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MELANOMA (RJ SULLIVAN, SECTION EDITOR)

The World of Melanoma: Epidemiologic, Genetic, and Anatomic Differences of Melanoma Across the Globe

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Abstract

Purpose of Review As cancer remains an increasing problem in industrial countries, the incidence of melanoma has risen rapidly in many populations during the last decades and still continues to rise. Current strategies aiming to control the disease have largely focused on improving the understanding of the interplay of causal factors for this cancer.

Recent Findings Cutaneous melanoma shows clear differences in incidence, mortality, genomic profile, and anatomic presentation, depending on the country of residence, ethnicity, and socioeconomic status. Known risk factors are multiple atypical nevi, positive family and/or personal history, immune suppressive diseases or treatments, and fair skin phenotype. Besides new adjuvant therapeutic options, changed attitude toward leisure and sun exposure, primary prevention, and early detection are major contributors to disease control.

Summary Melanoma is a disease of multifactorial causality and heterogeneous presentation. Its subtypes differ in origin, anatomical site, role of UV radiation, and mutational profile. Better understanding of these differences may improve prevention strategies and therapeutic developments.

Keywords Melanoma · Epidemiology · Ethnicity · Melanoma genetics · Targeted therapy · Immunotherapy

Introduction

Melanoma arises through malignant transformation of melanocytes and is considered a neural crest neoplasia. It is the most aggressive and lethal form of all skin cancers. Although it represents approximately 5% of all cutaneous malignancies, it is responsible for the vast majority of skin cancer-related deaths [1].

Embryologically, melanocytes are derived from the neural crest and colonized in the skin, the eyes, and several tissues during the development. Benign proliferation is commonly observed and results in melanocytic nevi. With the presence of diverse mutations, aberrations, translocations, and deletion, however, malignant transformation can take place, giving rise to various types of melanomas [2]. Although early stages can be cured with surgical excision, a proportion of patients still develop metastatic disease. As novel treatments are being rapidly developed, a tremendous improvement in the survival of metastatic patients has been achieved. For example, the average 1-year survival for stage IV melanoma patients are reported to be 74.5% with BRAF/MEK inhibitors and 71.9% for anti-PD-1 blockade alone or combined with anti-CTLA-4 [3•]. However, the treatment of advanced melanoma stages still remains challenging.

As the incidence of melanoma steadily increases in both sexes, further improvement in primary prevention and early detection strategies is crucial [4]. Still, the epidemiologic, genomic, and anatomic profiles of the disease significantly differ across the world and mostly depend on a constellation of environmental and (epi) genetic factors.

In the current review, we aim to outline the major epidemiologic, genetic, and anatomic differences of the various melanoma types across the globe and attempt to provide a background which is relevant to better understand the disease and its treatment.

This article is part of the Topical Collection on *Melanoma*

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Melanoma Incidence

Cutaneous melanoma is the 12th most common cancer worldwide with an estimated age-standardized incidence rate of 3.0 per 100,000 [5]. The incidence of the disease varies among populations, with highest rates reported in Australia and New Zealand (40.3 per 100,000 and 30.5 per 100,000, respectively) followed by North America and Northern and Western Europe. Lowest incidences are documented in South-Central and South-Eastern Asia (below 0.5 per 100,000) (Table 1). This variation is mainly attributed to heterogeneity of risk factors, such as ultraviolet (UV) exposure and genetically determined phenotypic characteristics. Recent epidemiological data show an annual overall rising incidence of melanoma with 232,000 new cases (1.6% of all cancers) in 2012 [5] and 351,880 cases (95% CI 281,633–445,036) in 2015 with an age-standardized rate of five cases per 100,000 persons (95% CI 4–7) [6]. The overall number of patients being diagnosed with melanoma is estimated to continue to increase in the decades ahead, mostly due to the lengthening of human lifespan and the aging of population [7].

In Australia, melanoma is the fourth most common cancer and accounts for 9.7% of all new cancer cases between 2009 and 2013 [8]. Between 1982 and 2016, the incidence rate of melanoma has increased from 27 cases per 100,000 in 1982 to 49 per 100,000 in 2016 for all age groups [8]. Among Australians aged 15–34, melanoma is the most common cancer (excluding non-melanoma skin cancers originating from keratinocytes). However for this age group, the incidence rate has dropped from 13 new cases per 100,000 in 1982 to 9.4 per 100,000 in 2016 [8]. With 72 cases per 100,000 per annum on average (2010–2014), the incidence of invasive melanoma in Queensland remains the highest recorded worldwide. A recent study analyzing incidence and mortality data in Queensland between 1995 and 2014, showed a stable or falling incidence of both thin (≤ 1 mm) and invasive (> 1 mm) melanoma in people under 60 years. This might serve as a good marker of effective prevention campaigns, reducing sunburns in early age, one of the strongest risk factors of melanoma. However, in the population over 60 years, the trend in incidence is still increasing [9]. Melanoma mortality rates remain stable or declining in both sexes under 40, while in males over 60, the mortality seems to increase with a rate of 2% per annum. These results suggest that long-running melanoma prevention campaigns and early detection strategies can contribute to reduce the incidence and mortality rates of melanoma in susceptible populations around the world. Yet, it also reflects that prevention has to be started in young age [10].

