HHS Public Access

Author manuscript

Curr Oncol Rep. Author manuscript; available in PMC 2023 May 23.

Published in final edited form as:

Curr Oncol Rep. 2016 January ; 18(1): 6. doi:10.1007/s11912-015-0485-6.

Molecular Targeted Therapy Approaches for BRAF Wild-Type Melanoma

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Abstract

Patients with metastatic melanoma have historically had dismal outcomes. The last several years has seen the emergence of effective immune and targeted therapies for metastatic melanoma. Targeted therapies have primarily impacted the 40–50 % of patients with B*RAF*^{V600} mutated melanoma. The remainder of patients with advanced melanoma harbor a wide spectrum of mutations other than *BRAF*^{V600} that are associated with unique pathophysiological, prognostic, and therapeutic implications. The treatment of this subset of patients is a challenging problem. In recent years, preclinical and early clinical studies have suggested that inhibitors of mitogen activated protein kinase (MAPK) pathway and parallel signaling networks may have activity in treatment of *BRAF*^{V600} wild-type (WT) melanoma. In this review, we will discuss available and developing therapies for *BRAF* WT patients with metastatic melanoma, particularly focusing on molecular targeted options for various genetically defined melanoma subsets.

Keywords

Melanoma; BRAF wild-type; Mutation; NRAS; MAPK; MEK; Inhibitor; GNAQ; GNA11; Angiogenesis; CDK4; CKIT; NF; Immunotherapy; Ipilimumab; Atypical; Trametinib; Binimetinib; Selumetinib; Bevacizumab

Introduction

Melanoma of the skin constitutes the sixth most common cancer among American men and women, and its incidence continues to rise [1]. While many patients with localized disease have a favorable outcome following complete surgical resection, others present later with either advanced regional or metastatic disease and have historically had dismal outcomes. Standard chemotherapy was associated with a median survival of 6–8 months

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Compliance with Ethical Standards

Conflict of Interest Romany A. N. Johnpulle declares that she has no conflict of interest.
Douglas B. Johnson has received compensation from Genoptix and Bristol-Myers Squibb for service on advisory boards.
Jeffrey A. Sosman has received compensation from Merck for service as a consultant, and has received research funding from Bristol-Myers Squibb and Novartis.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

with objective responses only in the 10–15 % range in metastatic disease [2]. A growing understanding of the biology and pathogenesis of melanoma has led to the discovery of crucial signaling pathways and the developmentofimmuneand targeted therapies,which havedramatically improved the outcomes of patients with metastatic disease. Approximately 40–50 % of advanced melanomas harbor the *BRAF*^{V600} mutation and can be successfully treated with selective BRAF and MEK inhibitors, leading to significant prolongation of progression free survival (PFS) and overall survival (OS) [3–5]. However, the remaining 50–60 % of patients with advanced melanoma are BRAF wild-type (BRAF WT) and do not benefit from treatment with BRAF inhibitors. A number of other mutations are present in these *BRAF WT* tumors, such as *NRAS, NF1*, *MEK1/2, CKIT,* and *GNAQ/GNA11*, and atypical (non-V600) *BRAF* mutations or *BRAF* fusions. These other genetically defined cohorts are associated with unique risk factors, pathophysiologic, clinical, and prognostic features, that differ from those related to BRAF tumors. The treatment of this subset of patients without a *BRAF*^{V600} mutation is a challenging problem. In this review, we will discuss available targeted and immune therapies for *BRAF* WT patients with metastatic melanoma, particularly focusing on molecular targeted options for various genetically defined melanoma subsets.

