[4] The 5-year age-standardised relative survival for cutaneous melanoma diagnosed in 2000–07 in Europe ranged from 74·3% (Eastern Europe) to 87·7% (Northern Europe). Relative survival was highest in Northern Ireland (90·7%) and Switzerland (90·4%), and lowest in Bulgaria (49·6%) and Poland (61·5%). Relative survival decreased with patients' age and was higher in women than men.[5] In the USA, the 5-year relative survival (without age standardisation) is 92%. For primary melanoma without lymph node involvement, the 5-year relative survival in is 98% in stage-1 melanoma and 90% in stage-2 melanoma.[6]

Risk factors

Established risk factors for cutaneous melanoma include ultraviolet radiation by sun exposure and subsequent

Search strategy and selection criteria

We searched MEDLINE between Dec 1, 2017, and Dec 19, 2017, with no language restrictions. We used the search terms "melanoma" in combination with specific terms covering the different steps of diagnosis and treatment as appropriate. We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are also cited to provide readers with more details and references than this Seminar was able to. We also added research from the 2016 and 2017 American Society of Clinical Oncology and European Society for Medical Oncology conferences. Our reference list was modified based on comments from the peer reviewers.

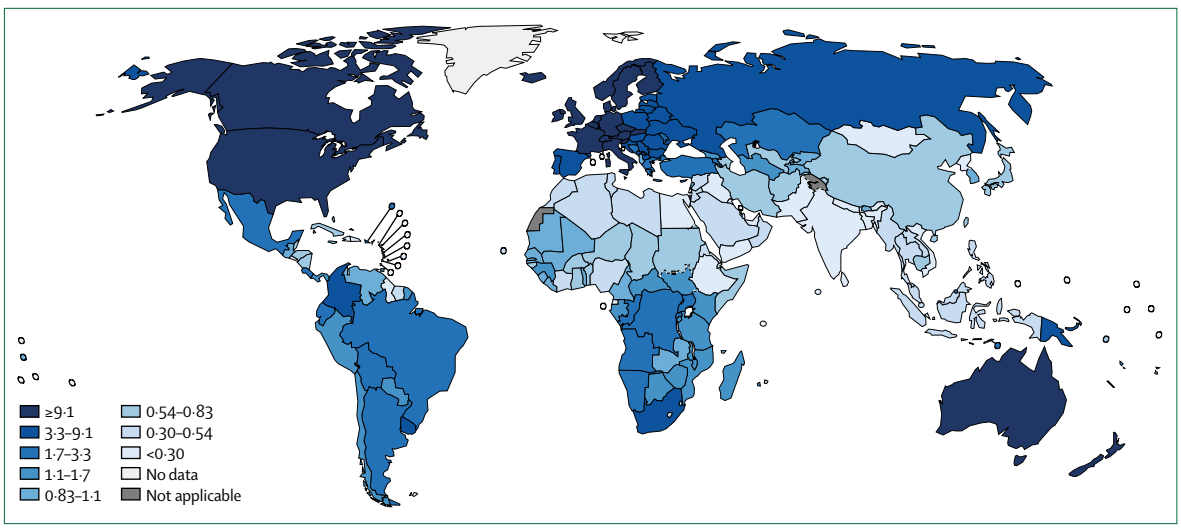

Figure 1: **Estimated age-standardised worldwide incidence of cutaneous melanoma in both men and women in 2012**
Incidences are expressed as the number of cases per 100 000 person-years. Data are from GLOBOCAN 2012.[1]

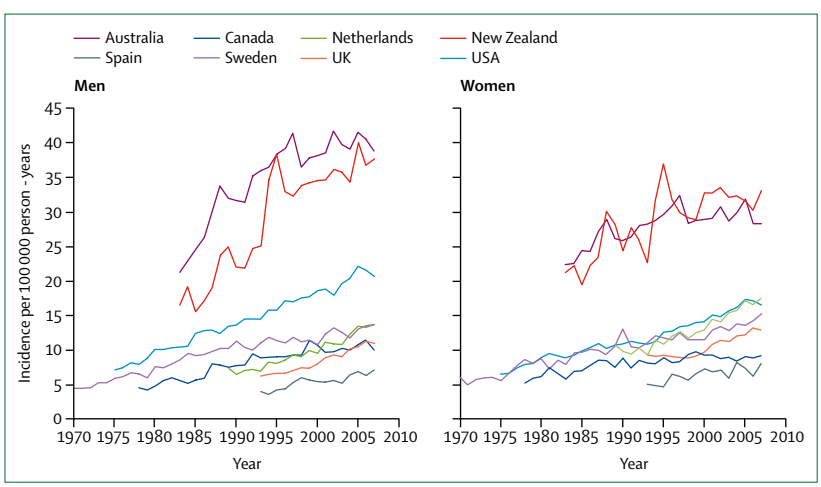

Figure 2: **Trends in age-standardised incidence of cutaneous melanoma for men and women in selected countries, 1970–2007**
All rates are age-standardised (world standard population) and expressed as the number of cases per 100 000 person-years. Data are from CI5.[2]

sunburns,[7] indoor tanning (especially before age 35 years),[8] the presence of melanocytic or dysplastic naevi,[9] a personal history of cutaneous melanoma,[10] a family history of cutaneous melanoma,[9] phenotypic characteristics including fair hair, eye, and skin colours and the tendency to freckle,[9] and a high socioeconomic status.[11] A systematic review of 34 guidelines from 20 countries for the identification, screening, and follow-up of individuals at high risk of primary cutaneous melanoma revealed that high-risk characteristics that prompt screening or surveillance include many melanocytic naevi, dysplastic naevi, and a personal and family history of melanoma.[12] Gene mutations account for only a small proportion of melanoma cases. Patients with a personal history of more than one melanoma, several members on one side of the family who had melanoma, a family member that has had more than one melanoma, or a family member that had melanoma and pancreatic cancer might have inherited a gene mutation. However, although tests for gene mutations are now available, these tests are not recommended because clinical benefit has not been shown so far.[13,14]

Regarding ultraviolet exposure as the most important risk factor of cutaneous melanoma, molecular and epidemiological data support two distinct aetiological mechanisms.[15] Early sun exposure and proneness to naevi, promoted by host factors and intermittent sun exposure, tends to result in a B-Raf proto-oncogene serine/threonine-kinase (*BRAF*)-associated naevus-prone pathway, which is characterised by young age at diagnosis, absence of chronic sun damage of the skin, superficially spreading melanoma, and melanoma occurrence on the trunk. Accumulated sun exposure results in the so-called chronic sun-exposure pathway, which is characterised by *NRAS* proto-oncogene GTPase (*NRAS*) mutations, without any association with naevus count or neval remnants.