Table 1 Estimated age-standardized rate (ASR) (per 100,000) of melanoma incidence and mortality by sex and region, 2012 (http://globocan.iarc.fr)

Region	Incidence		Mortality	
	M	F	M	F
World	3.3	2.8	0.9	0.6
More developed regions	10.2	9.3	2.0	1.2
Less developed regions	0.8	0.7	0.4	0.3
Africa	1.0	1.1	0.5	0.7
Northern Africa	0.3	0.4	0.2	0.2
Southern Africa	5.0	3.7	1.6	0.8
Northern America	16.1	12.2	2.6	1.2
Southern America	2.9	2.2	1.0	0.6
Asia	0.5	0.4	0.3	0.2
Eastern Asia	0.6	0.5	0.4	0.3
Western Asia	1.8	1.6	0.6	0.5
Europe	8.6	8.9	2.0	1.3
Northern Europe	14.0	15.4	2.5	1.6
Southern Europe	8.1	8.3	1.6	1.0
Australia/New Zealand	40.3	30.5	5.9	2.4

The incidence of melanoma is increasing in the US and in European countries as well and is anticipated to continue to rise. In the US, melanoma of the skin represents 5.2% of all new cancer cases with 22.3 per 100,000 numbers of new cases for 2010–2014 [11]. Notably, the incidence and mortality of the disease across the ethnic disparities seems to be heterogeneous. In the US in fact, melanoma is more common in Caucasians compared to African-Americans (AAs), with incidence rates of 34.4 per 100,000 men and 20.9 per 100,000 women compared to 1.1 per 100,000 men and 1.0 per 100,000 women, respectively [11]. Recent data have shown that ethnic minorities remain at greater risk for melanoma-associated mortality, probably due to the clinical heterogeneity and histological variation of the disease [12]. Whereas the most common form of melanoma among Caucasians is the superficial spreading melanoma (SSM); melanomas in the AA population occur more often on non-sun-exposed skin, such as the palms and the soles. Of these, acral lentiginous melanoma (ALM) is the most common form [12]. Although ALM accounts only 2–3% of all melanoma cases worldwide, they account for up to 70% of all melanomas in darker skin types [13]. The atypical localization and appearance seem to contribute to delayed diagnosis and lead therefore to outcomes.

In the European Union, melanoma was the seventh most common malignancy in 2012, accounting for 3% of all new cancers [14]. For the same year, the estimated age-standardized rates were 8.6 per 100,000 for males and 8.9 per 100,000 for females (Table 1) [15]. Between the European countries there are large incidence differences, varying from 19.2 in Switzerland to 2.2 per 100,000 in Greece

[16]. Central and Eastern European countries have the lowest reported rates in Europe. This rate spectrum may be explained through differences in socioeconomic status, linked to tendency for recreational sun exposure, cultural, as well as phenotypic dissimilarities. Rate differences accruing between neighboring countries however, imply diagnostic delays and differences in reporting or registration [16]. In 2012, Switzerland registered the highest melanoma incidence in Europe, followed by the Scandinavian countries and the Netherlands. Specific to the Scandinavian population, the high incidence of melanoma may be attributed to a high-risk phenotype (fair skin, hair, and eye color) in combination to a tanning culture, high levels of UV exposure during (intermittent) holidays and indoor tanning [16].

Several studies suggest a significant gender difference in melanoma incidence and survival across the globe. In 2017, melanoma incidence rates were about 60% higher in men than in women, while death rates were more than double [4]. Higher melanoma rates have been mostly observed in elderly and male populations, whereas the female sex seems to represent an independent risk factor for early onset melanoma for women < 45 years old [17]. Gender disparities, regardless of other known predictive factors such as tumor thickness, ulceration, histologic subtype, location, and age, are thought to represent an independent prognostic factor in melanoma incidence and survival [18, 19]. According to recent data, the rising melanoma trends mostly affect the older age groups, whereas in the youngest age groups (24–44 years), the incidence seems to stabilize [20]. However, melanoma still affects mostly younger patients, with a median age diagnosis of 57–64 worldwide. The anatomical location of melanoma also varies according to gender. Males tend to present with worse clinical and histological characteristics at primary diagnosis; melanomas in male are more often located on the head, neck, and trunk, commonly ulcerated and have a higher Breslow thickness. On the contrary, the survival benefit among female patients seems to be attributed to those treated with early stage I–II of melanoma, but the survival advantage decreases in patients with a higher metastatic tumor burden [21]. The lower mortality rates in females seem to depend on both biological and behavioral differences regarding primary (sun behavior, UV protection) and secondary (skin checks) prevention [22].

Melanoma Mortality

Paradoxically, although the incidence of melanoma continues to rise, the mortality rates seem to be rising less rapidly. Melanoma mortality accounts for 0.7% of all cancer deaths, with global mortality rates ranging from 0.1 in women of South-Central Asia to 6 per 100,000 in men of Australia/New Zealand [5]. Most deaths occur in more developed regions and mostly among males, with a sex ratio of 1:3 [5] (Table 1). In the US, the number of deaths was reported to be 2.7 per 100,000 men and women per year (time period 2010–2014), with higher mortality rates among the middle-aged and elderly population (24.1% among people aged 75–84 with advanced melanoma) [11]. Across the European continent, there are important differences concerning the mortality, with highest rates of 3.2 in Norway and lowest of 1.0 and 0.9 in Romania and Greece, respectively. Countries from Central and Eastern Europe reported higher rates of advanced tumors and lower survival as compared to Romania and Greece [15]. This discordance between incidence and mortality of Central and Eastern European countries in comparison with their neighboring countries might be contributed to an extended secondary prevention through regular skin checks in Northern and Southern European countries. Indeed, the development of early detection strategies is thought to underlie a shift toward the increasing reporting of thin melanomas around the globe [23–25]. Recent epidemiological data confirm higher survival rates of thinner (≤ 1 mm) compared to thicker melanomas [26••]. However, an analysis of melanoma incidence and mortality in Queensland, Australia, showed that an increasing proportion of melanoma deaths occurred among patients who were initially diagnosed with thin melanomas (≤ 1 mm), compared to a melanoma thickness of > 4 mm [27]. This thin melanoma paradox has been also reported in a US study, investigating the melanoma thickness trends for 1988–2006 [28] and indicates a widespread of early detection strategies. It is possible that specific histological characteristics or other factors, such as genetic mutations, could explain this phenomenon; however, further clinical and molecular features need to be identified.

