EXPERT REVIEWS

Molecular targets in melanoma: time for 'ethnic personalization'

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Worldwide, the incidence of melanoma continues to rise. Although not the most common cutaneous malignancy, it is the most lethal. Until recently, while other oncologic patients benefited from the nuances of targeted therapy, those afflicted with melanoma lacked that option. In 2011, the US FDA approved an oral agent that targets the *BRAF* oncogene. As this information is promising, it is essential that other populations (in addition to Caucasians) are examined, in order to further comprehend the biology of melanoma. Recent studies profiling various ethnicities, including Asians, have provided novel data with respect to the molecular characterization (*c-KIT*, *BRAF*, *NRAS*) of melanoma. It is hopeful that the management of melanoma will be universally applicable to all ethnic groups.

Keywords: BRAF • c-KIT • ethnic personalization • melanoma • molecular profiling • NRAS • targeted therapy • vemurafenib

Although not the most common skin cancer, melanoma is the most lethal. The incidence of melanoma has continued to increase globally over the last 25 years [1]. When melanoma is diagnosed at an advanced stage, prognosis is poor and treatment becomes a daunting challenge [2]. Historically, the median progression-free survival for a patient with metastatic melanoma is less than 60 days, and the median overall survival is less than 12 months [3].

However, there is optimism for a promising future. The US FDA has recently approved novel therapies within the past year, including vemurafenib, an oral agent that targets the *BRAF* molecular oncogene. With the continued paradigm shift in the management of oncologic patients to a more personalized approach, one can hope that studying melanoma in various populations will glean insight into the biology of this abhorrent disease. Distinct groups may undoubtedly harbor a different genetic profile. Since Caucasians are most commonly affected by melanoma, most of the public acumen and clinical effort is focused on this cohort. However, in the minority population, melanoma is usually detected at a more advanced stage, distributed on sun-protected areas and associated with a worse survival [4]. Hu and colleagues found that non-Caucasians present with a more advanced stage; specifically, 18% of Hispanics and 26% of African–Americans had regional or distant disease, compared with 12% in Caucasians [5].

Previously, we reported in our study cohort of 185 patients that mean tumor thickness was 1.62 mm for Caucasians and 2.59 mm for non-Caucasians; interestingly, the acral lentiginous subtype comprised six out of 33 (18%) of the non-Caucasian patients with melanoma [6]. Cormier and investigators performed a large-scale review on the ethnic differences of melanoma among Hispanics, African–Americans, Native Americans, Asians and Caucasians. They found that the overall 5-year survival was 72–81% for minorities in comparison to 90% for Caucasians [7].

Although numerous studies have been conducted focusing on the epidemiology of melanoma, a paucity of molecular analysis exists in non-Caucasians. Therefore, investigation of this malignancy and its relevant signaling cascades among a wide range of ethnicities is warranted. This article will summarize the major receptor tyrosine kinases (RTKs) as well as signaling cascades, and subsequently highlight specific studies that have examined melanoma in under-represented minorities. The authors propose the term 'ethnic personalization'.

The poignant study by Curtin and colleagues in 2005 introduced a novel scheme to the classification of melanoma. They suggested that

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melanoma could be categorized based on the molecular characteristics [8]. Somatic alterations in several oncogenes were assessed and included *c-KIT*, *NRAS* and *BRAF*. They represent a milieu of cross-talking components of receptor tyrosine kinases as well as the MAPK and mTOR pathways.