Mechanisms and pathophysiology

The malignant transformation of melanocytes into metastatic melanoma is the result of a process that requires a complex interaction between exogenous and endogenous triggers as well as tumour-intrinsic and immune-related factors. Although melanocytes only rarely divide (less than twice per year),[16] the proliferative index steadily increases as melanocytic neoplasms sequentially evolve, a process accompanied by a constant increase of point mutations and copy-number alterations.[17] Cross-cancer genetic-landscape analyses revealed that cutaneous melanomas carry a particularly high mutational load (>10 mutations per megabase) and harbour a high number of ultraviolet-signature mutations, such as C→T

(caused by ultraviolet B) or G→T (caused by ultraviolet A) transitions.[18–20] Although many pathogenetically relevant mutations in melanoma are assumed to originate from a direct mutagenic effect of ultraviolet B and ultraviolet A,[19–22] indirect effects such as the production of free radicals resulting from the biochemical interaction of ultraviolet A with melanin[23] also cause mutations and genetic aberrations.[24]

Similarly to other cancers, malignant transformation into melanoma follows a sequential genetic model that results in constitutive activation of oncogenic signal transduction. The frequently found activating *BRAF*^{V600} (Val600) mutation is already a typical feature of benign naevus formation. Further progression into intermediate lesions and melanomas in situ requires additional mutations—eg, mutations in the telomerase reverse-transcriptase (*TERT*) promoter. To gain invasive potential, tertiary mutations in cell-cycle controlling genes (cyclin-dependent kinase-inhibitor 2A [*CDKN2A*]) or chromatin-remodelling (AT-rich interaction domain [*ARID*]*1A*, *ARID1B*, *ARID2*) are required. Finally, metastatic melanoma progression is associated with mutations in phosphatase-and-tensin homologue (*PTEN*) or tumour-protein p53 (*TP53*).[17,19,22,25] At the protein level, these genetic alterations yield a reciprocal overstimulation of the affected cellular pathways, mainly the mitogen-activated-protein-kinase (MAPK) pathway and the phosphoinositide-3-kinase (PI3K), protein-kinase-B (AKT), PTEN, and mammalian-target-of-rapamycin (mTOR) pathway (figure 3). Melanoma cells also evade the immune system, for example, by reinforcing immune checkpoints that physiologically prevent the organism from escalating immune responses (eg, during viral infections). The interferon, Janus-kinase (JAK), and signal-transducer-and-activator-of-transcription (STAT) pathway is a major regulator of the programmed-cell-death-protein-1 (PD-1) immune checkpoint (figure 3). Upon tumour antigen recognition by T cells, released interferons trigger JAK-STAT-mediated expression of PD-1 ligands PD-L1 and PD-L2 on the surface of melanoma cells. Binding of PD-L1 and PD-L2 to PD-1

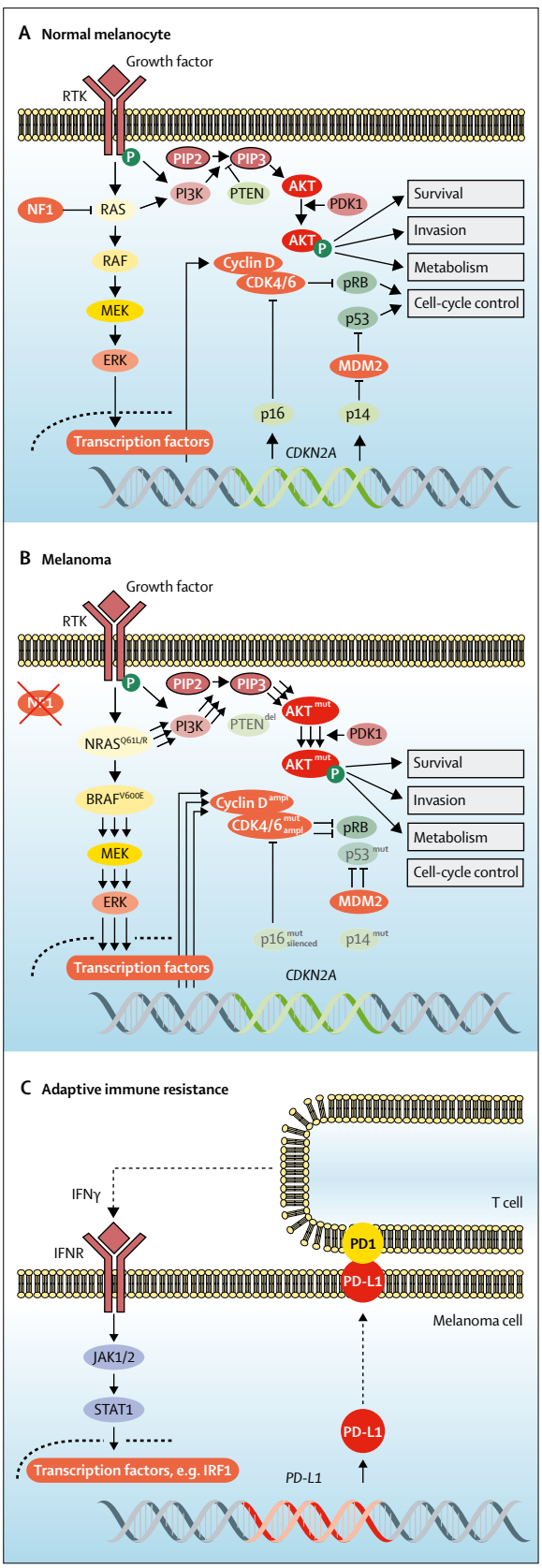

***Figure 3*: Selected key signalling pathways and therapeutic targets in melanoma**

(A) MAPK, PI3K-AKT signalling, and cell-cycle regulation under normal conditions permits balanced control of basic cell functions. (B) In melanomas, genetic alterations lead to constitutive pathway activation with loss of cellular homeostasis. (C) The PD-1-PD-L1 immune checkpoint is primarily regulated by interferon-γ signalling. AKT=protein kinase B. *BRAF*^{V600E}=B-Raf proto-oncogene serine/threonine-kinase (Val600Glu). CDK=cyclin-dependent kinase. ERK=extracellular signal-regulated kinase. IFNR= interferon receptor. IFNγ=interferon γ. MAPK=mitogen-activated protein kinase. MDM2=mouse double-minute-2 homologue. MEK=mitogen-activated protein kinase kinase. NF1=neurofibromin 1. NRAS=NRAS proto-oncogene GTPase. P=phosphorylated. PD-1=programmed cell-death protein 1. PDK1=phosphoinositide-dependent protein kinase. PD-L1=programmed cell-death ligand 1. PIP=phosphatidylinositol phosphate. PI3K=phosphoinositide-3 kinase. pRB=retinoblastoma protein. PTEN=phosphate and tensin homologue. RTK=receptor tyrosine kinase. STAT1=signal transducer and activator of transcription 1.