Melanoma Risk Factors and Anatomic Differences

Melanoma arises through multiple different causal pathways and reflects a dynamic interdependence between environmental factors and genetic alterations. Several factors have been identified that significantly influence the incidence and the clinical and oncogenic characteristics of cutaneous melanoma. These factors mainly comprise increased UV exposure, tanning bed use, family and personal history of melanoma, and certain phenotypical characteristics, such as fair skin and hair color.

Exposure to UV radiation is the major known environmental risk factor for melanoma development. More than 70% of cutaneous melanomas are thought to be caused by UV radiation exposure [29], while the association of melanoma risk and intermittent sun exposure has been also verified in a number of large analytical epidemiological studies [30]. The effect of UV spectrum differs between the UV components,

subdivided by wavelength into UVA (320–400 nm), UVB (280–320 nm), and UVC (100–280 nm). UVC is blocked by ozone and does not reach surface of the earth; thus, UVB and UVA are responsible mainly for the UV-induced skin damage. Due to different electrophysical properties, UVB causes direct DNA damage, whereas UVA causes indirect DNA damage through generation of reactive oxygen species [31].

Observations based on the incidence of the disease and its association with the UV radiation show an increased incidence on population exposed to natural or artificial sunlight over long periods of time, as well as on sporadically sun-exposed skin in sites which are more susceptible to sunburns [30]. Since UVA (320–400 nm) is the primary source used in indoor tanning beds, indoor tanning is associated with increased risk of melanoma, with recent data providing strong evidence of higher melanoma risk with younger age at initiation and longer duration of usage of indoor tanning systems [10, 32]. Australia has already undertaken comprehensive skin cancer awareness campaigns to reduce the burden of skin cancer and has enacted a nationwide ban on tanning beds [9]. Indoor tanning legislation is constantly evolving, with youth access restriction now in place in many countries of Europa and in several states in the US [33].

Epidemiological data support two major pathways in the pathogenesis of cutaneous melanoma: one by cumulative sun exposure to the site of the future melanoma in sun sensitive people and other by early sun exposure and nevus proneness, promoted by host factors, intermittent sun exposure, or both. Approximately 25–33% of cutaneous melanomas derive from a benign, melanocytic nevus, whereas in patients with numerous nevi, this number may be as high as 50% [34, 35]. The divergent pathway model for the development of melanoma on sun-exposed skin identified differences in the sun exposure and the anatomic distribution of melanoma [36]. Transformation of nevi to melanoma most commonly occurs in non-chronically sun-damaged skin. Nevus-prone patients who have increased number of melanocytic nevi tend to develop melanomas at a younger age and on axial locations. On the other side, *nevus resistant* patients with fewer nevi tend to develop de novo melanomas on habitually sun-exposed skin, and at older ages [37]. Chronically sun-damaged (CSD) melanomas have higher mutation burden, later age of onset, and mostly occur on the head and neck areas [38•]. Non-CSD melanomas present earlier in life have lower mutation burden and appear on anatomical sites with intermediate levels of sun exposure, such as the trunk.

In contrast to cutaneous superficial spreading melanoma, the occurrence of nodular melanoma (NM) and mucosal melanoma (MM) seems to be independent of UV exposure. Specifically, in the case of NM, the influence of UV is controversially discussed in the literature. Some studies reported a higher prevalence of NM on sun-exposed skin such as the lower limbs, head, and neck. However, NM can also affect non-chronically sun-exposed body areas such as the trunk in fair- but also dark-skinned patients [39, 40].

Apart from environmental risk factors, phenotypic and genetic characteristics also have been consistently associated with an increased risk of melanoma development. A recent observational study investigating the clinical features associated with individuals at higher melanoma risk showed that a positive family history of melanoma is associated with higher risk for melanoma development in younger ages and on non-sun-exposed areas [41]. Notably, individuals with large or giant congenital melanocytic nevi (CMNs) at birth are at higher risk of melanoma development, which increases according to the size of CMN and is highest in those nevi traditionally designated as garment nevi [42, 43]. Also, personal history of a prior melanoma is a strong predictor for the development of a subsequent melanoma, with approximately tenfold increased risk [44]. However, subsequent melanomas appear to be thinner than the first melanomas, which can be explained through regular clinical examinations during the follow-up. Additionally, melanoma seems to appear more commonly in immunosuppressed patients, including patients with prior organ transplantation, hematologic malignancies, or human immunodeficiency virus infection, as well as patients taking immunosuppressive medication [45]. Direct drug-associated effects on melanoma carcinogenesis as well as drug-dependent impacts on a preferred environment promoting melanoma carcinogenesis are discussed in the literature as possible etiologic explanations [45].

Mutation Overview

Many phenotypic factors are genetically determined. The presence of certain pathogenic mutations determines distinct subsets of melanoma, which can be defined on the basis of their molecular phenotype. These findings have been already translated into recent therapeutic developments, and may lead to further therapeutic modalities and improve prevention strategies.

Using whole exome sequencing (WES) and whole genome sequencing (WGS), skin cancers have been identified as the most mutated cancers in human [46, 47] (10–110 mutations/Mb [48, 49••, 50]). Identification of mutated genes, implementation of this knowledge and creation of targeted therapies in melanoma have continued to serve as one of the highlight stories in translational medicine.

Among the discovered genetic aberrations, no universal mutation for all cutaneous melanomas has been identified. However, oncogene or tumor suppressor gene mutations almost always led to constitutive activation through mitogen-activated protein kinase (MAPK) pathway [51, 52]. Together with mutations in phosphoinositol 3-kinase (PI3K) pathway and in Wnt signaling pathway, they affect the majority of

melanoma samples [53•, 54] (Fig. 1). The two most common mutations, BRAF and NRAS, are oncogenes within the MAPK pathway, whereas NF1 is a tumor suppressor gene, which contributes to regulation of the activation of RAS [55]. According to the frequency of mutations, TCGA Network proposed four genomically defined subdroups: BRAF-, RAS-, NF1-mutated, and triple wild-type (wt) [49••].