Pathogenesis

Nearly all melanomas, including *BRAF* WT melanomas, harbor mutations that activate the mitogen activated protein kinase (MAPK) signaling pathway. *NRAS,* the most frequent non-*BRAF* oncogene activated in melanoma, belongs to a family of GTP-binding proteins connected with the plasma membrane. RAS proteins exert their influence on a multitude ofcellularfunctions including promotion ofcellgrowth, transformation, and survival. They achieve this by activating an array of downstream signaling pathways, including the RAF/MEK/ERK, MAPK, and the PI3K/AKT pathways.These signaling pathways are crucial to the development and progression of melanoma that cause [6] uncontrolled cell growth, defective apoptosis, angiogenesis, cell migration, invasion, and metastasis [7]. Loss of the tumor suppressor gene neurofibromatosis 1 (*NF1*) is another frequent event in melanoma and functionally activates MAPK and PI3K/AKT pathway signaling. Other less common events in melanoma causing dysregulated MAPK signaling include mutations in *GNAQ, GNA11, BRAF* (non-V600), *MEK1/2, KRAS, HRAS*, and *RAF1*. Stepwise acquisition of alterations in genes regulating key cellular functions cooperates with these MAPK-activating mutations, including loss of *CDKN2A, TP53* mutations, *RAC1* mutations, and *CCND1* amplifications. Overexpression and/or mutations of various growth factor receptors (*MET, EGFR, VEGFR, KIT*) also play key roles in melanoma growth and progression. Each of these genetic alterations contributes to melanoma pathogenesis but also may present therapeutic targets. These targets and their frequencies are noted in Fig. 1.

Treatment

Immune Therapy

At this time, the current standard of care for patients with *BRAF* WT melanoma is various immune therapy strategies. In fact, other than cytotoxic chemotherapy, immune therapies

are the only approved agents for *BRAF* WT melanoma. A full review of these incredibly promising treatments is beyond the scope of this review, but we will briefly discuss available agents.

A number of clinical trials have demonstrated the activity of immune therapy in *BRAF* mutant and *BRAF* wild-type melanoma. High-dose interleukin-2 (IL-2) has shown durable responses in 5–8 % of patients, albeit with significant toxicities, thus limiting therapy to young and otherwise healthy individuals [8–10]. Ipilimumab is a monoclonal antibody against cytotoxic T lymphocyte antigen-4 (CTLA4), which abrogates T cell inhibition, thereby activating a T cell antitumor response. In a phase III clinical trial, ipilimumab with or without a peptide vaccine versus a peptide vaccine showed improved OS in pretreated patients with metastatic melanoma [11]. Similar results were seen with ipilimumab in combination with dacarbazine versus chemotherapy alone as front-line therapy for metastatic melanoma [12]. Toxicities, including skin rash, colitis, endocrinopathies, and hepatitis, are a reflection of aberrant immune activation by therapy and in some cases can be formidable.

The advent of programmed cell death-1 receptor (PD-1) and ligand (PD-L1) inhibitors has further broadened the therapeutic armamentarium for metastatic melanoma. Treatment with nivolumab and pembrolizumab are accompanied by response rates of 25–45 %, many of which are durable [13–16]. Furthermore, immune-related toxicities occur at a lower rate than with ipilimumab. Pembrolizumab and nivolumab are each FDA-approved for metastatic melanoma and are now commonly used as first-line and salvage therapy for patients failing other treatments. Of note, a pooled analysis of several trials suggests that clinical outcomes are similar in patients with and without *BRAF* mutations [17]. More recently, ipilimumab and nivolumab in combination demonstrated an impressive 59 % response rate. In September 2015, the FDA-approved nivolumab and ipilimumab for previously untreated metastatic *BRAF* WT melanoma based on significantly better overall response rate (ORR), duration of response, and PFS compared to ipilimumab alone.

Finally, talimogene laherparepvec, a distinct immunotherapeutic, was approved by the FDA in October 2015. This agent [18] is a modified herpes simplex virus that replicates selectively within tumors and produces granulocyte macrophage colony stimulating factor (GM-CSF) within the tumor microenvironment. This directly injectable agent improved the durable response rate (defined as 6 months of objective response) compared to GM-CSF alone (16.3 vs. 2.1 %, $p<0.001$). A trend toward improved OS was also observed (median 23.3 vs. 18.9 months, $p=0.051$).

NRAS Mutation

NRAS mutations are seen in approximately 15–20 % of cutaneous, mucosal, and acral melanoma and are largely mutually exclusive with $BRAF^{V600}$ mutations [19, 20]. Patients with these mutations are more often older individuals with a longer duration of sun exposure. Their tumors also tend to be thicker with increased mitotic activity and located on the extremities [21]. *NRAS* mutations portend a worse overall survival [21–23]. Currently, direct targeting of *NRAS* has not been successful. Single agents and combination treatments

targeting downstream effectors of NRAS (MEK, PI3K/mTOR, and cell-cycle-related targets) may hold promise, however.