leads to the suppression of T-cell effector activity and inhibits the antitumour immune response (adaptive immune resistance).[26] Further immunosuppressive mechanisms include the downregulation of tumour-associated antigens and class-1 major histocompatibility complex, and the secretion of inhibitory factors like tumour growth factor β.[27]

	Definition
T classification	
T1	
A	<0·8 mm thickness, no ulceration
B	0·8–1 mm thickness (<0·8 mm with ulceration)
T2	
A	>1–2 mm thickness, no ulceration
B	>1–2 mm thickness with ulceration
T3	
A	>2–4 mm thickness, no ulceration
B	>2–4 mm thickness with ulceration
T4	
A	>4 mm thickness, no ulceration
B	>4 mm thickness with ulceration
N classification	
N0	No regional lymph nodes affected
N1a–c	One lymph node affected, micro-metastasis or macro-metastasis, or in-transit or satellite metastasis
N2a–c	Two to three lymph nodes affected, or at least one lymph node affected and in-transit or satellite metastasis
N3a–c	At least four lymph nodes affected or at least two lymph nodes affected and matted nodes
M classification	
M0	No evidence of distant metastasis
M1	
a	Distant metastasis to skin
b	Distant metastasis to lung
c	Distant non-CNS metastasis
d	CNS metastasis

Table 1: **TNM classification according to the American Joint Committee on Cancer eighth edition staging manual, 2017[30]**

	T classification	N classification	M classification
Stage 0	Tis	N0	M0
Stage 1A	T1a or T1b	N0	M0
Stage 1B	T2a	N0	M0
Stage 2A	T2b or T3a	N0	M0
Stage 2B	T3b, T4a, or T4b	N0	M0
Stage 2C	T0	N1b and N1c	M0
Stage 3A	T1a–b to T2a	N1a of N2a	M0
Stage 3B	T0	N2b, N2c, N3b, or N3c	M0
Stage 3B	T1a–b to T2a	N1b–c or N2b	M0
Stage 3B	T2b–T3a	N1a–N2b	M0
Stage 3C	T1a–T3a	N2c or N3a–c	M0
Stage 3C	T3b–T4a	Any N ≥N1	M0
Stage 3C	T4b	N1a–N2c	M0
Stage 3D	T4b	N3a–c	M0
Stage 4	Any T and Tis	Any N	M1

Table 2: **Pathological stage group according to the American Joint Committee on Cancer eighth edition staging manual, 2017[30]**

Melanoma classification and genetic alterations

Histopathological classification

Melanoma is diagnosed histopathologically, with subsequent treatment decisions being based on histological classification and risk calculation. Classification is established with tumour thickness (T stage; Breslow staging),[28] lymph node involvement (N stage), and presence of metastasis (M stage). The majority of melanomas are diagnosed before lymph node or distant metastases occur (N0 and M0 stage).[29,30] According to Breslow,[28] the most crucial criterion for assessing prognosis and further treatment, including required safety margins and sentinel lymph node biopsy, is tumour thickness. Ulceration is another relevant histopathological marker that is independently associated with poor prognosis and is also incorporated in the T stage (table 1, 2).[29,30]

The American Joint Committee on Cancer classification of melanoma was updated to the eighth edition in 2017.[31] Histopathologically, mitotic counts are no longer relevant for staging, and tumour depth is rounded to tenths of millimetres. Prediction of patient survival, particularly in low-risk melanoma stages, has been improved (table 1, 2). Tumours are classified less frequently as stage 2, and more frequently as stage 3.[31] Advancing therapeutic approaches, including more effective adjuvant treatments, will probably result in further improvement of melanoma-specific survival rates in the future.

Different histological subtypes of melanoma can also be distinguished, including superficial spreading, nodular, acral lentiginous, and lentigo-maligna melanoma;[32] however, these tumour types are less relevant for establishing prognosis and further treatment.

Genetic classification

The past decade has brought about a detailed understanding of the genetic basis of melanoma.[22,33,34] Disease progression is associated with an acquisition of gene alterations. Benign naevi frequently harbour only one activating mutation, mostly $BRAF^{V600E}$ (ie, Val600Glu). Additional events such as *TERT* promoter mutations or *CDKN2A* losses are frequently detected in borderline lesions, and multiple gene alterations are observed in melanoma.[17]

The Cancer Genome Atlas analysis[22] of a large cohort of melanoma tissue samples made use of modern molecular techniques and applied bioinformatic algorithms to introduce the delineation of four different genetic melanoma subtypes on the basis of activating gene mutations (figure 4). These subtypes are: *BRAF*-mutant melanomas, which represent around 50% of melanomas; N-*Ras*, K-*Ras*, and H-*Ras*-mutant melanomas, which represent around 25% of melanomas;

NF1-mutant melanomas, which represent around 15% of melanomas; and triple-wild-type melanomas, which represent around 10% of melanomas.[22] Other frequent genetic alterations include activating *TERT*-promoter mutations,[41–43] found in 30–80% of melanomas. Additionally, various tumour suppressors are frequently altered, including *CDKN2A*, *PTEN*, *TP53*, and *ARID2*.[22,33]

The frequency of mutations and copy-number alterations varies considerably depending on the melanoma type. *BRAF* mutations are most common (50–60%) in cutaneous melanomas, arising on intermediate sun-damaged skin.[44] *BRAF* mutations are rare and mutations occur frequently in melanomas that arise in heavily sun-damaged skin,[35,45] as well as mucosal[46] and acral[47] sites. Non-ultraviolet-exposed acral and mucosal melanomas have considerably fewer mutations but more frequent chromosomal alterations.[33,44]

Molecular markers of prognosis and therapy

Despite considerable advances in understanding the genetic underpinnings of melanoma, the use of genetic alterations for diagnostic, prognostic, or therapeutic purposes remains limited. *BRAF* mutation status is crucial to decide whether a patient will benefit from BRAF inhibitor therapy.[48] The other attractive therapeutic approach is immunotherapy.[49,50] Despite considerable debate, the most widely used test to predict therapy response is PD-L1 immunohistochemistry (PD-L1 expression is clearly associated with response rate, progression-free survival, and overall survival in melanoma);[51,52] however, this test has in most cases no influence on treatment decisions. Genetic approaches that estimate responses to immunotherapy by establishing neo-epitopes or overall mutational load are still experimental, and not in routine clinical use.[53,54] The clinical value of two recently introduced commercial gene expression assays aiming to predict melanoma prognosis remains to be verified.[36,55]