Receptor tyrosine kinases

RTKs play an essential role in melanoma development and progression. Several RTKs including the PDGF receptor (PDGFR) and c-KIT have been deemed important. However, c-KIT appears to be the most clinically relevant RTK in melanoma. c-KIT, first identified in 1987 owing to the similarity in sequence to the Hardy–Zuckerman 4 feline sarcoma virus oncogene, is a proto-oncogene [9]. The ligand associated with c-KIT is stem cell factor. When initiated, c-KIT modulates tumor growth, migration and survival [9]. It is upstream to both the MAPK and mTOR pathways [10]. When c-KIT becomes phosphorylated, these signaling cascades become activated, leading to increased growth and survival in melanoma cells [11]. *c-KIT* mutations in cutaneous melanoma are associated with patients that are older in age and who have an extensive history of chronic sun exposure; acral and mucosal subtypes have been found to have a higher frequency of *c-KIT* mutations in comparison to other variants [12]. Curtin and colleagues noted that the incidence of *c-KIT* mutations and/or increased copy number was 39% in mucosal, 36% in acral and 28% in melanomas with chronic sun-damaged skin [12]. The most common type of *c-KIT* mutations include those that occur on exon 11 (L576P, V559A), exon 13 (K642E) and exon 17 (D816H) [13]. From a therapeutic standpoint, targeting this gene may be an effective strategy in melanoma. Imatinib, a multikinase inhibitor originally approved for the treatment of gastrointestinal tumors, has been tested in the treatment of melanoma. Although earlier studies did not demonstrate a clinical benefit utilizing imatinib, it was surmised that assessing for c-KIT was not performed *a priori*, which explained its failure in participants whose tumors lacked the somatic mutation [14,15]. The hope of imatinib as a therapeutic agent in melanoma began in 2008. Hodi and colleagues chronicled a patient with advanced mucosal melanoma whose tumor was found to have a *c-KIT* mutation on exon 11, who experienced a partial response [16]. This success was recapitulated by Lutzky and colleagues who demonstrated complete response in a patient with metastatic mucosal melanoma, whose tumor had a *c-KIT* mutation on exon 13 [17]. Shortly thereafter, preliminary results of a Phase II trial involving melanoma patients with unresectable acral, mucosal or chronic sun-damaged skin subtypes led by Carvajal and colleagues reported that three out of seven (43%) of those treated with *c-KIT* mutations achieved a partial response to imatinib [18]. Their follow-up study of the entire 25 patients treated and assessed with either a *c-KIT* mutation (21 subjects) or amplification (four subjects) noted an overall durable response rate of 16%, with a median overall survival of nearly 1 year (46.3 weeks) [19]. The authors also ascertained whether specific mutations of the *c-KIT* oncogene would be more susceptible to imatinib. Mutations in *c-KIT* were found in 18 out of 84 (21%) of acral melanomas, 17 out of 93 (18%) of mucosal melanomas and five out of 32 (16%) of melanomas with chronic sun-damaged skin. A total of 21 patients that exhibited a *c-KIT* mutation were treated with imatinib and had their responses monitored. Six of these patients had an objective repose (four partial and two complete). They observed that all of the responders possessed either a mutation on exon 11 (specifically L576P) or exon 13 (specifically K642E). What is compelling is that several mutations that were not thought to be common in melanoma were identified including exon 9 (N463S) and exon 18 (V85212); additionally mutations on exon 13 (V654A) and exon 17 (D820Y) were observed. This is significant because these mutations are thought to be resistant to imatinib therapy. Current trials employing similar agents such as dasatinib, nilotinib and masitinib require the presence of a *c-KIT* mutation as a prerequisite for enrollment. These targeted agents are classified as second-generation c-KIT inhibitors and are thought to be more specific.