BRAF-, RAS-, and NF1-Mutated Melanoma

Described over a decade ago, BRAF mutation remains the most relevant in terms of its implications on treatment decision making [56]. Affecting 40–60% of cutaneous melanomas, these are typically point mutations that lead to one amino acid substitution resulting in a constantly activated state [49••, 57]. The substitution from valine to glutamic acid (V600E) contributes for 74–86% of BRAF mutations, followed by V600K (10–30%) and less common substitutions of V600M, V600D, or V600R [49••, 58]. Although first approved for BRAF V600E-mutated melanomas, BRAF inhibitors proved to also be effective in tumors harboring other BRAF V600 mutations [59, 60]. Interestingly, over 80% of benign melanocytic nevi harbor mutations in BRAF gene [61]. However, in contrast to melanoma, MAPK pathway activation is brief in these lesions, and is followed by a growth arrest phase [62]. In the analysis of melanomas evolving from the preexisting nevi, the benign lesions harbored BRAF mutation exclusively, whereas additional mutations could be identified in each step of the invasion [63]. If compared to triple wt tumors, BRAF-mutated melanomas show much higher UV signature (30% vs 90%), which might represent an additional trigger for the melanoma-genesis [57, 58].

Of all melanomas, 28–30% harbor an activating mutation within the oncogene RAS family, most commonly NRAS, followed by KRAS and HRAS. NRAS mutations also have been identified in 18% of benign nevi [61]. Yet, as recently reported by Shain and colleagues [63], NRAS mutation was only present in the intermediate lesions. This mutation is routinely assessed in clinical practice, and, although no

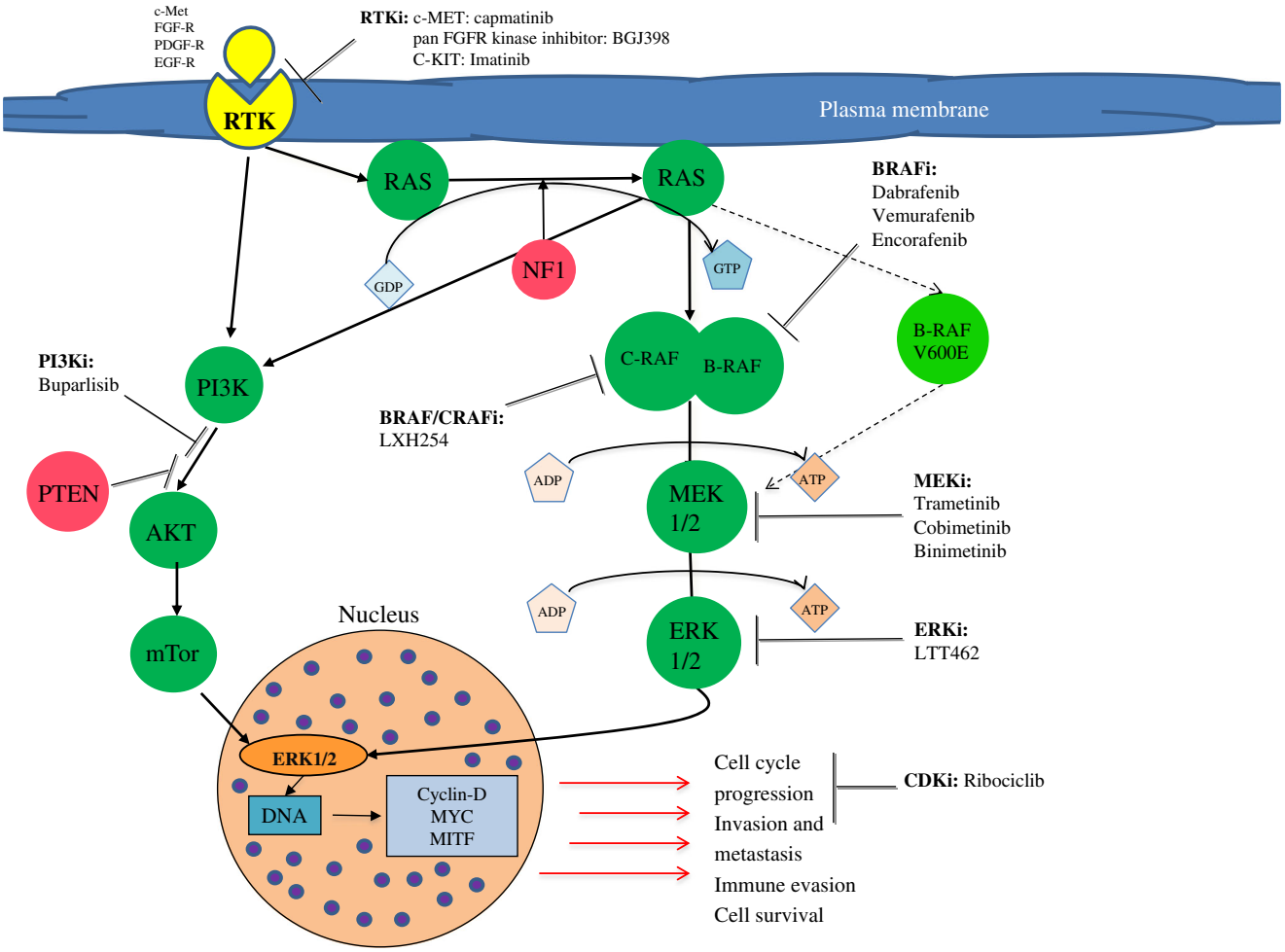

Fig. 1 Mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways play a key role in the pathogenesis of melanoma [51–53•]

medication is approved for this genetic subtype of melanoma, MEK inhibitors lead to responses some in preclinical models [64] as well as clinical trials [65–67].