NRAS-mutant disease may be particularly responsive to immune therapy. In one retrospective study, high-dose IL-2 therapy resulted in a 47 % response rate among a small number of patients [24, 25]. In a more recent study, 229 patients with metastatic melanoma treated with a variety of immune therapies (IL-2, ipilimumab, or anti-PD-1/PD-L1) were compared for clinical outcomes based on their NRAS status. Patients with NRAS mutation had superior response rates with a trend toward improvedPFSandOS.Ofinterest,inthesamestudy,*NRAS*-mutant tumors seemed to have higher expression of PD-L1, which may contribute to superior responses [25]. Ultimately, prospective validation is needed to confirm these findings.

Direct targeting of *NRAS* (or other activated RAS proteins) has been challenging. Through downstream activation of MAPK signaling, mutant *NRAS* drives tumorigenesis and unrestrained tumor growth. Hence, targeted therapy against *NRAS* has been focused on blocking key downstream molecules, particularly inhibitors of MEK.

Binimetinib (MEK162), a dual MEK1/2 inhibitor, is the first targeted agent to show robust efficacy against *NRAS*-mutant melanoma. In a phase II trial of patients with NRAS mutation treated with binimetinib, partial responses (PR) were seen in 20 % and stable disease (SD) in 43 %. Median PFS was 3.7 months and was comparable to the patients with *BRAF*-mutant melanoma [26••]. Toxicities were manageable and comparable to other MEK inhibitors, including acneiform dermatitis, peripheraledema,and diarrhea. Elevated creatinine kinase also occurred in approximately one third of treated patients but was not associated with any clinical morbidity. Based on these promising results, a randomized, phase III, open-label, multicenter, study comparing the efficacy of binimetinib versus dacarbazine in patients with advanced *NRAS* mutation-positive melanoma is ongoing (NCT01763164).

Other MEK inhibitors (trametinib and RO4987655) have also shown modest clinical efficacy in early studies with *NRAS*-mutant melanoma [27•, 28]. In two multicenter, phase I trials, patients with *NRAS*-mutant and WT melanoma (as well as other mutations and malignancies) were treated with MEK inhibitors. These trials demonstrated single agent clinical activity with anobjective response rate of10–20 % and SD in ~20 % of patients in *NRAS*-mutant and uveal melanoma. Other novel MEK inhibitors with preclinical activity against *NRAS*-mutant melanoma include GDC-0623, which disrupts feedback activation of MEK by RAF [29•]. Prior MEK inhibitors, by contrast, directly inhibit activated MEK and are more active in *BRAF*-mutant cancers.MEK inhibitors with differing mechanisms of action may be more effective in *RAS*-mutant tumors compared to those with *BRAF* mutations. Currently, GDC-0623 is being tested in a phase I clinical trial.

Results from preclinical and clinical studies of combination therapy incorporating MEK inhibitors are encouraging for further development. CDK pathway dysregulation occurs frequently in melanoma through loss of *CDKN2A*, *CCND1* amplification, and *CDK4* mutations [30, 31]. These alterations predict response to CDK4 inhibition in vitro [32, 33]. Inhibition of MEK and CDK4 induces both cell apoptosis and cell cycle arrest,

producing superior efficacy compared to MEK inhibition alone [34•]. Two phase I/II trials targeting *NRAS* mutation with this approach are ongoing with binimetinib+ribociclib (LEE011) (NCT01781572) and trametinib+palbociclib (NCT02065063). Early results from the binimetinib+ribociclib trial demonstrated encouraging clinical efficacy with 33 % ORR and 52 % experiencing SD [35].

Inhibition of PI3K/AKT may also be important in *NRAS*-mutant melanoma. Preclinical studies have suggested that MEK+PI3K inhibition is superior to MEK+mTOR inhibition, and a combination of MEK and PI3K/mTOR synergistically induces extreme tumor suppression [36, 37]. There are ongoing early phase trials of dual pathway inhibition including the combination of trametinib and an AKT inhibitor (uprosertib; GSK2141795) in *BRAF* wild-type melanoma (NCT01941927) and binimetinib and various PI3K/AKT pathway inhibitors (NCT01363232, NCT01337765, NCT01449058).