MAPK

Downstream to c-KIT, MAPK is an important pathway in melanoma progression and invasion [20]. Two prominent oncogenes include *RAS* and *RAF*. *RAS* was first noted in rats that had sarcoma viruses in the 1960s. *RAS* mutations occur in approximately 15% of cutaneous melanomas [21]. Most mutations that involve RAS in melanoma involve the NRAS isoform. Data linking *NRAS* mutational status with aggression and survival have been limited until recently. Devitt and his group from Australia reported that *NRAS* mutation on exon 2 was associated with higher rates of tumor proliferation and was predictive of a decreased melanoma-specific survival [22]. They found that 75% of *NRAS* mutations occurred in tumors that displayed a Breslow thickness of >1 mm and had >1 mitosis per mm^2. Although NRAS could be utilized as a potential prognosticator in the future, it lacks potential as a therapeutic target. The primary rationale is that NRAS is not a kinase and instead a GTPase [23]. RAF, which is downstream to RAS, is part of a family of serine/threonine kinases. The *BRAF* isoform has been widely regarded as the most common somatic mutation in melanoma; it has been reportedly present in approximately 50% of melanomas [24]. BRAF-related tumors tend to occur on skin that has been intermittently exposed to sun rather than chronically sun damaged. When altered, it can activate downstream signaling of the MAPK pathway that is involved in cell proliferation, survival and invasion.

Unlike NRAS, tumors harboring a *BRAF* mutation have been shown to possess a promising therapeutic target [25]. The primary V600E mutation occurs on exon 15. The V600E mutation is the most common alteration, present more than 80% of the time [26]. The introduction of targeted therapy against BRAF began with sorafenib. Sorafenib is a multikinase inhibitor that opposes BRAF, CRAF, VEGF receptor 2 and PDGFR activity. In 2006, Eisen *et al.* reported that it was not effective as single-agent therapy in patients with metastatic melanoma [27]. It was thought that combining this agent with chemotherapy would augment a therapeutic response. However, Phase II and III trials employing drugs such as carboplatin did not improve survival [28,29]. Sorafenib was abandoned as a viable option in

patients with advanced melanoma. The genuine promise of selective BRAF inhibitor therapy against melanoma began in 2010. PLX4032 (as it was named at the time) is an oral agent that was found in a Phase I trial to cause tumor shrinkage in 70% of the patients [25]. A subsequent multicenter Phase II trial in previously treated patients with *BRAF* V600E-mutation-positive melanoma revealed a response rate of more than 50%; the median duration of response was 6.7 months [30]. These results created enough optimism to allow the implementation of a multicenter Phase III trial in metastatic melanoma: BRIM 3.

This trial, which was completed in 2011, provided evidence that a small molecular inhibitor could provide survival benefit [26]. With this, the promise of targeted therapy for melanoma was validated. Overall survival was ascertained in 672 patients. Since the first interim analysis illustrated improved progression-free and overall survival in the vemurafenib cohort, participants who were in the dacarbazine arm were allowed to cross over. The median progression-free survival for the vemurafenib arm was 5.3 months, compared with 1.6 months for the dacarbazine arm. Assessment at 6 months revealed that overall survival was 84% in the vemurafenib group versus 64% for the dacarbazine group. Although there appeared to be a favorable response rate of 48%, the rest of the participants did not display sensitivity to this agent. In addition, 18% of recipients developed cutaneous squamous cell carcinoma or keratoacanthoma. Therefore, although there is optimism for selective BRAF inhibitors, there is concern that resistance and escape mechanisms are present that complicate the management of melanoma. Several investigators have discovered plausible evidence that implicates other components. Nazarian *et al.* found that resistance can be acquired via mutation in the *NRAS* oncogene or via increased expression of the RTK PDGFR-β [31]. In addition, Johannessen *et al.* found that the MAPK pathway is reactivated by MAPK 8 (COT), which promotes resistance to BRAF inhibitors [32]. It is thought that complete elimination of metastatic melanoma with single-agent BRAF inhibition is unlikely. Other downstream effectors within the MAPK cascade are believed to be essential targets. MEK can be activated by *BRAF* mutation. Thereafter, this leads to constitutive perpetuation of the MAPK pathway with subsequent melanoma cell proliferation and metabolism. MEK inhibitors initially appeared to be more efficacious in the setting of *BRAF*-mutant tumors [33].

