Chapter 10

Targeted Agents for the Treatment of Melanoma: An Overview

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Additional information is available at the end of the chapter

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1. Introduction

Malignant melanoma is an important healthcare issue. The incidence of melanoma has increased dramatically during the last few decades and melanoma is now one of the most common forms of cancer. This aggressive form of skin cancer is characterized by its high capacity for invasion and metastasis. Patients with advanced stages of the disease have universally poor prognoses with a median survival of 3–11 months, depending on various prognostic factors. Primary cutaneous melanomas are divided into four groups on the basis of histopathology: superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma. Superficial spreading melanoma is the most common form. In the early growth phase, tumor cells spread laterally into the epidermis, forming an irregular pattern with an uneven color on the skin. Nodular melanoma occurs most often on the chest or back where it has a tendency to grow vertically into the skin, penetrating deeply if not removed. Nodular melanoma lesions are often characterized by a darkly pigmented lump on the skin surface. Lentigo maligna melanoma most commonly occurs on the facial areas of elderly people. It grows slowly and may take several years to develop. Acral lentiginous melanoma is usually found on the palms of the hands, the soles of the feet, or around the toenails. Melanoma is usually curable in its early stages; however, the disease may be fatal if it spreads to other parts of the body. Malignant melanoma usually develops via the transformation and proliferation of melanocytes that reside in the basal cell layer of the epidermis. Melanoma can also develop when melanocytes no longer respond to normal cellular growth control mechanisms, which allows the tumor cells to metastasize into nearby tissues or other organs, where they invade and compromise organ function. Thus, the development of alternative treatment for melanoma is critically important. Recent advances in oncology have led to novel therapeutics that is capable of targeting

known oncogenes and immunotherapeutic antibodies. Clinical trials of these agents have demonstrated measurable benefits to patients with metastatic melanoma. In this chapter, we review clinical studies of recently developed targeted agents and summarize their current effectiveness in melanoma treatment.

2. Immune modulators for melanoma treatment

Melanoma is characterized as one of the most immunogenic tumors because of the presence of tumor-infiltrating lymphocytes in resected melanoma, occasional spontaneous regression, and clinical responses to immune stimulation. The immunogenicity of melanoma has led investigators to study novel immune strategies for overcoming immune system evasion by tumors. Therapies targeted at the immune checkpoints (e.g., cytotoxic T lymphocyte-associated antigen 4, CTLA-4) have transformed the treatment of advanced melanoma in recent years. T cells self-regulate their activation through CTLA-4 expression. CTLA-4 functions as a negative co-stimulatory molecule for the T cell; therefore, therapies that antagonize CTLA-4 remove the brakes from T cells leading to a net effect of T cell hyper-responsiveness [1]. At present, clinical trials of anti-CTLA-4 monoclonal antibody treatment are being conducted for melanoma. Several human monoclonal antibodies, i.e., tremelimumab (CP-675,206; Pfizer Pharmaceuticals, New York), ipilimumab (MDX-010; Bristol-Myers Squibb, Medarex, Princeton, NJ) and urelumab (BMS-663513), are under investigation. These antibodies have been demonstrated to induce tumor regression and may prolong time to disease progression [2-3]. As shown in Table 1, three such antibodies, i.e., tremelimumab, ipilimumab, and urelumab, are in clinical development.

Drug Name	Mechanisms
Tremelimumab (CP-675,206)	Anti-CTLA-4
Ipilimumab (MDX-010)	Anti-CTLA-4
Urelumab (BMS-663513)	Anti-CD137

Table 1. Clinical trials of selected monoclonal antibodies for melanoma treatment

2.1. Tremelimumab

Melanoma is an immunogenic tumor, which suggests that manipulation of the immune system using monoclonal antibody treatment to suppress the CTLA-4 inhibitory function could produce a favorable clinical result. Tremelimumab is a fully human IgG2 antibody, which is directed against human CTLA-4. CTLA-4 plays a pivotal role in this interaction by dampening immune responses to self-antigens. CTLA-4 is a cell surface receptor expressed on activated T cells. In mice, the T cell-mediated killing of tumors is enhanced by blocking CTLA4 binding to its natural ligands, such as CD80 and CD86, which are expressed on antigen-presenting cells. Blocking antibodies to CTLA-4 were shown to induce tumor regression in selected mouse