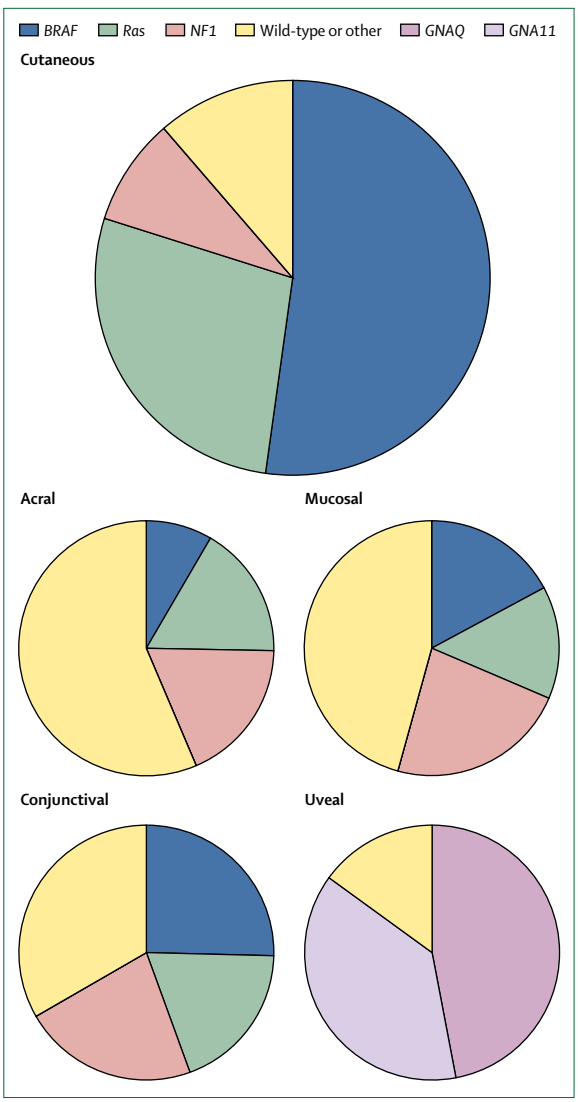

Figure 4: **Distribution of activating mutations in different melanoma subtypes**
Genetic classification with distribution of tumour types according to the activating gene mutation. Mutations with a frequency of more than 5% are shown. Frequencies are as reported for cutaneous,[33] acral,[32] mucosal,[35] conjunctival,[36] and uveal[37–40] melanoma. *BRAF*=B-Raf proto-oncogene serine/threonine kinase.

Screening and clinical diagnosis

Screening and melanoma surveillance

People at an increased risk for melanoma (ie, those who have a fair skin type, multiple atypical moles, or a family history of melanoma) should be screened at regular intervals. The screening populations and methods differ between countries, and often no exact guidelines exist. Generally, screening for melanoma includes a total body skin examination supported by dermoscopy or other imaging techniques, with both examinations performed by an experienced physician. Screening is usually not restricted to melanoma, and is useful for early detection of all types of skin cancer, including biopsy and histopathological diagnosis in case of suspicious lesions. One advantage of regular skin cancer screenings is that they can lead to the diagnosis of melanomas with lower invasion depths than melanomas detected by patients or other caregivers.[56] However, regular screenings have been argued to lead to an overdiagnosis of thin melanomas,[57] with no effect on patient survival.[58] To this end, the benefit of regular screening on melanoma mortality has not yet been shown, and randomised trials on regular versus no skin cancer screenings are absent. Thus, skin cancer screening programmes are differentially implemented between countries; for example, in Germany, regular skin cancer screenings are recommended for individuals over age 35 years,[59] whereas in the USA, skin cancer screenings are not generally recommended.[60] To date, no evidence has suggested that nationwide skin cancer screening programmes decrease skin cancer-associated mortality.[58,61] A crucial evaluation of the German skin cancer screening programme is awaited

within the next years.

Many clinical guidelines recommend that people at high risk of melanoma receive regular surveillance to improve survival through early detection and to reduce unnecessary excisions. Results of an Australian study comparing risk-adapted specialised skin surveillance with regular skin surveillance suggest a higher rate of detection of melanomas at an earlier stage together with lower cost per patient for the specialised approach.[62,63]

Clinical diagnosis

The majority of high-risk melanomas are readily detected and diagnosed by visual inspection by an experienced physician because of their prominent pigmentation and morphological pattern. However, for thin or non-pigmented (amelanotic) melanomas, supportive imaging techniques have been shown to improve diagnostic accuracy. The most widely used technique is dermoscopy, also known as epiluminescence microscopy, a magnifying handheld optical device that uses a light source to inspect skin lesions unobscured by skin surface reflections. Use of dermoscopy requires considerable training, but when appropriately used, this method substantially enhances the diagnosis of unclear or doubtful lesions that are suspected to be melanoma.[64] This easy-to-use technique can be additionally equipped with a digitisation device, enabling storage and comparisons of dermoscopy images over time (digital video dermoscopy). This methodology has been shown to reduce unnecessary surgical procedures in benign lesions and to detect melanomas of clinically atypical appearance.[65,66] Other imaging techniques, such as in-vivo reflectance confocal laser microscopy,[67] computer-aided multispectral digital analysis,[68] and electrical impedance spectroscopy[69] are available to assist the physician in the differentiation of melanoma and its precursors from benign lesions. Generally, approximately 70% of melanomas are correctly diagnosed using clinical inspection by a dermatologist; with dermoscopy, this detection proportion can be increased to up to 90%. About 10% of melanomas are not reliably detected by these methods.

After the histopathological diagnosis of an invasive melanoma is made, palpatory and sonographical examination of the regional lymph-node basin should be done before further surgical procedures to exclude macroscopic lymphogenic metastatic spread. In case of any evidence for metastasis, or in patients with high-risk primary tumours of a least 4-mm invasion depth, radiographic imaging using CT or MRI should be done to exclude distant metastatic spread.