However, in a Phase II trial employing the MEK inhibitor AZD6244, only five out of 42 (12%) patients that possessed the *BRAF* mutation exhibited an objective response. Furthermore, a recently described mutation in *MEK1* was discerned in a patient who recurred 23 weeks after a dramatic response to targeted BRAF therapy [34]. A Phase III trial comparing a MEK1/2 inhibitor versus either dacarbazine or paclitaxel in patients whose tumors manifest the *BRAF* mutation is currently underway. Undoubtedly, combining BRAF and MEK inhibitors will become a viable strategy for future trials.

mTOR

In addition to the MAPK pathway, another signaling cascade that has been implicated in the pathogenesis of melanoma is the mTOR pathway. It plays a central role in cell proliferation, apoptosis, angiogenesis, metabolism and chemoresistance [35]. PI3K, which is at the pinnacle of this pathway, can be stimulated by activating mutations in its own subunits, RTK or NRAS, thus demonstrating the potential influence by the MAPK pathway. Downstream to PI3K is Akt. Akt, also known as protein kinase B, is an oncogene that plays a crucial task in cellular survival and apoptosis [36]. Prior studies have demonstrated that increased expression of Akt in melanoma is associated with tumor progression and worse outcome [36,37]. No agent targeted against either PI3K or Akt has shown to be clinically beneficial in melanoma patients. mTOR in itself is a serine/threonine kinase that effectively regulates the production of VEGF, cell growth and proliferation [38].

Although a North Central Cancer Treatment Group Phase II study utilizing everolimus (an mTOR inhibitor) with temozolamide did not demonstrate a therapeutic benefit over temozolamide alone, the treatment was well tolerated [39]. The patients were not molecularly profiled before enrollment. A Phase II study that incorporated an angiogenesis inhibitor bevacizumab with the mTOR inhibitor everolimus reported that 12% of melanoma patients achieved a major response [40]. Currently, a Phase II trial of the mTOR inhibitor temsirolimus combined with the MEK inhibitor AZD 6244 in treatment-naive patients with *BRAF*-mutant stage IV melanoma is ongoing. Fundamentally, targeting these constituents of the mTOR pathway in melanoma has not exhibited clinical benefit, as it has for other histologies including renal cell carcinoma and pancreatic neuroendocrine tumors. It is hopeful that combinatorial therapy incorporating the MAPK and mTOR pathways will become a valuable tool in the armamentarium against melanoma.

Molecular studies in non-Caucasians

Despite all of the aforementioned molecular studies that have been conducted in melanoma, there is a significant lack of large-scale analyses amongst the minority population. The literature provides a paucity of data in African–Americans, Native Americans, Hispanics and Hawaiian/Pacific Islanders; recently, comprehensive molecular studies have been performed in Asians.

African–Americans

African–Americans have a low incidence of melanoma; however, they have a worse outcome when compared with their Caucasian counterparts [7]. In a Surveillance, Epidemiology and End Results analysis of nearly 50,000 patients with melanoma, African–Americans were noted to have a 5-year melanoma-specific survival of only 72% in comparison to Caucasians' 90%. When compared with Caucasians, they had a nearly 1.5-fold higher rate of risk-adjusted, stage-specific mortality. Despite this disparity, there is a significant lack of mutational investigation to account for this discrepancy. A prior study in 2008 by Akslen *et al.* analyzed 26 African–American patients with acral melanoma [41]. The investigators found that three patients (12%) had *NRAS* mutations and two patients (8%) had *BRAF* mutations. Interestingly, all of the *NRAS* mutations were on exon 1, while the vast majority of Caucasians had their mutations on exon 2.

In addition, one of the two African–American patients who had a *BRAF* mutation possessed it on exon 11 and not on the most frequent exon 15.