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models [4]. When translated to the clinic, the administration of blocking antibodies to CTLA-4 produced objective tumor responses in a subset of patients with metastatic melanoma [5]. Tremelimumab is a fully human IgG2 monoclonal antibody tested in patients with cancer, the majority of whom have had metastatic melanoma. Pfizer previously developed tremelimumab for the potential intravenous (i.v.) treatment of cancers. They were also developing tremelimumab as a potential treatment for melanoma. Clinical trials using tremelimumab demonstrated that this antibody could induce long-lasting tumor regressions in 7%–10% of patients with metastatic melanoma. These tumor responses are mediated by the intratumoral infiltration of cytotoxic T cells, as demonstrated in patient-derived tumor biopsies. Grade 3 or 4 toxicities in the range of 20% to 25% are mainly inflammatory or autoimmune in nature, which are on-target effects after inhibiting CTLA-4-mediated self-tolerance. The lack of any survival advantage during the early analysis of a phase III clinical trial comparing tremelimumab with standard chemotreatment for metastatic melanoma highlights the importance of gaining a better understanding of how this antibody modulates the human immune system and how to better select patients for this mode of treatment [6].

Tremelimumab is being developed by Pfizer for the treatment of various cancers. It is currently in worldwide phase III development for malignant melanoma. Tremelimumab at 15 mg/kg every 3 months was compared with standard chemotreatment during a pivotal phase III clinical trial in patients with previously untreated metastatic melanoma without brain metastasis and a baseline lactate dehydrogenase level below double the upper normal limit. The Data Safety Monitoring Board (DSMB) determined that the second interim analysis crossed the prospectively defined futility boundaries for improvement in overall survival (OS). The trial had a very short follow-up, with most patients only followed for 6–11 months after the initial dose. During that period, the survival curve of the tremelimumab group was ahead of the curve of the chemotreatment arm by 1 month [7]. The interim results of this trial have been updated recently; however, insignificant improvements in survival were observed with tremelimumab. A subset analysis suggested that patients with a low baseline C-reactive protein (CRP) had a markedly improved outcome when treated with tremelimumab compared with chemotreatment. CRP may be an indicator of the tumor microenviroment because this acute reactive protein is produced in the liver in response to peripheral inflammation [8]. Furthermore, Pfizer and the Debiopharm Group entered into a co-development agreement to conduct a phase III trial of tremelimumab for the treatment of patients with unresectable, stage IV melanoma. A biomarker will be used to select patients considered likely to respond to tremelimumab. Under the terms of the agreement, Debiopharm will assume responsibility for conducting the phase III trial of tremelimumab, while Pfizer will retain responsibility for the worldwide commercialization of the compound. The financial terms of the agreement were not disclosed [9]. In addition, tremelimumab had been discontinued for melanoma. Therefore, the clinical development of tremelimumab has provided evidence of long-lasting responses in a small subset of patients with metastatic melanoma.

2.2. Ipilimumab

Ipilimumab is a fully human monoclonal IgG1κ antibody against CTLA-4, an immune inhibitory molecule expressed in activated T cells and suppressor T regulatory cells. Activation

of the cellular immune response involves the interaction of T cell receptors with major histocompatibility complex molecules on antigen-presenting cells (APCs). This requires co-stimulation where ligand B7 on APC binds to CD28 on T cells, which triggers T cell proliferation. A negative co-stimulation signal is transduced by CTLA-4, which is present in T cells, and interaction of CTLA-4 with the same B7 ligand inhibits T cell activation and proliferation [10]. Ipilimumab is a human MAB against CTLA-4 that enhances the co-stimulation of cytotoxic T cells, resulting in their proliferation and an antitumor response. It is licensed for the treatment of unresectable or metastatic malignant melanoma, and multiple clinical trials using this medication for the treatment of other malignancies are ongoing. As the clinical response to ipilimumab is derived from immunostimulation, predictably it also generates autoimmunity, leading to immune-related adverse events in the majority of patients [11]. Ipilimumab was approved by the Food and Drug Administration (FDA) in February 2011 and by the European Medicines Agency in July 2011 for use in the treatment of advanced malignant melanoma in patients not responding to chemotreatment, with or without previous exposure to immunotreatment [12]. Two significant phase III clinical trials of ipilimumab in patients with unresectable/metastatic malignant melanoma have been conducted. In the first trial, ipilimumab at 3 mg/kg significantly improved OS from 6.4 to 10 months [13]. In the second trial, ipilimumab at 10 mg/kg in combination with dacarbazine significantly improved the 3-year survival rate from 12.8 to 20.2% compared with dacarbazine alone [14]. Therefore, the dose of ipilimumab used in clinical trials ranged from 3 to 10 mg/kg.