Several other ongoing phases I/II trials with preclinical support in *NRAS*-mutant and other subsets include studies utilizing inhibitors of Aurora kinase A (MLN8237/alisertib, GSK1070916A), CDK (PD0332991, dinaciclib, LY2835219, BAY1000394, LEE011), and the Notch pathway (RO4929097). XL888 (HSP90 inhibitor), BI-69-A11 (inhibitor of NF-KB and AKT), inhibitors of ERK, RAF-265 (inhibitor of BRAF and VEGFR2), interruption of IQGAP1 (a scaffolding protein in the MAPK pathway), are all potential therapeutic targets for NRAS-mutant melanoma [38, 39].

KIT Mutations

KIT amplifications or mutations are seen in up to 30 % of mucosal, 20 % of acral, and 2 % of melanomas occurring in patients with chronic sun-damaged skin (CSD). *BRAF* and *NRAS* mutations, by contrast, are found less frequently in these populations. *KIT* mutations are heterogeneously distributed across the gene and are most commonly encountered in exon 11 (L576P) and exon 13 (K642E) [40–42]. Although *KIT* mutations portend an overall poor prognosis compared to *KIT* wild-type melanomas, specific mutations, particularly in exon 11, confer sensitivity to *KIT* inhibitors [43]. Clinical efficacy *of KIT* inhibitors in chronic myelogenous leukemia (CML) [44] and gastrointestinal stromal tumors (GIST) [45] has already been reported.

Several studies in unselected melanoma populations using the *KIT* inhibitor imatinib as a single agent demonstrated minimal clinical benefit [46]. More recently, three phase II clinical trials of imatinib limited to melanoma patients with *KIT* alterations (mutations and amplifications) have been conducted [43, 47, 48•]. In one study [47] that enrolled 43 patients, 23 % had a PR and 42 % exhibited tumor regression. The 1-year OS rate was 51 %. Of note, nine of the 10 PRs were recorded in patients with mutations in exons 11 or 13. In another series [48], 24 patients with metastatic mucosal, acral, or CSD melanoma with *KIT* mutations (33 %), amplifications (46 %), or both (21 %) were treated with imatinib. Best overall response rate was seen in 54 % of patients with *KIT* mutations versus 0 % in *KIT* amplified patients. Furthermore, overall disease control (defined as PR or SD) also favored tumors with *KIT* mutation (77 % versus 18 %). Imatinib therefore can be considered a treatment option for patients with *KIT* mutations (but not *KIT* amplifications), particularly in exons 11 and 13. There have been other case reports and studies utilizing various *KIT*

inhibitors, including dasatinib [49], sorafenib [50], sunitinib [51], and nilotinib [52], that reported responses in patients with *KIT* exon 11 or 13 mutations. Studies also suggest that preexisting *NRAS* mutations and *KIT* amplifications may confer intrinsic resistance to *KIT* inhibition [48•, 51]. There are also ongoing trials exploring the efficacy of combination therapy such as ipilimumab and imatinib.

Atypical *BRAF* Mutations

As mentioned, discovery of the activating BRAF V600E mutation [19, 53] in approximately 40–50 % of melanomas has revolutionized treatment of metastatic disease by the use of targeted therapy with *BRAF* inhibitors, leading to improved outcomes [3, 4, 54]. However, identification of less common variant *BRAF* mutations is crucial, as they confer sensitivity to *BRAF* and/or *MEK* inhibitors in many cases. The standard *BRAF* V600E assay may not detect these alternative mutations, including V600K/R/M/D mutations. The activity of *BRAF* inhibitors in patients with *BRAF* V600K and R mutations has now been well-described [55, 56]. In less common V600 variants, activity has also been demonstrated. A 66-year-old female with metastatic melanoma harboring a rare and complex mutation V600DK601del, was treated with vemurafenib with symptomatic improvement and stable disease on imaging [57]. In another case report, a 54-year-old man with a *BRAF* V600M mutation was treated with combination therapy of the *BRAF* inhibitor dabrafenib and *MEK* inhibitor trametinib, resulting in a clinical and radiological response [58].