Management

Primary tumour: surgical excision and lymph node biopsy

The primary treatment of localised disease (primary tumours) consists of wide local excision with different safety margins, depending on the Breslow[22] thickness of the melanoma. Usually, 0·5 cm margins are recommended for in-situ melanomas, 1 cm margins for tumours with a thickness of up to 2 mm, and 2 cm margins for tumours thicker than 2 mm. Several studies analysed narrow versus wide margins, and although they found a reduction in local recurrences for wide margins, they did not show any subsequent overall survival effect.[70–73] An update of the UK study seemed to show a survival benefit after long-term follow-up, but this study was criticised for not routinely using sentinel node staging, which might have introduced a bias.[74] Therefore, modifications with reduced safety margins are acceptable for functional areas (ie, melanomas on the joints) or for cosmetic reasons (ie, facial melanomas).

Elective lymph-node dissection has not shown any significant survival benefit and is not recommended.[75–78] Sentinel lymph-node biopsy is recommended for primary melanomas with a tumour thickness of at least 1·0 mm. Primary melanoma of less than 1·0 mm are considered only if additional risk factors such as ulceration and young age are found together. Sentinel node staging is considered of high relevance for adequate staging, risk assessment, and potentially also for choosing the right follow-up and adjuvant treatment strategy.

In a study in patients with intermediate and thick melanoma, the Multicentre Selective Lymphadenectomy Trial (MSLT)-1[79] did not shown any survival benefit after long-term follow-up for wide local excision with sentinel lymph node biopsy versus wide local excision with nodal observation only.

Completion lymph node dissection for patients who had sentinel lymph node biopsy was considered the appropriate treatment until 2017. However, both the German DeCOG-SLT study[80] and the international MSLT-2 study[81] did not find any significant improvement in melanoma-specific survival when comparing routine complete lymph node dissection to periodic ultrasound observation of the sentinel node–lymph node basin. Complete lymph node dissection did (logically) improve regional nodal relapse-free survival (RFS), but did not improve relapse-free and overall survival. Complete lymph node dissection provides additional staging information, because approximately 20% of patients who are positive for sentinel lymph node biopsy involvement will have additional non-sentinel node involvement that can be found by complete lymph node dissection. However, this additional information does not necessarily lead to upstaging, because only a maximum of 6% of patients will subsequently move to a higher stage.[82,83] Thus, immediate complete lymph node dissection for sentinel lymph node biopsy-positive disease should not be done.[84] Finally, in case of clinically detectable (macroscopic, non-sentinel node) regional disease, therapeutic lymph node dissection is considered the standard of care. In the future, results of neoadjuvant treatments[85] might lead to less extensive surgery (and subsequently less morbidity) in people who have a complete response.

Adjuvant treatment

Recurrence of melanoma after definitive surgery is a substantial risk for patients with stage-2B, stage-2C, stage-3, and resectable stage-4 melanoma. In these tumour stages, an adjuvant treatment, which makes use of agents already approved or in clinical trials, should be considered to prevent disease relapse and spread to distant organ sites, and ultimately to improve overall survival. A meta-analysis of trials that investigated the efficacy of interferon-α treatment versus no treatment revealed a significant effect on RFS, but only a small benefit on overall survival with a 3% in survival after 5 years.[86] The EORTC-18071 trial[87] on the adjuvant use of the cytotoxic T-lymphocyte-associated protein-4 (CTLA-4)-blocking antibody ipilimumab (10 mg per kg for 3 years) compared with placebo in 951 patients with stage-3 melanoma showed a clear improvement of RFS[87] and overall survival,[88] establishing an active regimen for the adjuvant treatment of stage-3 melanoma. On the basis of these results, the US Food and Drug Administration (FDA) licensed ipilimumab for patients with stage-3 melanoma after lymphadenectomy. The ipilimumab scheme showed substantial toxicity, including life-threatening autoimmune events and treatment-related deaths.[87,88] Therefore, the US intergroup trial ECOG-1609[89] tested ipilimumab 10 mg per kg versus 3 mg per kg over just 1 year. Preliminary results indicate no difference for RFS (hazard ratio [HR] 1·0).[89] A new finding in adjuvant melanoma was established by a meta-analysis, and suggested that RFS is a valid surrogate marker for overall survival if the HR for RFS is 0·77 or less.[90]

Following in the path of checkpoint blockade as active therapy in stage-4 disease, in September, 2017, another trial result was released after a median follow-up of 1·6 years: Checkmate-238[91] compared ipilimumab 10 mg per kg administered every 3 weeks to nivolumab 3 mg per kg given every 2 weeks over 1 year. This trial is the first to compare a new drug for adjuvant treatment (nivolumab) to an already approved and active agent (ipilimumab) in patients with stage-3B, stage-3C, and resected stage-4 melanoma. RFS significantly improved with nivolumab (HR 0·65), and this benefit was consistent in all subgroups.[91] Nivolumab showed excellent tolerability with just 4% treatment-related discontinuations compared with 30% discontinuations for ipilimumab. Nivolumab received US FDA approval for adjuvant use in December, 2017, and approval in Europe in August, 2018. The results of another randomised trial on the PD-1 antibody pembrolizumab versus placebo in patients with stage-3 melanoma (the EORTC 1325/Keynote-054 trial)[92] were released in April, 2018. Pembrolizumab showed a clear RFS benefit (HR 0·57) compared with placebo after a median follow-up of 15 months.[92]

The first adjuvant use of targeted therapies in patients with *BRAF*$^{V600E/K}$ mutations (the COMBI-AD trial)[93] was published after a median follow-up of 2·8 years. The combined use of dabrafenib and trametinib in patients with stage-3A–C melanoma showed not only a significant RFS benefit (HR 0·47) but also an overall survival benefit (HR 0·57) when compared with oral placebo. The COMBI-AD trial[93] had a considerably longer follow-up than the Checkmate-238[91] and EORTC-054[92] studies, and explains why this adjuvant study showed an effect on overall survival. Notably, no unexpected toxicities were found with BRAF-MAPK kinase (MEK) inhibition in the adjuvant setting. A trial comparing vemurafenib to placebo (BRIM-8 trial)[94] did not show favourable treatment outcomes for monotherapy with a BRAF inhibitor.[94]

In conclusion, nivolumab (for all comers) and dabrafenib and trametinib (for patients with *BRAF*-mutated melanoma) will become the new standards of care in stage-3 melanoma in 2018.