Asians (Japanese)

An earlier study by Maldonado and colleagues determined that in their 27 Japanese patients with melanoma, there was no difference in the frequency of *BRAF* mutation when compared to the rest of the non-Japanese cohort [42]. However, they did not specify the exact figures. In 2004, Sasaki *et al.* evaluated 35 Japanese patients for *NRAS* and *BRAF* mutations [43]. No *NRAS* mutations were found. However, *BRAF* mutations were disclosed in nine out of 35 (26%) of the patients. This included five out of 15 patients (33%) in the acral subtype. Takata and colleagues analyzed 28 Japanese patients with acral melanoma and found that one out of 28 patients (4%) had a *NRAS* mutation and three out of 28 patients (11%) had a *BRAF* mutation [44]. In 2010, Terada assessed 12 Japanese patients with melanoma for c-KIT. Two patients had the acral subtype, three had chronic sun-damaged skin and seven had nonchronically sun-damaged skin. Only one acral melanoma patient had a *c-KIT* mutation, which occurred on exon 11 [45].

Asians (Koreans)

A recent study detailed the molecular alterations in Korean patients with melanoma [46]. The authors chose to measure the frequency of *NRAS*, *BRAF* and *c-KIT* mutations, as well as *c-KIT* alterations, in what is believed to be the largest cohort of Korean patients analyzed to date. Ninety-seven patients with acral or mucosal melanoma between 1997 and 2010 were included. Among 47 patients screened for *NRAS* (exon 1), only one patient with rectal melanoma had a mutation. *BRAF* was ascertained in 49 patients and only one (rectal melanoma) had a mutation (exon 15). However, when mutations for *c-KIT* on exons 11, 13, 17 and 18 were ascertained in 92 cases of acral/mucosal melanoma, seven mutations (8%) were found. For these seven *c-KIT* mutations, five were on exon 11, one on exon 17 and one on exon 18. A mutation on exon 11 that was previously not reported was identified (Thr574Ala). Increased *c-KIT* copy number was detected in 15 out of 49 patients (31%). What is compelling is that the authors did not find the common *c-KIT* missense mutations such as W557R, V559A and V559D. They suggest that there may be ethnic differences. This validates the impetus for similar studies that need to be conducted in minority populations. The same aforementioned investigators from Korea also reported the preliminary results of a Phase II trial implementing nilotinib in metastatic melanomas harboring *c-KIT* mutations or amplifications [47]. Nilotinib is a multikinase inhibitor of c-KIT and PDGFR. Eleven patients were enrolled, including nine that were available for assessment of response to therapy. Among those nine patients, eight were from acral sites and one was mucosal (vagina). Response rate was two out of nine patients (22%). Five (56%) of the patients had stable disease. The two patients that partially responded harbored mutations on exon 11. Patients that contained the *c-KIT* mutation had a better outcome than those that displayed increased amplification; median progression free-survival was 8.4 months versus 1.7 months, respectively. Although this study had a small number of patients enrolled, it demonstrated that nilotinib may have promise in melanoma patients that are appropriately selected on the basis of their precise molecular profile.

Asians (Chinese)

The worldwide population of non-Caucasians, including the Chinese who comprise nearly 20% of the 7 billion people, continues to expand. Although rare in comparison to other ethnicities, there is concern that prognosis in Chinese patients may be worse. A study by Chi and colleagues published in 2011 reviewed 522 Chinese patients from January 2006 to March 2010 [48]. Not surprisingly, acral melanoma comprised the most common variant (218 out of 522 patients; 42%); mucosal melanoma was the second most frequent type (118 out of 522 patients; 23%). Nearly 20% were nodular, 6% superficial spreading, with the remainder consisting of lentigo maligna and unspecified types. In comparison to the USA, the overwhelming majority of patients had either acral or mucosal melanoma. The 5-year overall survival for the entire cohort was 42%, with a median survival time of 43 months, while disease-free survival was 12%, with a median survival time of 20 months. Stage and ulceration were predictors of overall survival. Of note is that the majority of patients had stage II or higher disease. Owing to the rarity, it is surmised that the lack of recognition and awareness contributed to the poor outcomes.