Ipilimumab was approved by the FDA in March 2011 as a monotreatment (3 mg/kg every 3 weeks for 4 doses) for the treatment of advanced melanoma in pre-treated or chemotreatment-naive patients. Four months later, ipilimumab received rapid approval by the European Commission, after a positive opinion was expressed by the Committee for Medicinal Products for Human Use. However, the EU limits its use to previously treated patients with advanced melanoma. Phase III trials are testing ipilimumab in an adjuvant setting in patients with high-risk stage III or IV melanoma after surgical removal of the tumor. A neoadjuvant potential use of ipilimumab is currently under evaluation in patients with stage IIIB/C melanoma before lymphadenectomy. In this trial, ipilimumab is also administered after surgery as maintenance treatment. The trial aims to analyze the host immune responses in nodal metastatic melanoma and in the peripheral blood by comparing the immunological parameters at baseline and after treatment. Data on 17 patients indicated that ipilimumab induces a significant increase in the frequency of circulating regulatory T cells (Tregs), i.e., increase in the induction of tumor-infiltrating Tregs at 6 weeks [15]. Ipilimumab is the first agent that has been demonstrated to improve OS in patients with metastatic melanoma, which has a very poor prognosis, in randomized phase III clinical trials [16].

2.3. Urelumab (BMS-663513)

CD-137 is a member of the tumor necrosis factor receptor (TNFR) family and functions as a costimulatory molecule. BMS-663513 is a fully human monoclonal antibody agonist of CD-137, which is a TNFR expressed on the surfaces of activated white blood cells [17]. CD-137 stimulation enhances the immune response, specifically an antitumor immune response, via various

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mechanisms [18]. Phase I and II trials initially focused on patients with melanoma, but they were expanded to patients with renal cell carcinoma (RCC) and ovarian cancer. Urelumab (BMS-663513) was tolerable across a wide dose range (0.3–15 mg/kg). As a single agent, urelumab has demonstrated clinical activity that justifies its further evaluation as a single agent and in combination with other treatment modalities [19].

3. c-KIT inhibitors for melanoma treatment

Targeted treatments act by selectively inhibiting molecules, usually proteins, the expression or overexpression of which have specific roles in the growth of the target neoplasm. Thus, one of the main characteristics of targeted antineoplastic treatment is that the drugs act specifically on their intended target and that those targets have specific effects on the tumor [20]. The number of possible therapeutic targets in melanoma is increasing with an improvement in our understanding of the biology of this tumor. One of these, c-KIT, has been considered a potential therapeutic target in melanoma for a long time. Indeed, c-KIT is a protein that acts as a fundamental growth factor receptor in epidermal melanocytes and has an essential role in the differentiation and migration of melanocytic cells during embryonic development [21]. c-KIT inhibitors have been used for melanoma treatment. c-KIT, which is also known as CD117, is a receptor tyrosine kinase (RTK) that is mutated in approximately 20% of acral, mucosal, and chronic sun-induced skin damage [22]. The ligand for KIT is stem cell factor (SCF) and binding of SCF to c-KIT induces the activation of downstream signaling pathways that mediate growth and survival signals within the cell, including the PI3K-AKT-mTOR and RAS-RAF-MEK-ERK pathways. KIT has been implicated in the pathogenesis of several cancers including acute myeloid leukemia (AML) and gastrointestinal stromal tumors (GIST). Unlike GIST, where c-KIT mutations tend to be deletions or insertions in exon 11, c-KIT mutations in melanoma occur at multiple sites in the gene, including the juxtamembrane domain at exons 11 and 13 and the kinase domain at exon 17. They are usually point mutations that do not correlate with the KIT copy number or CD117 expression [23]. As shown in Table 2, two c-KIT inhibitors, i.e., imatinib and dasatinib, are under evaluation for treating melanoma.

Name	Mechanisms
Imatinib	c-KIT inhibitors
Dasatinib	c-KIT inhibitors

Table 2. Clinical trials of c-KIT inhibitors for treating melanoma

3.1. Imatinib

Targeting KIT may be a therapeutic strategy for patients with CSD, acral, or mucosal melanomas that harbor an activating c-KIT mutation in exons 9, 11, or 13 [24]. Imatinib (Figure 1), an oral tyrosine kinase inhibitor (TKI) with known activity against c-KIT-activated tumors, was tested in three phase II trials in patients with melanomas that harbored c-KIT mutations. The

first trial enrolled patients with metastatic melanomas that expressed at least one protein tyrosine kinase [c-KIT, platelet-derived growth factor receptors (PDGFRs), c-abl, or abl-related gene], and a response was observed in only 1 patient, i.e., in the patient who had the highest level of c-KIT expression. Of note, c-KIT mutations were not required prior to entry in this trial. In the second trial, 28 patients with c-KIT mutations and amplifications with advanced unresectable melanoma arising from acral, mucosal, and chronic sun-induced skin damage were orally administered 400 mg imatinib mesylate twice daily in 6-week cycles until disease progression or unacceptable toxicity [25].