Metastatic disease

Targeted therapy in stage-4 melanoma

For *BRAF*^{V600}-mutated melanoma, oral small-molecule kinase inhibitors are approved for first-line therapy of locally advanced and metastatic disease. Several randomised phase 3 clinical trials[95–100] have shown unprecedented objective response rates to BRAF inhibitors of approximately 50%, which could be increased to 70% when combined with MEK inhibitors. Although complete responses were reported in only 16% of patients, the disease control rate (complete response, partial response, or stable disease) exceeded 90%, meaning that all patients benefit initially from this treatment. Additionally, since median progression-free survival (PFS) increased from 7–9 months with single-agent BRAF inhibitors to 11–14·9 months with BRAF and MEK inhibitors, combination therapy has become an established standard regimen. Another positive effect of adding a MEK inhibitor was the reduction of paradoxical activation of the MAPK pathway by BRAF inhibitor monotherapy, resulting in reduced skin toxicity and the development of non-melanoma skin cancer lesions.[95–100]

Two BRAF-MEK inhibitor combinations are presently on the market: vemurafenib and cobimetinib, and dabrafenib and trametinib. Another combination, encorafenib and binimetinib, is expected shortly (table 3). Essentially, the efficacy data for these treatment combinations are highly comparable, whereas their pharmacokinetics and toxicity profiles differ in some regards. For instance, the vemurafenib-cobimetinib combination can be taken with or without food and is more commonly associated with increased photosensitivity, whereas the dabrafenib-trametinib combination should be taken under fasting conditions and is more commonly associated with pyrexia, which is the most common reason for interruption and dose modification of the medication.

A rapid response within days to a few weeks regardless of tumour burden and localisation of metastasis is a typical feature of all BRAF inhibitor-based therapies, which can be particularly beneficial for patients with

	Type of inhibitor	Dosage
Dabrafenib combined with trametinib		
Dabrafenib*	BRAF inhibitor	150 mg administered orally two times per day
Trametinib*	MEK inhibitor	2 mg administered orally once per day
Vemurafenib combined with cobimetinib		
Vemurafenib*	BRAF inhibitor	960 mg administered orally two times per day
Cobimetinib*	MEK inhibitor	60 mg administered orally once per day (days 1–21); repeat day 29
Encorafenib combined with binimetinib		
Encorafenib*†	BRAF inhibitor	450 mg administered orally once per day
Binimetinib*†	MEK inhibitor	45 mg administered orally two times per day
Imatinib combined with nilotinib		
Imatinib‡	KIT inhibitor	400–800 mg administered orally once per day
Nilotinib‡	KIT inhibitor	400 mg administered orally two times per day

BRAF=B-Raf proto-oncogene serine/threonine kinase. MEK=mitogen-activated protein kinase kinase. KIT=KIT proto-oncogene receptor tyrosine kinase. *Only in the case of a *BRAF*^{V600} mutation. †Approval awaited. ‡Only in the case of a *KIT* mutation (exons 9, 11, 13, 17, and 18); not yet approved.

Table 3: **Kinase inhibitor combinations frequently used in melanoma therapy**

symptomatic melanoma with rapidly progressing tumours. Additionally, efficacy on melanoma metastases in the brain has been shown, with intracranial response rates of up to 55% using dabrafenib and trametinib.[101] Caution should be taken when applying concurrent radiation therapy, because increased toxicity when combining BRAF inhibitor and radiation treatment has been reported, including cases of severe dermatitis, radionecrosis, and follicular cystic proliferation.[102]

Median overall survival in patients with stage-4 melanoma either untreated or treated with BRAF inhibitor and MEK inhibitor is between 22–25 months, and 3–5-year overall survival has reached 40%.[103,104] Normal lactate dehydrogenase concentrations, less than three metastatic sites, and good Eastern Cooperative Oncology Group performance were associated with a favourable prognosis.[103,104] Nevertheless, one major problem with targeted therapy in *BRAF*-mutated melanoma is the development of resistance while on therapy. Multiple mechanisms of resistance against BRAF and MEK inhibitors have been identified, which eventually lead to reactivation of the MAPK signalling pathway or activation of the PI3K-AKT pathway. Among these mechanisms, *BRAF* gene amplifications and MEK1 and MEK2 mutations are the best described.[105,106]

BRAF-inhibitor and MEK-inhibitor combination therapy has a good safety and tolerability profile. Common adverse events comprise gastrointestinal symptoms, such as nausea (36–41%), diarrhoea (31–56%), vomiting (21–30%), arthralgia (26–32%), fatigue (29–39%), photosensitivity (28%), increase in creatine kinase (23–31%) and liver transaminases (23%), pyrexia (18–59%), peripheral oedema (22%), headache (22–34%), rash (14–39%), alopecia (9–14%), hyperkeratosis (7–14%), and palmo-plantar skin reactions (9%). Although less common, in case of the occurrence of retinopathy (12%), cardiac left ventricular dysfunction (8%), and QT-interval prolongation (3–4%), close monitoring is needed. In clinical practice, dose modifications or switching to another available BRAF-MEK inhibitor combination is common to manage adverse events, whereas permanent discontinuation of drug intake is rarely necessary.[95–99]

For patients with *BRAF* wild-type melanoma, the options for targeted therapies are scarce. In an open-label phase 2 trial,[107] patients with *NRAS*-mutated advanced melanoma treated with the MEK inhibitor binimetinib showed an overall response rate of 20%. In a subsequent phase 3 trial, the efficacy of binimetinib was supported, with a 15% overall response rate and a median PFS of 2·8 months.[108] Even though these results were better than those achieved with chemotherapy with dacarbazine, which had a response rate of 7% only and a median PFS of 1·5 months, median overall survival (11 months *vs* 10·1 months) was not significantly different between the two groups.[108] Hence, targeted therapy in *BRAF* wild-type melanoma is not a first-line option, and new agents or combinations are urgently needed for this patient population, especially if those who do not respond to immunotherapy.

In the rare subgroups of melanomas in which *KIT* proto-oncogene-receptor tyrosine kinase (*KIT*) is mutated, tyrosine kinase inhibitors with potent c-kit inhibition—ie, imatinib mesilate, dasatinib, sunitinib malate, and nilotinib—have shown a small amount of clinical activity in selected cases and small clinical trials.[109–112] Imatinib mesilate achieved a 23% response rate and 30% stable disease with *KIT* mutations in exons 11 and 13, the most sensitive to treatment.[110] Similarly, a 26% response rate and 46% stable disease was found for nilotinib.[111] However, our clinical experience showed that the duration of response is usually short.