In 2012, Si and colleagues analyzed mutations for both *BRAF* and *NRAS* in 432 Chinese melanoma patients [49]. Overall, mutations for *BRAF* were seen in 110 out of 432 patients (26%) and mutations for *NRAS* in 31 out of 432 patients (7%). Acral (148 out of 432 patients; 34%) and mucosal (120 out of 432 patients; 28%) subtypes together comprised the vast majority of the sample size. Unlike other reports with a large non-Caucasian sample size, their study also included patients with chronic sun-induced damage (n = 22) and those without chronic sun-induced damage (n = 98), while the primary was unknown in 44 patients. For acral melanoma, *BRAF* mutation was found in 16% of patients, as opposed to Curtin and colleagues who reported a higher rate of 23%; for melanomas that arise from skin without chronic sun-induced damage, *BRAF* mutation was seen in 57% of patients, similar to Curtin and colleagues' reported rate of 59% [8]. For melanomas that were associated with chronic sun-induced damage, Si's group reported a *BRAF* mutational rate of 18% while Curtin's group reported 11%. Similar to Curtin's study, in which *NRAS* mutations in the acral subtype were reported in 10% of patients, Si's group reported that these mutations occurred in 9% of their patients. However, for other subtypes of melanoma, *NRAS* mutation rates were disparate between studies. For melanomas that arose from skin without chronic sun-induced damage, *NRAS* mutation frequency was only 2% as opposed to Curtin and colleagues' findings of 22%; in addition, for melanomas that are associated with chronic sun-induced damage, *NRAS* mutation frequency was only 5% in comparison to Curtin's 15%. As is true with

other studies, the most common *BRAF* mutation was on exon 15 V600E. However, what is fascinating is that three novel mutations on exon 11 were discovered, for example G442S, W450Stop and I457T. The most common *NRAS* mutation was on exon 2. Furthermore, what is intriguing is that two cases of patients with metastatic melanoma concomitantly had *BRAF* and *NRAS* mutations, although they are commonly believed to be mutually exclusive [50]. The authors examined whether mutational status was associated with traditional negative prognostic features. Ulceration was present in 228 out of 383 (60%) patients. They found that *BRAF*-mutant patients (61%) had a higher chance of ulceration as opposed to *BRAF*-wild-type patients (41%). In addition, *NRAS*-mutant patients (64%) had a higher likelihood of ulceration than their nonmutant counterparts (41%). The authors suggest that *BRAF* or *NRAS* patients with melanoma had higher proclivity for ulceration. Furthermore, they found that patients who had a *BRAF* mutation had a worse median survival (33 months) than patients who lacked this mutation (53 months). In addition, patients that possessed the *NRAS* mutation had a worse outcome (33 months) when compared with those that did not have the *NRAS* mutation (48 months). The finding of NRAS as a negative prognosticator has also been declared by Devitt and colleagues in 2011 [22]. Earlier investigators who primarily analyzed a Caucasian cohort of patients with melanoma did not find that *BRAF* or *NRAS* influenced survival [51]. Although Si and colleagues found that the *BRAF* mutational rate was 26%, Qi and investigators who analyzed 195 Chinese patients with melanoma found that the frequency was 15% [52]. Si and colleagues speculate that this could be attributed to a smaller sample size [49]. Nevertheless, Si's study, whereby principally primary lesions were inspected, provides data that *BRAF* and *NRAS* may be potentially utilized as surrogate predictors of outcome. Their group also advocated a similar concept for *c-KIT* mutational status [53]. These investigators analyzed 502 patients with all major variants of melanoma. Acral (193 out of 502 patients; 38%) and mucosal (167 out of 502 patients; 33%) subtypes were the most common entities within the cohort. The remainder consisted of 62 out of 502 patients (12%) with nonchronic sun-damaged skin, 51 out of 502 patients (10%) unknown primary and 29 out of 502 patients (6%) with chronic sun-damaged skin. *c-KIT* mutational rates were 54 out of 502 patients (11%) for the entire study sample and were distributed as follows: acral 12%, mucosal 10%, nonchronic sun-damaged skin 8%, unknown primary 8% and chronic sun-damaged skin 21%. Increased copy number was seen in 37 patients (7% of the entire cohort) and categorized accordingly: acral 7%, mucosal 10%, nonchronic sun-damaged skin 3%, unknown primary 6% and chronic sun-damaged skin 3%. With respect to the types of *c-KIT* mutations, 39 different mutations were detected; the most common was L576P on exon 11. More importantly is that 25 of the 39 different types of mutations were novel. The authors found that patients who had a *c-KIT* mutation had a worse overall survival (30 months) than those who did not harbor a mutation (53 months). The investigators combined *c-KIT* mutation with increased copy number to determine if aberrations were deemed to be an adverse prognostic indicator of survival. They found that those with *c-KIT* aberrations had a worse outcome (32 months) than those without (55 months). No other study has claimed this conclusion and therefore it is imperative that continued analyses of this nature be performed.