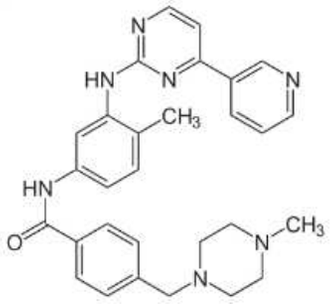

Figure 1. Chemical structure of imatinib.

Novartis developed and launched imatinib, an inhibitor of tyrosine kinases including Bcr-Abl and c-KIT. The product is indicated for the treatment of newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) and Ph+ CML in blast crisis during the accelerated phase or chronic phase after interferon treatment. It is also indicated for the treatment of KIT-positive GIST, including unresectable and/or metastatic disease and resected disease after surgery, in adults with newly diagnosed Ph+ acute lymphoblastic leukemia (ALL) in combination with chemotreatment, as a single agent for relapsed or refractory Ph+ ALL. It is also indicated for the treatment of adults with unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP); hypereosinophilic syndrome (HES); chronic eosinophilic leukemia (CEL); aggressive systemic mastocytosis (ASM); and myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR gene rearrangements.

3.2. Dasatinib

Dasatinib (Figure 2, BMS-354825; Sprycel®; Bristol-Myers Squibb Co) is a multi-targeted inhibitor of RTKs, including BCR-ABL fusion protein, stem cell factor receptor (c-KIT) and Src family kinases (SFKs). The phase II trial results were presented at the 45th ASCO meeting in 2009, showing that daily treatment with dasatinib has modest activity in patients with melanoma. Accrual is almost complete. Toxicity is frequent; therefore, alternate schedules to allow breaks in dosing might be better and should be evaluated. Combination studies may be warranted on the basis of preclinical evaluations of molecularly defined subsets of patients. Dasatinib is indicated for the treatment of newly diagnosed adults with Ph+ CML in the chronic phase and of adults with chronic, accelerated, myeloid, or lymphoid blast phase Ph+ CML with

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resistance or intolerance to prior treatment, including imatinib. Dasatinib is also indicated for the treatment of adults with Ph+ ALL with resistance or intolerance to prior treatment, including imatinib. Dasatinib was launched in the US in July 2006 for the second-line treatment of CML and Ph+ ALL. The drug was launched in the UK and some European countries for the second-line treatment of CML by the end of 2006. Dasatinib was launched in Japan in April 2009. In October 2010, the drug was approved in the US for the first-line treatment of Ph+ CML. By December 2010, the drug was approved in the EC for the treatment of newly diagnosed, chronic phase CML in adult patients. In June 2011, the drug was approved for the first-line treatment of CML in Japan. The company is also developing the drug for other cancer indications, including breast, prostate, and pancreatic cancers, and non-small-cell lung cancer (NSCLC). By October 2008, phase III trials began for castration-resistant prostate cancer. Therefore, an application for this indication was expected in 2012 or 2013. In December 2006, phase II trials were initiated for breast cancer. By December 2006, a phase II trial for systemic mastocytosis was also initiated. In May 2007, a phase II trial for sarcoma began in the US. A phase II trial for NSCLC was initiated in November 2007. In December 2007, Bristol-Myers Squibb were also investigating dasatinib for multiple myeloma (MM) and other hematological malignancies, and a phase I/II trial was also underway for melanoma. By May 2009, a phase II trial was ongoing for head and neck cancer. By October 2009, a phase II trial was completed for polycythemia vera. By June 2010, a phase II trial began for colorectal cancer. In June 2011, a phase II trial began in the US for locally advanced pancreatic cancer, while phase II trials also began in Europe for pancreatic cancer by September 2011.