The most commonly mutated tumor suppressor gene NF1 is mutated in 13–17% of melanomas [49••, 68] and it is reported to carry loss of function mutations only in malignant tumors [63]. So far, no final clinical translation has been made for this mutation.

Triple Wild-Type Melanoma

Triple wt melanomas not only fails to show any of the most common mutations but these also harbor less UV signature, as compared to BRAF-, NRAS-, or NF1-mutated tumors [49••] (30% vs over 90%). Yet, these melanomas have more copy number alterations and complex structure changes. The triple wt tumors also show less loss of function mutations in tumor suppressor genes CDKN2A and TP53 [53•, 57, 69], but more of those seen in non-cutaneous melanomas, such as KIT, GNAQ, GNA1, and CTNNB1 [49••]. As KIT-mutated melanomas can be targeted with KIT inhibitors (imatinib and nilotinib), testing for KIT mutation is reasonable in BRAF wild-type melanomas [70, 71].

UV Signature and Epigenetic Regulation

UV light has long been reported to contribute highly to the development of melanoma, and the highest mutational load is observed in primary melanomas of ultraviolet (UV)-exposed non-glabrous skin (111 per Mb), whereas the lowest load is reported in patients with primary melanomas of glabrous skin and without the history of chronic sun exposure (3–14 per Mb) [50]. In 2015, the Cancer Genome Atlas (TCGA) Network published the data from the largest patient integrative analysis of cutaneous melanomas and observed mutations, representing the UV signature in 76% of primary and 84% of metastatic melanomas, independent of the site of primary tumor [49••]. This is, in part, an explanation for the impressive response to immunotherapies seen in cutaneous melanoma [72••, 73•, 74•], as high tumor mutational burden has been reported to be associated with higher response rates in anti-PD-1 therapy in a wide range of malignancies [75].

Epigenetic regulation causes changes in gene expression without affecting the DNA sequence alterations [76], typically through histone modification, chromatin remodeling complexes, and DNA methylation or demethylation [77]. A third of the 40 most commonly mutated genes in melanoma were found in the genes of epigenetic regulation, with up to 90% of melanoma samples showing a mutation in at least one gene associated with epigenetic regulation (e.g., genes responsible for histone modification and/or chromatin remodeling) [57].

A recent publication on high response rate to immunotherapy with anti-PD-1 antibody in desmoplastic melanomas (DM) hypothesize that high mutational burden, known to be typical for DM and also for other cutaneous melanomas [48, 49••, 50], is strongly contributing to the efficacy of the therapy [78]. Since immunotherapy is being more actively implemented in early adjuvant setting [79•], the mutational burden might be used as a biomarker for response to treatment.

Mutations in Different Subtypes of Melanoma

The genetic diversity of the various melanoma subtypes can be translated into optimal choices in the pharmacological treatment. SSM and NM often carry genomic alterations of clinical relevance, such as BRAF mutations. On the contrary, only 10–20% of melanomas arising in mucosal or acral locations harbor a MAPK pathway mutation [80]. Mutations or genomic amplification of KIT are predominantly found in acral and mucosal melanoma, with incidences of 10–20% and 20–30%, respectively; whereas, they are rarely identified in other subtypes of melanoma [13, 81]. In contrast, NRAS mutations occur with a fairly consistent prevalence rate of 15–20% in all subtypes of cutaneous and mucosal melanoma [82].

Pharmacological Treatment Approaches

Kinase inhibitors targeting the BRAF and MEK oncoproteins as well as checkpoint inhibitors have become indispensable treatment agents in the treatment of metastatic patients [3•, 72••]. Still, the mechanisms of resistance as well as potential biomarkers of response to these agents are currently elucidated, giving rise to innovative treatments and treatment combinations. Genomic alterations in the BRAF oncogene is associated with response to BRAF and MEK inhibitors. Also, MEK inhibitors have been evaluated to show some significant therapeutic response in NRAS-mutant subtypes [67]. The addition of a third inhibitor is currently being investigated in clinical trials, aiming to overcome resistance mechanisms and improve the patient outcomes. Candidates for third agents are cyclin-dependent kinase inhibitors (CDK), receptor tyrosine kinase (RTK) inhibitors, or an inhibitor targeting the phosphoinositide 3-kinase of the PI3K-pathway (Fig. 1) (NCT02159066) [83, 84]. Moreover, further molecular targets of the MAPK pathway are being tested in ongoing phase I trials, including ERK and CRAF/BRAF inhibitors (NCT02711345 and NCT02607813). As BRAF inhibition has also been shown to be associated with an increased expression of

programmed death-ligand 1 (PD-L1) [85], combination therapy of BRAF/MEK inhibitors and anti-PD1 is currently examined in ongoing clinical studies (NCT02130466, NCT02967692, and NCT02908672). Checkpoint inhibitors targeting the interaction between the immune system and the tumor cell are particularly interesting as they are mutation independent and therefore seem to possibly target all melanomas. Yet, not all melanomas respond to immunotherapy, and further research has to elucidate the mechanisms of resistance here. As ALM and MM rarely carry BRAF mutations, studies were recently performed, investigating the effect of KIT inhibitors on KIT-mutated melanoma (NCT00424515 and NCT00788775). A clinical trial in patients with KIT-mutated or amplified ALM and MM showed treatment responses of 23.3% with imatinib [86].

Conclusion

Melanoma of the skin shows clear differences in incidence, mortality, genomic profile, and anatomic presentation dependent on the patient's country of residence, ethnicity, and socioeconomic status. As the incidence of melanoma is increasing in both industrial and non-industrial countries, the development of new treatment options and strategies is crucial. Although the implementation of innovative therapies has dramatically improved patient outcomes during the recent years, the high costs are beyond affordable possibilities of health care systems in many non-developed countries. This leads to important treatment and subsequently overall survival disparities. Improved understanding of marked ethnical and genetic differences in melanoma causality and presentation may improve therapeutic developments and prevention strategies.