Other non-V600 *BRAF* alterations may have clinical relevance,including those at the L597,K601, and G466positions. *BRAF* fusions have also been recently described. Together, these atypical, non-V-600 *BRAF* alterations comprise up to 5 % of all melanomas [59]. Critically, preclinical and early clinical data suggest that these alterations confer sensitivity to MEK inhibitors [60••, 61•, 62]. Several case reports have described responses to various MEK inhibitors in patients with *BRAF* L597 and K601 mutations [63]. Moreover, in vitro data and case reports suggest that *BRAF* fusions are sensitive to trametinib or sorafenib [64]. Thus, identification of atypical *BRAF* mutations is important,as more patients may be eligible for targeted therapy and improved clinical outcomes. There have been several case reports demonstrating responses with MEK inhibitors in patients with rare *BRAF* mutations. A prospective phase II study is ongoing to characterize the activity of trametinib across the spectrum of *BRAF* non-V600 mutations and fusions (NCT02296112).

NF1 Mutations

Mutations and loss of *NF1* also activate MAPK signaling. *NF1* mutations are identified in approximately 14 % of all melanomas and up to 70 % of *BRAF/NRAS* WT [65]. Several preclinical studies suggest that *NF1* loss of function mutations or loss confer sensitivity to MEK inhibition [66, 67]. The clinical experience is not quite so clear, however, since the majority of patients with *BRAF/NRAS* WT melanoma failed to respond to MEK inhibitors [27•]. Still, MEK inhibition in combination with other agents is an attractive strategy for this group. *NF1* mutations are also associated with a high overall mutational burden, which may correlate with high response rates to immune therapy as well.

GNAQ and *GNA11* Mutations

Uveal melanoma comprises tumors arising from the iris, ciliary body, and choroid. Based on large population studies [68, 69], the 5-year disease-specific survival is approximately 70 %. It is an extremely aggressive tumor, and outcomes have been poor in the metastatic setting secondary to limited therapeutic options [70]. According to the Collaborative Ocular Melanoma Study (COMS), the 10-year overall metastasis rate is 34 %, and among these patients, 80 % will die within 1 year ofdiagnosis ofadvanceddisease [71].Historically, the median OS for patients with metastatic uveal melanoma has ranged from 2 to 12 months [72, 73]. When compared to patients with advanced cutaneous melanoma, those with uveal melanoma are characterized by more systemic symptoms, hepatic dysfunction, and oligometastatic disease [74, 75].

Similar to cutaneous melanoma, uveal melanoma is driven by activation of the MAPK pathway. However, uveal melanoma has a unique mutational profile that is characterized by the absence of *BRAF* and *NRAS* mutations, and the presence of activating mutations in the G-protein α-subunits q (GNAQ) and 11 (GNA11) that are identified >80 % of primary uveal melanomas. These mutations are found most frequently at the Q209 position of exon 5, or less often, at the R183 position of exon 4 [76, 77]. However, to date, no approved targeted therapy against these genes is available.

Although the advent of immunotherapy has changed the treatment landscape for metastatic cutaneous melanoma, there is paucity of data for patients with advanced uveal melanoma. In landmark studies of ipilimumab or anti-PD-1, uveal melanoma patients were largely excluded [12]. A multicenter, retrospective analysis of 39 patients with advanced uveal melanoma treated with ipilimumab suggested uncommon durable responses with acceptable side effects [78]. These findings were supported by a phase II clinical trial enrolling patients with advanced uveal melanoma, who were treated with ipilimumab. Results demonstrated favorable outcomes in some patients, with 34 % immune-related disease control, 1-year OS of 31 %, and tolerable sides effects similar to those seen in patients with cutaneous melanoma [79]. Studies evaluating anti-PD-1 with or without ipilimumab are ongoing.