Checkpoint blockade in stage-4 melanoma

The improvement of systemic therapy in advanced melanoma has been further driven by checkpoint inhibitors against CTLA4 (ipilimumab) and PD-1 (pembrolizumab and nivolumab). Melanoma is the lead indication for the approval of checkpoint inhibitors because of their superior efficacy compared with chemotherapy (table 4). Initial studies showed that ipilimumab treatment increased the percentage of long-term survival (beyond the third year) in patients with metastatic melanoma to around 20%.[127] These studies also reported a range of inflammatory side-effects associated with checkpoint inhibitor therapy, so-called immune-related adverse events (irAE). With ipilimumab, irAEs mainly affect the gastrointestinal system (colitis and diarrhoea), skin (dermatitis and pruritus), liver (hepatitis and increased liver function tests), and endocrine organs (hypophysitis and thyroiditis), and are dose dependent.[115] Subsequently, guidelines for monitoring and managing ipilimumab treatment-associated irAE have been developed.[128]

Nivolumab and pembrolizumab that target the PD-1

checkpoint were investigated, and showed superior efficacy compared with ipilimumab and chemotherapy (table 4), with lower toxicity rates. Compared with nivolumab 3 mg per kg administered every 2 weeks, ipilimumab 3 mg per kg given as four administrations in 3-week intervals resulted in 28% of patients having grade-3 and grade-4 treatment-related adverse events (versus 21% for nivolumab) and 16% discontinuing treatment (*vs* 8% with nivolumab) in Checkmate-067.[121] In the Keynote-006 study,[125] ipilimumab caused treatment-related grade-3 and grade-4 adverse events in 20% of patients and treatment discontinuations in 9%, whereas pembrolizumab 10 mg per kg given every 2 or 3 weeks caused treatment-related grade-3 and grade-4 adverse events in 17% of patients and treatment discontinuation in 7–11%.[125] PD-1 inhibitor-associated irAEs more often

	Design	Treatment groups and regimen	Overall response rate (%)	Duration of response (median, months)	Progression-free survival (median, months)	Overall survival (median, months)
Hodi et al (2010)[113]	Pretreated patients; double-blind, phase 3 trial	Ipilimumab 3 mg per kg + gp100 (n=403) *vs* ipilimumab 3 mg per kg (n=137) *vs* gp100 (n=136)	5·7% *vs* 11·0% *vs* 1·5%, p=0·04	11·5 months *vs* NR *vs* NR	Ipilimumab + gp100 2·76 months (HR *vs* gp100 0·81, p<0·05); ipilimumab 2·86 months (HR *vs* gp100 0·64, p<0·001); gp100 2·76 months	Ipilimumab + gp100 10·0 months (HR *vs* gp100 0·68, p<0·001); ipilimumab 10·1 months (HR *vs* gp100 0·66, p=0·003); gp100 6·4 months
Robert et al (2011)[114]	Untreated patients; double-blind, phase 3 trial	Ipilimumab 10 mg per kg + dacarbazine (n=250) *vs* placebo + dacarbazine (n=252)	15·2% *vs* 10·3%, p=0·09	19·3 months *vs* 8·1 months, p=0·03	Median survival in both groups similar, HR 0·76, p<0·006 in favour of ipilimumab + dacarbazine	11·2 months *vs* 9·1 months, HR 0·72, p<0·001
Ascierto et al (2017)[115]	Pretreated and untreated patients; double-blind, phase 3 trial (CA184-169)	Ipilimumab 10 mg per kg (n=364) *vs* ipilimumab 3 mg per kg (n=362)	15% *vs* 12%	..	2·8 months *vs* 2·8 months, HR 0·89, p=0·16	15·7 months *vs* 11·5 months, HR 0·84, p=0·04
Ribas et al (2013)[116]	Untreated patients; open-label, phase 3 trial	Tremelimumab (n=328) *vs* chemotherapy (n=327)	10·7% *vs* 9·8%	35·8 months *vs* 13·7 months, p=0·0011	..	12·6 months *vs* 10·7 months, HR 0·88, p=0·127
Robert et al (2015)[117]	Untreated patients (with melanoma without *BRAF* mutation); double-blind, phase 3 trial (Checkmate 66)	Nivolumab (n=210) *vs* dacarbazine (n=208)	40·0% *vs* 13·9%, p<0·001	NR *vs* 6·0 months	5·1 months *vs* 2·2 months, HR 0·43, p<0·001	NR *vs* 10·8 months, HR 0·42, p<0·001
Weber et al (2015)[118] and Larkin et al (2018)[119]	Patients pretreated with ipilimumab and *BRAF* inhibitor; open-label, phase 3 trial (Checkmate 37)	Nivolumab (n=272) *vs* chemotherapy (n=133)	27% *vs* 10%	31·9 months *vs* 12·8 months	3·1 months *vs* 3·7 months, HR 1·0	15·7 months *vs* 14·4 months, HR 0·95
Weber et al (2016)[120]	Untreated and pretreated patients; open-label, phase 2 trial (Checkmate 64)	Nivolumab followed by ipilimumab (n=68) *vs* ipilimumab followed by nivolumab (n=70)	56% *vs* 31%	NR *vs* NR	..	NR *vs* 16·9 months, HR 0·48
Larkin et al (2015)[49] and Wolchok et al (2017)[121]	Untreated patients; double-blind, phase 3 trial (Checkmate 67)	Nivolumab + ipilimumab (n=314) *vs* nivolumab (n=316) *vs* ipilimumab (n=315)	58% *vs* 44% *vs* 19%	NR *vs* NR *vs* 19·3 months	Nivolumab + ipilimumab 11·5 months (HR *vs* ipilimumab 0·43, p<0·001; HR *vs* nivolumab 0·78, 95% CI 0·64–0·96); nivolumab 6·9 months (HR *vs* ipilimumab 0·55, p<0·001); ipilimumab 2·9 months	Nivolumab + ipilimumab NR (HR *vs* ipilimumab 0·55, p<0·001; HR *vs* nivolumab 0·85, 95% CI 0·68–1·07); nivolumab 37·6 months (HR *vs* ipilimumab 0·65, p<0·001); ipilimumab 19·9 months
Postow et al (2015)[50] and Hodi et al (2016)[122]	Untreated patients; double-blind, phase 2 trial (Checkmate 69)	Nivolumab + ipilimumab (n=95) *vs* ipilimumab (n=47)	59% *vs* 11%, p<0·0001	NR *vs* NR	NR *vs* 3·0 months, HR 0·36, p<0·0001	Crossover from ipilimumab to nivolumab allowed; median overall survival NR in both groups, HR 0·74, p=0·26
Ribas et al (2015)[123] and Hamid et al (2017)[124]	Patients pretreated with ipilimumab and *BRAF* inhibitor; open-label, phase 2 trial (Keynote 2)	Pembrolizumab 2 mg per kg (n=180) *vs* pembrolizumab 10 mg per kg (n=181) *vs* chemotherapy (n=179)	22% *vs* 28% *vs* 4%, p<0·0001	22·8 months *vs* NR *vs* 6·8 months	Pembrolizumab (2 mg per kg) 2·9 months (HR *vs* chemotherapy 0·57, p<0·0001); pembrolizumab (10 mg per kg) 2·9 months (HR *vs* chemotherapy 0·50, p<0·0001); chemotherapy 2·7 months	Crossover allowed; pembrolizumab (2 mg per kg) 13·4 months (HR *vs* chemotherapy 0·86, p=0·117); pembrolizumab (10 mg per kg) 14·7 months (HR 0·74, p=0·011); chemotherapy 11·0 months
Schachter et al (2017)[125] and Robert et al (2015)[126]	Untreated and pretreated patients; double-blind, phase 3 trial (Keynote 6)	Pembrolizumab once every 2 weeks (n=279) *vs* pembrolizumab once every 3 weeks (n=277) *vs* ipilimumab (n=278)	37% *vs* 36% *vs* 13%	NR *vs* NR *vs* NR	5·6 months *vs* 4·1 months *vs* 2·8 months; pooled pembrolizumab groups *vs* ipilimumab HR 0·61, p<0·0001	Pembrolizumab once every 2 weeks NR (HR *vs* ipilimumab 0·68, p=0·0009); pembrolizumab once every 3 weeks NR (HR *vs* ipilimumab 0·68, p=0·0008); ipilimumab 16·0 months