Compliance with Ethical Standards

Conflict of Interest Florentia Dimitriou declares that she has no conflict of interest.

Regina Krattinger declares that she has no conflict of interest.

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References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. American Cancer Society. Cancer facts and figures 2018. Atlanta: American Cancer Society; 2018.
2. Mort RL, Jackson IJ, Patton EE. The melanocyte lineage in development and disease. Development. 2015;142(7):1387.
3.• Ugurel S, Rohmel J, Ascierto PA, Flaherty KT, Grob JJ, Hauschild A, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies. Eur J Cancer. 2016;53:125–34. **An exploratory analysis of survival data from selected clinical trials representative for the new treatment strategies in advanced metastatic melanoma.**
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30.
5. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–86.
6. Karimkhani C, Green AC, Nijsten T, Weinstock MA, Dellavalle RP, Naghavi M, et al. The global burden of melanoma: results from the global burden of disease study 2015. Br J Dermatol. 2017;177(1):134–40.
7. Whiteman DC, Green AC, Olsen CM. The growing burden of invasive melanoma: projections of incidence rates and numbers of new cases in six susceptible populations through 2031. J Invest Dermatol. 2016;136(6):1161–71.
8. Australian Institute of Health and Welfare (AIHW). 2014 Australian Cancer Database pivot table. Canberra: AIHW; 2017. <http://www.aihw.gov.au/cancer-data>
9. Aitken JF, Youlden DR, Baade PD, Soyer HP, Green AC, Smithers BM. Generational shift in melanoma incidence and mortality in Queensland, Australia, 1995–2014. Int J Cancer. 2018;142(8):1528–35.
10. Ghiasvand R, Rueegg CS, Weiderpass E, Green AC, Lund E, Veierod MB. Indoor tanning and melanoma risk: long-term evidence from a prospective population-based cohort study. Am J Epidemiol. 2017;185(3):147–56.
11. National Cancer Institute Surveillance, Epidemiology and End Results program. SEER stat fact sheets: melanoma of the skin. Available at: https://seer.cancer.gov/statfacts/html/melan.html.
12. Mahendraraj K, Sidhu K, Lau CS, McRoy GJ, Chamberlain RS, Smith FO. Malignant melanoma in African-Americans: a population-based clinical outcomes study involving 1106 African-American patients from the surveillance, epidemiology, and end result (SEER) database (1988-2011). Medicine (Baltimore). 2017;96(15):e6258.
13. Desai A, Ugorji R, Khachemoune A. Acral melanoma foot lesions. Part 1: epidemiology, aetiology, and molecular pathology. Clin Exp Dermatol. 2017;42(8):845–8.
14. Steliarova-Foucher E, O'Callaghan M, Ferlay J, Masuyer E, Forman D, Comber H, Bray F: European cancer observatory: cancer incidence, mortality, prevalence and survival in Europe. Version 1.0 (September 2012) European Network of Cancer Registries, International Agency for Research on Cancer. Available from http://eco.iarc.fr.
15. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374–403.