Another area of great interest is targeted therapy, particularly focusing on MEK inhibition. In a randomized, open-label, multicenter phase II clinical trial, 101 patients with either untreated or previously treated metastatic uveal melanoma were randomized to receive either selumetinib, a selective MEK1/2 inhibitor, versus chemotherapy (investigator's choice of dacarbazine or temozolomide). This study demonstrated improved median PFS in the selumetinib arm of 15.9 versus 7 weeks in the chemotherapy arm ($P < 0.001$). Objective responses were observed in 14 vs. 0 % in the selumetinib and chemotherapy arms, respectively, and 49 % of patients treated with selumetinib had some tumor regression. Only a trend toward improved overall survival favoring selumetinib was seen ($P = 0.09$), although crossover from chemotherapy to selumetinib was allowed after progression. Although treatment-related toxicity was noted in 97 % of patients on selumetinib that included rash, visual symptoms, edema, and abnormal creatine kinase, the majority of patients were managed successfully with supportive therapy, and only 6 % discontinued therapy secondary to intolerable side effects [80••]. Preliminary results from the randomized phase III SUMIT trial (NCT01974752) of selumetinib in combination with dacarbazine versus chemotherapy

alone for the treatment of patients with metastatic uveal melanoma failed to meet its primary endpoint of PFS. In addition, greater toxicity was seen in the combination arm.

GNAQ/GNA11 mutations activate both MAPK and PI3K/AKT signaling. [81]. Inhibition of both pathways by various combinations has shown synergy in preclinical studies. However, currently, there are no clinical trials testing these combinations. A trial of the mTOR inhibitor everolimus (Rad001) and the somatostatin- receptor-activating peptide pasireotide/SOM232 in advanced uveal melanoma is ongoing (NCT01252251). Protein kinase C (PKC) is also involved in signal transduction from GNAQ to MEK. PKC inhibitors, Enzastaurin and AEB071, have demonstrated activity against uveal melanoma in vitro [82, 83]. Phase I and II clinical trials are studying these findings further [82], (NCT01430416, NCT01801358).

GNAQ/GNA11 mutants found in uveal melanoma promote tumorigenesis by activating YAP [84, 85]. Mutant GNAQ/GNA11, but not wild-type GNAQ/GNA11, trigger dephosphorylation and nuclear localization of YAP, associated with YAP-dependent transcription. Pharmacologic targeting of this novel YAP-dependent pathway may be critical for effective therapy against GNAQ/GNA11 mutant cancers.

Angiogenesis Inhibitors

Bevacizumab is a monoclonal antibody targeted at the vascular endothelial growth factor (VEGF) receptor. In many different tumor types, including advanced colorectal, breast, and non-small-cell lung cancer, the combination of standard chemotherapy plus bevacizumab conferred favorable outcomes [86–88]. Overexpression of VEGF receptor has been identified in melanoma [89]. Preclinical studies have demonstrated that VEGF results in the growth and maintenance of melanoma, while anti-VEGF therapy leads to the inhibition of melanoma cell growth [90, 91]. Other data have shown a direct correlation between tumor VEGF concentration and tumor survival [92].

The clinical utility of adding anti-VEGF therapy to chemotherapy was studied in a single-arm multicenter phase II trial in which 62 patients with previously untreated melanoma were treated with temozolomide and bevacizumab until disease progression or intolerable side effects. The primary end point of disease stabilization rate at 12 weeks (DSR12), defined as complete response (CR), PR, or SD, was found in 52 % of patients. A statistically significant improvement in both median PFS and OS was found, favoring the *BRAF* WT group. Grade 3–4 toxicity was seen in 32 % of all patients and included thrombocytopenia, neutropenia, hypertension, fatigue, and hemorrhage [93]. The BEAM trial, a phase II, randomized, multicenter trial, evaluated PFS and OS in 214 patients with previously untreated metastatic melanoma treated with carboplatin and paclitaxel with or without bevacizumab. Although this trial did not achieve its primary endpoint, in the absence of any phase III data, the study suggests modest efficacy of VEGF inhibitors and chemotherapy in advanced melanoma. The BEAM trial demonstrated numerically greater but generally not statistically significant improvements in ORR, PFS, and OS at most analysis time points [94].