Another study conducted by Guo and colleagues involved a large cohort of Chinese patients with advanced melanoma with *c-KIT* alterations [54]. Since Asians have a higher preponderance of acral and mucosal melanomas, this population warranted investigation. Forty three patients with metastatic melanoma were enrolled in a Phase II trial with imatinib. All patients had to harbor a *c-KIT* mutation (40 out of 43 patients; 93%) or amplification (three out of 43 patients; 7%). The variants of melanoma included acral (n = 21), mucosal (n = 11), chronic sun-damaged skin (n = 5), nonchronic sun-damaged skin (n = 4) and unknown primary (n = 2). The median progression-free survival was 3.5 months while the 6-month progression-free survival was 37%. Ten out of the 43 (23%) patients exhibited a partial response. Approximately 42% of the cohort experienced some regression of tumor. The 1-year overall survival rate was 51%. Interestingly, of the ten patients who had a partial response, nine possessed their *c-KIT* mutation on either exon 11 or 13. Patients who had mutations on exon 9, 17 or 18 did not experience a response to therapy. This is consistent with the US Phase II trial by Carvajal and colleagues, who reported that all six of their responders harbored *c-KIT* mutations on exon 11 or 13 [19]. In Guo's study, although 26 out of 43 patients (60%) had a *c- KIT* mutation on exon 11 or 13, only nine out of 26 patients (35%) responded [54]. It appears that it may not be the histologic type that determines responsiveness, but the specific somatic mutation of the tumor.

Expert commentary

A decade ago in 2002, a revolution commenced in the management of solid malignancies with the FDA approval of imatinib, targeting the *c-KIT* oncogene for gastrointestinal stromal tumors [55]. During that same year, a landmark report hailed *BRAF* as a prominent oncogene in melanoma [56]. A decade later, targeted therapy has finally arrived as a legitimate option for melanoma treatment; we have bore witness this past year to a renaissance with the FDA approval of vemurafenib [57]. More work needs to be carried out as resistance and escape mechanisms are recognized, which attenuate the quest for durable responses. Concomitant utilization of BRAF and MEK inhibitors may be an acceptable strategy. Wild-type *BRAF* variants exist and complicate treatment. Other agents that appear promising in melanoma include those that target the *c-KIT* oncogene. Analyzing effectors, including components of the mTOR pathway, may shed light onto other potential therapeutic targets. As an example, our group in Hawaii examined a cohort of Filipinos and Pacific Islanders with acral melanoma, and found that the vast majority of patients possessed tumors with high mTOR expression (14 out of 20 patients; 70%); translation to eIF4E expression was variable (nine out of 20 patients; 45%) [58]. We recommend that studies focusing on molecular analyses be conducted on both primary lesions to serve

as a prognosticator and on metastatic lesions to function as a potential candidate for therapy. This recommendation is supported by the aforementioned studies which have demonstrated that *NRAS*, *BRAF* and *c-KIT* may predict the course of the disease as well as response to targeted therapy.