NR=not reached. HR=hazard ratio.

Table 4: **Randomised trials on the effect of checkpoint inhibitors in palliative therapy of melanoma**

affect the lung (pneumonitis) and the thyroid gland (hyperthyroidism or hypothyroidism) than ipilimumab. Guidelines for managing and monitoring irAEs associated with PD-A inhibitors were developed by several interdisciplinary groups.[129,130] Nivolumab (3 mg per kg every 2 weeks or a flat dose of 480 mg every 4 weeks) and pembrolizumab (2 mg per kg every 3 weeks or a flat dose of 200 mg every 3 weeks) were approved for the treatment of metastatic melanoma, and melanoma guidelines recommend the preferred use of PD-1 inhibitors over ipilimumab (eg, the National Comprehensive Cancer Network guideline for melanoma).[131] Nivolumab followed by ipilimumab was also superior to ipilimumab followed by nivolumab in the Checkmate-64 study.[120]

In a pivotal phase-3 study, the Checkmate-067 study,[132] nivolumab monotherapy, ipilimumab monotherapy, and the combination of nivolumab and ipilimumab were compared.[121] The efficacy of the combination was superior to the monotherapies (table 4), which resulted in the approval of nivolumab combined with ipilimumab for the treatment of metastatic melanoma. However, treatment-related grade-3 and grade-4 adverse events occurred in 56% of patients, and 30% of patients needed to discontinue nivolumab and ipilimumab because of adverse events.[121] Health-related quality of life was comparable in the group treated with nivolumab and in the group treated with nivolumab and ipilimumab.[132] More intense monitoring is recommended for the combination therapy than for monotherapy.[133] Comparison of patients who needed to discontinue nivolumab and ipilimumab versus patients who received the planned treatment schedule showed a similar efficacy in both groups.[134] Both monotherapy with PD-1 inhibitors and the combination of nivolumab and ipilimumab are considered the standard of care at this time. However, since multiple and irreversible irAEs are more common during combination therapy compared with PD-1 monotherapy, an intense discussion is ongoing with regards to which patients require combination therapy. Combination therapy appears to be more efficacious in patients with poor prognostic factors, such as an increased lactate dehydrogenase concentration,[121] mucosal melanoma as a primary tumour,[135] asymptomatic brain metastases,[136,137] and PD-L1 expression on less than 1% of melanoma cells.[121]

Approximately 60% of patients show primary (de-novo) resistance to PD-1 checkpoint inhibition (table 4), and 20–30% of initial responders will develop secondary (acquired) resistance. Increased understanding of resistance mechanisms helps to develop biomarkers for prediction of efficacy and for future therapeutic strategies,[138] although no biomarker is widely accepted for routine clinical use. Potential biomarkers assess immunological tumour-cell recognition, such as mutational load and neoantigen expression,[139] and the presence of an immune-permissive tumour environment, such as PD-L1 expression,[140] presence and location of tumour infiltrating lymphocytes,[141] or activity of the interferon-γ signalling pathway in tumour cells.[142,143] Composition of the microbiome in the gut and other sites might also represent a biomarker for efficacy of checkpoint inhibitors.[138,144]

Conclusion

Prevention, early detection, and the arrival of effective adjuvant treatment strategies in stage-3 melanoma will increase overall survival and cure rates for patients with melanoma. Using PD-1-based treatment algorithms and targeted agents in $BRAF^{v600}$-mutant melanoma, 5-year overall survival rates for metastatic melanoma have increased substantially from less than 10% to up to 40–50% today in countries that have access to these innovations.[145] Patients with high tumour burden, brain metastasis, and elevated lactate dehydrogenase still have a poor prognosis (3-year survival <10%).[146] There is considerable interest in combining active agents independent of their mode of action. One strategy is combining MEK-inhibitors with or without BRAF-inhibitors and checkpoint inhibitors (PD-1-blocking or PD-L1-blocking antibodies) in clinical phase-3 registration studies (NCT02967692, EuDraCT-Nr:2016-002482-54). Another strategy is to focus on applying PD-1 antibodies as a standard of care and adding other immune-modulating or microenvironment-modulating agents such as LAG3 antibodies, which are also being tested in phase 3 studies. Particularly with checkpoint inhibition, the optimal duration of treatment is unknown in the adjuvant and metastatic setting. Furthermore, numerous clinical trials are investigating other molecules usually with a standard of care of PD-1 antibodies or BRAF-MEK inhibition. Additionally, further questions include whether a full combination is always needed as a first-line treatment (with all its inherent toxicity) or whether giving one drug after the other (ie, the sequencing approach) could lead to a comparable overall survival. Several main challenges to treating the metastatic stage remain, which include establishing the most reliable study endpoint (median PFS, median overall survival, or PFS or overall survival at defined landmarks) to judge whether relevant progress has been made after initial release of clinical study results leading to a changing standard of care. Lastly, developing treatment options for patients who do not initially respond to systemic therapy will be crucial to increase the number of long-term survivors.

Contributors

All authors contributed equally to this manuscript.

Declaration of interests

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