Given equivocal results of concurrent chemotherapy and VEGF inhibition, a prospective, single-arm, phase II trial enrolled 38 previously treated patients with advanced melanoma to

receive sequential therapy with axitinib, a potent VEGF inhibitor, followed by carboplatin plus paclitaxel every 3 weeks. The median PFS was 8.7 months, the median OS was 14.0 months, 22 % had a PR, and 55 % had SD. Therapy was well tolerated. *BRAF* WT patients did significantly better than those with *BRAF* mutation [95]. Most current development approaches for angiogenesis inhibitors is proceeding in combination with immune therapy.

Other Agents

Glembatumumab vedotin is an antibody-drug conjugate that has shown efficacy in advanced melanoma and triple negative breast cancer. This agent is a monoclonal antibody to glycoprotein NMB (gpNMB) linked to a microtubule inhibitor (monomethyl auristatin E). Many melanomas (including uveal melanomas) overexpress gpNMB, a molecule that has been linked to poor prognosis in several cancers [96, 97]. Glembatumumab [98•] was evaluated in a phase I/II study and produced a 15 % ORR with an additional 24 % stable disease rate at the recommended phase II dose level. Although treatment-related toxicities (including rash, neutropenia, and fatigue) were manageable overall, there were three treatment-related deaths from sepsis, renal failure, and toxic epidermal necrolysis at doses above the maximum-tolerated dose (MTD). A phase II study is currently ongoing to determine efficacy and whether gpNMB overexpression is a biomarker of response.

Conclusion

The landscape of melanoma therapy is rapidly advancing to include numerouseffective immuneand targeted therapies.As 50–60 % of patients harbor mutations other than $BRAF^{V600}$ and are associated with various unique pathophysiological, prognostic, and therapeutic implications, it remains critical to capture this cohort of patients in clinical trials to determine effective treatment options. Elucidating biomarkers predictive of response to therapy and determining the best combination and/or sequence of therapies will be crucial in further improvement of treatment and outcomes in these patients.

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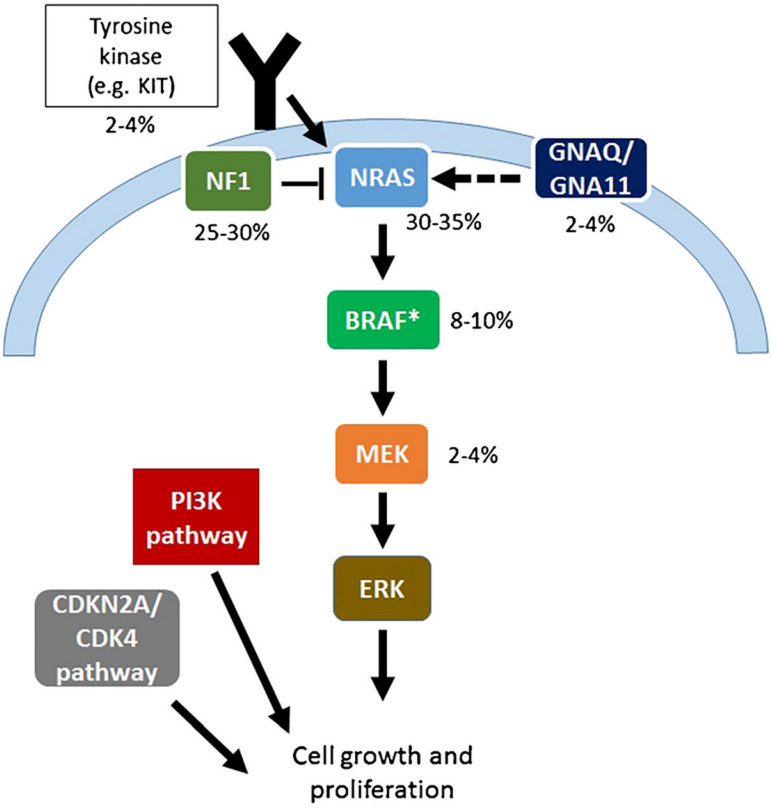

Fig. 1.

Genetic alterations and their frequency in *BRAF*^{V600} wild-type melanoma. The *asterisk symbol* indicates atypical (non-V600) BRAF mutations and BRAF fusions