16. Forsea AM, Del Marmol V, de Vries E, Bailey EE, Geller AC. Melanoma incidence and mortality in Europe: new estimates, persistent disparities. Br J Dermatol. 2012;167(5):1124–30.
17. Liu F, Bessonova L, Taylor TH, Ziogas A, Meyskens FL Jr, Anton-Culver H. A unique gender difference in early onset melanoma implies that in addition to ultraviolet light exposure other causative factors are important. Pigment Cell Melanoma Res. 2013;26(1):128–35.
18. Liu-Smith F, Farhat AM, Arce A, Ziogas A, Taylor T, Wang Z, et al. Sex differences in the association of cutaneous melanoma incidence rates and geographic ultraviolet light exposure. J Am Acad Dermatol. 2017;76(3):499–505.e3.
19. Liu-Smith F, Ziogas A. An age-dependent interaction between sex and geographical UV index in melanoma risk. J Am Acad Dermatol. 2017. https://doi.org/10.1016/j.jaad.2017.11.049.
20. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER cancer statistics review, 1975–2014, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.
21. Joosse A, Collette S, Suciu S, Nijsten T, Patel PM, Keilholz U, 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. 2013;31(18):2337–46.
22. Courtenay WH. Constructions of masculinity and their influence on men's well-being: a theory of gender and health. Soc Sci Med. 2000;50(10):1385–401.
23. Baade P, Meng X, Youlden D, Aitken J, Youl P. Time trends and latitudinal differences in melanoma thickness distribution in Australia, 1990-2006. Int J Cancer. 2012;130(1):170–8.
24. de Vries E, Bray FI, Eggermont AM, Coebergh JW, European Network of Cancer R. Monitoring stage-specific trends in melanoma incidence across Europe reveals the need for more complete information on diagnostic characteristics. Eur J Cancer Prev. 2004;13(5):387–95.
25. Geller AC, Clapp RW, Sober AJ, Gonsalves L, Mueller L, Christiansen CL, et al. Melanoma epidemic: an analysis of six decades of data from the Connecticut Tumor Registry. J Clin Oncol. 2013;31(33):4172–8.
26.•• Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(6):472–92. **An evidence-based revision of the AJCC melanoma staging for 2017.**
27. Whiteman DC, Baade PD, Olsen CM. More people die from thin melanomas (1 mm) than from thick melanomas (>4 mm) in Queensland. Australia J Invest Dermatol. 2015;135(4):1190–3.
28. Criscione VD, Weinstock MA. Melanoma thickness trends in the United States, 1988-2006. J Invest Dermatol. 2010;130(3):793–7.
29. Koh HK, Geller AC, Miller DR, Grossbart TA, Lew RA. Prevention and early detection strategies for melanoma and skin cancer. Current status Arch Dermatol. 1996;132(4):436–43.
30. Armstrong BK, Cust AE. Sun exposure and skin cancer, and the puzzle of cutaneous melanoma: a perspective on Fears et al. mathematical models of age and ultraviolet effects on the incidence of skin cancer among whites in the United States. Am J Epidemiol. 1977;105:420–7. Cancer Epidemiol. 2017;48:147–56
31. D'Orazio J, Jarrett S, Amaro-Ortiz A, Scott T. UV radiation and the skin. Int J Mol Sci. 2013;14(6):12222–48.
32. Colantonio S, Bracken MB, Beecker J. The association of indoor tanning and melanoma in adults: systematic review and meta-analysis. J Am Acad Dermatol. 2014;70(5):847–57. e1–18
33. Pawlak MT, Bui M, Amir M, Burkhardt DL, Chen AK, Dellavalle RP. Legislation restricting access to indoor tanning throughout the world. Arch Dermatol. 2012;148(9):1006–12.
34. Bevona C, Goggins W, Quinn T, Fullerton J, Tsao H. Cutaneous melanomas associated with nevi. Arch Dermatol. 2003;139(12):1620–4. discussion 4
35. Haenssle HA, Mograby N, Ngassa A, Buhl T, Emmert S, Schon MP, et al. Association of patient risk factors and frequency of nevus-associated cutaneous melanomas. JAMA Dermatol. 2016;152(3):291–8.
36. Whiteman DC, Stickley M, Watt P, Hughes MC, Davis MB, Green AC. Anatomic site, sun exposure, and risk of cutaneous melanoma. J Clin Oncol. 2006;24(19):3172–7.
37. Whiteman DC, Pavan WJ, Bastian BC. The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin. Pigment Cell Melanoma Res. 2011;24(5):879–97.
38.• Shain AH, Bastian BC. From melanocytes to melanomas. Nat Rev Cancer. 2016;16(6):345–58. **A review analysis of tumour evolution that integrate genetic, histopathological, clinical and biological insights for melanoma.**
39. Demierre MF, Chung C, Miller DR, Geller AC. Early detection of thick melanomas in the United States: beware of the nodular subtype. Arch Dermatol. 2005;141(6):745–50.
40. Lino-Silva LS, Dominguez-Rodriguez JA, Aguilar-Romero JM, Martinez-Said H, Salcedo-Hernandez RA, Garcia-Perez L, et al. Melanoma in Mexico: clinicopathologic features in a population with predominance of acral lentiginous subtype. Ann Surg Oncol. 2016;23(13):4189–94.
41. Watts CG, Madronio C, Morton RL, Goumas C, Armstrong BK, Curtin A, et al. Clinical features associated with individuals at higher risk of melanoma: a population-based study. JAMA Dermatol. 2017;153(1):23–9.
42. Barysch MJ, Levesque MP, Cheng P, Karpova MB, Mihic-Probst D, Civenni G, et al. Coexpression of SOX10/CD271 (p75(NTR)) and beta-galactosidase in large to giant congenital melanocytic nevi of pediatric patients. Dermatopathology (Basel). 2014;1(1):35–46.
43. Krengel S, Hauschild A, Schafer T. Melanoma risk in congenital melanocytic naevi: a systematic review. Br J Dermatol. 2006;155(1):1–8.
44. van der Leest RJ, Flohil SC, Arends LR, de Vries E, Nijsten T. Risk of subsequent cutaneous malignancy in patients with prior melanoma: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2015;29(6):1053–62.
45. Kubica AW, Brewer JD. Melanoma in immunosuppressed patients. Mayo Clin Proc. 2012;87(10):991–1003.
46. Bonilla X, Parmentier L, King B, Bezrukov F, Kaya G, Zoete V, et al. Genomic analysis identifies new drivers and progression pathways in skin basal cell carcinoma. Nat Genet. 2016;48(4):398–406.
47. Lawrence MS, Stojanov P, Polak P, Kryukov GV, Cibulskis K, Sivachenko A, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature. 2013;499(7457):214–8.
48. Alexandrov LB, Nik-Zainal S, Wedge DC, Campbell PJ, Stratton MR. Deciphering signatures of mutational processes operative in human cancer. Cell Rep. 2013;3(1):246–59.
49.•• Cancer Genome Atlas N. Genomic classification of cutaneous melanoma. Cell. 2015;161(7):1681–96. **Clinicopathological and multi-dimensional analysis of the genomic alterations in cutaneous melanomas.**
50. Berger MF, Hodis E, Heffernan TP, Deribe YL, Lawrence MS, Protopopov A, et al. Melanoma genome sequencing reveals frequent PREX2 mutations. Nature. 2012;485(7399):502–6.
51. Sullivan RJ, Flaherty K. MAP kinase signaling and inhibition in melanoma. Oncogene. 2013;32(19):2373–9.