It is essential that for targeted therapy to be universally applicable, a wide scope of patients is included in studies. The BRIM 3 trial was highly successful in articulating that patients derive benefit from vemurafenib [26]. However, 99% of those patients were Caucasians. In that trial, only 48% of the patients whose tumors were *BRAF*-mutant responded to vemurafenib. By expanding research to multiethnic populations, it will address a critical barrier to progress in the field. Although the majority of patients afflicted with melanoma are Caucasians, investigating the non-Caucasians may allow us to glean insight into disease biology. By analyzing biospecimens and the mutational status of key oncogenes among multiple ethnicities, one is able to better characterize the individual tumor and thus potentially provide appropriate therapeutic recommendations that are tailored to the individual patient. Perhaps one may understand why a particular group has a higher propensity to respond to a specific type of therapy or in some cases not benefit from that therapy. For example, patients with non-small-cell lung cancer who are Japanese have a better affinity to small-molecule inhibitors (e.g., EGFR antagonists) in comparison to other ethnicities. Specifically, two Phase II trials using gefitinib, the IDEAL-1 and IDEAL-2 trials, demonstrated that the Japanese had a 28% response rate as opposed to other ethnicities that had response rates of 9–12% [59,60]. Perhaps non-Caucasians diagnosed with melanoma will have a similar recourse.

Five-year view

The minority population will continue to rise and, as such, more patients from diverse ethnic backgrounds will become afflicted with melanoma. By 2050, the non-Caucasian group is projected to be the majority in the USA. The vast multitude of clinical trials employ Caucasians as participants, albeit because of their higher proclivity for melanoma. Molecular profiling of their tumors in real time after diagnosis will probably become the standard of care, given the likelihood that other targeted therapies will undoubtedly emerge. It is likely that distinct groups may have different profiles. More trials incorporating international sites will be necessary in order to augment the number of patients who could potentially derive benefit. Furthermore, it may lay the groundwork for clinical trials targeting other underanalyzed ethnicities such as African–Americans or Hispanics.

It is foreseeable that other targeted agents, some that have been already FDA approved for other histologies (e.g., imatinib for gastrointestinal stromal tumors) will become indicated for melanoma, provided that the tumor displays a favorable molecular profile. Combinatorial targeted therapy will become the mainstay of managing metastatic disease. Novel applications of targeted therapy will be implemented, for example combining a BRAF antagonist with an mTOR inhibitor should patients harbor a *BRAF* mutation with concomitant high mTOR expression. The premise is that it is difficult for one single agent to completely abrogate the entire tumor burden. Current trials incorporating targeted therapy with immune therapy will be expanded, in order to capitalize on the success of vemurafenib and ipilimumab. It is hopeful that the management of melanoma will be universally applicable to all ethnic groups. In the next 5 years, perhaps the term 'ethnic personalization' will be widely utilized as we continue to learn about the biology of melanoma in all facets and in all skin colors.

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Key issues

- Although not the most common skin cancer, melanoma is the most lethal. The incidence of melanoma has continued to increase globally over the last 25 years. Historically, the median progression-free survival for a patient with metastatic melanoma is less than 60 days, and the median overall survival is less than 12 months.
- The US FDA has recently approved novel therapies within the past year, including vemurafenib, an oral agent that targets the *BRAF* molecular oncogene.
- With the continued paradigm shift in the management of oncologic patients to a more personalized approach, one can hope that studying melanoma in various populations will glean insight into the biology of this abhorrent disease.
- Since Caucasians are most commonly affected by melanoma, most of the public acumen and clinical effort is focused on this cohort. However, in the minority population, melanoma is usually detected at a more advanced stage, distributed on sun-protected areas and associated with a worse survival. Recent studies have examined melanoma in the minority population and characterized their tumors.
- Receptor tyrosine kinases as well as the MAPK and mTOR pathways have been implicated in the pathogenesis of melanomas. Combinatorial targeted therapy will become the mainstay of managing metastatic disease.

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