52. Nissan MH, Pratilas CA, Jones AM, Ramirez R, Won H, Liu C, et al. Loss of NF1 in cutaneous melanoma is associated with RAS activation and MEK dependence. Cancer Res. 2014;74(8):2340–50.
53.• Hayward NK, Wilmott JS, Waddell N, Johansson PA, Field MA, Nones K, et al. Whole-genome landscapes of major melanoma subtypes. Nature. 2017;545(7653):175–80. **An analysis of whole-genome sequences from cutaneous, acral and mucosal subtypes of melanoma**
54. Kulikova K, Kibardin A, Gnuchev NV, Georgiev GP, Larin S. Wnt signaling pathway and its significance for melanoma development. CTM Modern Technologies in Medicine. 2012:107–11.
55. Sullivan RJ. The role of mitogen-activated protein targeting in melanoma beyond BRAFV600. Curr Opin Oncol. 2016;28(2):185–91.
56. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature. 2002;417(6892):949–54.
57. Lee JJ, Sholl LM, Lindeman NI, Granter SR, Laga AC, Shivdasani P, et al. Targeted next-generation sequencing reveals high frequency of mutations in epigenetic regulators across treatment-naive patient melanomas. Clin Epigenetics. 2015;7:59.
58. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. Cancer genome landscapes. Science. 2013;339(6127):1546–58.
59. Klein O, Clements A, Menzies AM, O'Toole S, Kefford RF, Long GV. BRAF inhibitor activity in V600R metastatic melanoma–response. Eur J Cancer. 2013;49(7):1797–8.
60. Dahlman KB, Xia J, Hutchinson K, Ng C, Hucks D, Jia P, et al. BRAF (L597) mutations in melanoma are associated with sensitivity to MEK inhibitors. Cancer Discov. 2012;2(9):791–7.
61. Damsky WE, Bosenberg M. Melanocytic nevi and melanoma: unraveling a complex relationship. Oncogene. 2017;36(42):5771–92.
62. Damsky W, Micevic G, Meeth K, Muthusamy V, Curley DP, Santhanakrishnan M, et al. mTORC1 activation blocks BrafV600E-induced growth arrest but is insufficient for melanoma formation. Cancer Cell. 2015;27(1):41–56.
63. Shain AH, Yeh I, Kovalyshyn I, Sriharan A, Talevich E, Gagnon A, et al. The genetic evolution of melanoma from precursor lesions. N Engl J Med. 2015;373(20):1926–36.
64. Dong M, Liu X, Evert K, Utpatel K, Peters M, Zhang S, et al. Efficacy of MEK inhibition in a K-Ras-driven cholangiocarcinoma preclinical model. Cell Death Dis. 2018;9(2):31.
65. Sosman JA, Kittaneh M, Lolkema MPJK, Postow MA, Schwartz G, Franklin C, et al. A phase 1b/2 study of LEE011 in combination with binimetinib (MEK162) in patients with NRAS-mutant melanoma: early encouraging clinical activity. J Clin Oncol. 2014;32(15_suppl):9009.
66. Ascierto PA, Schadendorf D, Berking C, Agarwala SS, van Herpen CM, Queirolo P, et al. MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, open-label phase 2 study. Lancet Oncol. 2013;14(3):249–56.
67. Dummer R, Schadendorf D, Ascierto PA, Arance A, Dutriaux C, Di Giacomo AM, et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(4):435–45.
68. Krauthammer M, Kong Y, Bacchiocchi A, Evans P, Pornputtapong N, Wu C, et al. Exome sequencing identifies recurrent mutations in NF1 and RASopathy genes in sun-exposed melanomas. Nat Genet. 2015;47(9):996–1002.
69. Hodis E, Watson IR, Kryukov GV, Arold ST, Imielinski M, Theurillat JP, et al. A landscape of driver mutations in melanoma. Cell. 2012;150(2):251–63.
70. Tran A, Tawbi HA. A potential role for nilotinib in KIT-mutated melanoma. Expert Opin Investig Drugs. 2012;21(6):861–9.
71. Hodi FS, Corless CL, Giobbie-Hurder A, Fletcher JA, Zhu M, Marino-Enriquez A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol. 2013;31(26):3182–90.
72.•• Hodi FS, Chesney J, Pavlick AC, Robert C, Grossmann KF, DF MD, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol. 2016;17(11):1558–68. **This study reports a 3-year overall survival outcomes of a phase 3 clinical trial of nivolumab combined with ipilimumab in patients with advanced melanoma and shows that significantly longer overall survival occurred with combination therapy with nivolumab plus ipilimumab or with nivolumab alone than with ipilimumab alone.**
73.• Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320–30. **This phase 3 clinical trial showed that nivolumab was associated with significant improvements in overall survival and progression-free survival compared with dacarbazine.**
74.• Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015;16(8):908–18. **The results of this phase 2 clinical trial establish pembrolizumab as a new standard of care for the treatment of ipilimumab-refractory melanoma.**
75. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015;348(6230):124–8.
76. Moran B, Silva R, Perry AS, Gallagher WM. Epigenetics of malignant melanoma. Semin Cancer Biol. 2018;51:80–8.
77. Dawson MA, Kouzarides T. Cancer epigenetics: from mechanism to therapy. Cell. 2012;150(1):12–27.
78. Eroglu Z, Zaretsky JM, Hu-Lieskovan S, Kim DW, Algazi A, Johnson DB, et al. High response rate to PD-1 blockade in desmoplastic melanomas. Nature. 2018;553(7688):347–50.
79.• Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med. 2017;377(19):1824–35. **This randomized, double-blind, phase 3 trial of adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma showed that nivolumab resulted in significantly longer recurrence-free survival and lower rate of grade 3 or 4 adverse events than ipilimumab.**
80. Sullivan R, LoRusso P, Boerner S, Dummer R. Achievements and challenges of molecular targeted therapy in melanoma. Am Soc Clin Oncol Educ Book. 2015;35:177–86.
81. Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol. 2006;24(26):4340–6.
82. Munoz-Couselo E, Adelantado EZ, Ortiz C, Garcia JS, Perez-Garcia J. NRAS-mutant melanoma: current challenges and future prospect. Onco Targets Ther. 2017;10:3941–7.
83. Lee B, Sandhu S, McArthur G. Cell cycle control as a promising target in melanoma. Curr Opin Oncol. 2015;27(2):141–50.
84. Sullivan RJ, Fisher DE. Understanding the biology of melanoma and therapeutic implications. Hematol Oncol Clin North Am. 2014;28(3):437–53.
85. Jiang X, Zhou J, Giobbie-Hurder A, Wargo J, Hodi FS. The activation of MAPK in melanoma cells resistant to BRAF inhibition promotes PD-L1 expression that is reversible by MEK and PI3K inhibition. Clin Cancer Res. 2013;19(3):598–609.
86. Guo J, Si L, Kong Y, Flaherty KT, Xu X, Zhu Y, et al. Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. J Clin Oncol. 2011;29(21):2904–9.