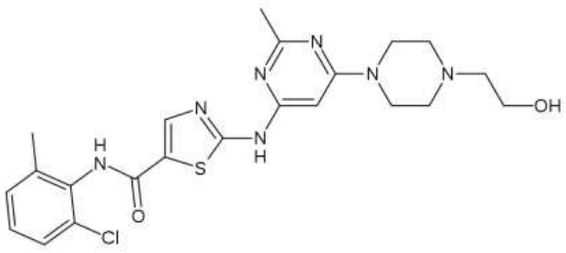

Figure 2. Chemical structure of dasatinib.

4. BRAF/MEK inhibitors for melanoma treatment

The mitogen-activated protein kinase (MAPK) pathway relays extracellular signals from the plasma membrane of the cell to the nucleus via an ordered series of phosphorylation events. MAPKs regulate diverse cellular programs including embryogenesis, proliferation, differentiation, and apoptosis via the cell surface sensing the metabolic state and environment of the cell [26]. The RAS/RAF/MEK/ERK pathway plays a role in normal organogenesis; however, it can lead to malignant cellular proliferation, inhibition of apoptosis, and invasion when aberrantly activated. In melanoma, the most commonly mutated gene is BRAF, with a frequency of 50%–70%. More than 90% of these mutations result in a substitution of valine for

glutamic acid at position 600 (V600E). BRAF V600E leads to ERK activation, which results in the proliferation and survival advantage of melanoma cells [27-28]. BRAF phosphorylates regulatory serine residues on MEK1/2, and BRAF mutation results in the activation of the RAS/RAF/MEK/ERK pathway, leading to cellular proliferation and a series of antiapoptotic and potentially immunoregulatory events that culminate in tumor progression. Advanced melanomas harboring BRAF mutations appear to be associated with truncal primaries and an earlier age at onset; however, chronic UV-induced skin damage may be absent. Clinically, the disease associated with BRAF mutation has been shown to follow a more aggressive clinical course with a shorter OS for patients not treated with BRAF inhibitors [29]. As shown in Table 3, five BRAF inhibitors are under evaluation for melanoma.

Name	Mechanisms
Sorafenib	Multi-target BRAF inhibitors
RAF265	Multi-target BRAF inhibitors
Dabrafenib	Selective BRAF inhibitors
Vemurafenib	BRAF V600E inhibitor
Selumetinib	MEK inhibitor

Table 3. Clinical trials of BRAF inhibitors for treating melanoma

4.1. Sorafenib

Sorafenib (Figure 3, Nexavar, BAY-43-9006; Bayer) is a small molecule and a multikinase inhibitor (including the vascular endothelial growth factor receptors VEGFR-1, VEGFR-2, and VEGFR-3, PDGFR, as well as FLT3, C-KIT, and BRAF). It yielded negative results in metastatic melanoma trials when tested as a single agent and in combination with other chemotherapeutic agents, despite its success in treating metastatic renal, hepatocellular carcinomas (HCCs) [30], and thyroid cancer. In first-line treatment, a phase III, randomized, double-blind, placebo-controlled trial using chemotreatment-naive patients with unresectable stage III or IV melanoma was initiated for sorafenib treatment in 2005. The objective was to compare improvements in OS in patients receiving sorafenib or placebo in combination with both carboplatin and paclitaxel. In 2010, the results were presented at the 46th ASCO meeting, showing that the addition of sorafenib to carboplatin and paclitaxel did not improve OS, i.e., no significant differences were observed between the treatment groups in terms of OS, PFS, or RR. The median OS for the sorafenib combination group was 11.1 months compared with 11.3 months for the carboplatin plus paclitaxel group. The median PFS was 4.9 months versus 4.1 months, respectively. Grade 3 or 4 adverse events occurred in 78% patients in the sorafenib group (versus 84%). As a second-line treatment, a total of 270 patients received placebo plus carboplatin and paclitaxel (median PFS, 17.9 weeks) or sorafenib plus carboplatin and paclitaxel (median PFS, 17.4 weeks). The addition of sorafenib to carboplatin and paclitaxel did not improve any of the endpoints compared with that of placebo to carboplatin and paclitaxel. Therefore,

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it cannot be recommended in a second-line setting for patients with advanced melanoma [31]. In the first phase II trial, which included 39 patients and used sorafenib as monotreatment, one complete response and seven partial responses were achieved. In a second phase I/II trial with 35 patients, where the drug was combined with carboplatin and paclitaxel, the number of partial responses increased to 11, while 19 minor responses were observed. Subsequently, a two-armed phase II trial was undertaken. In this trial, an increase in the disease-free interval was observed in the group that received sorafenib, although there was no improvement in OS. Since then, other phase III trials have been undertaken in which sorafenib has been combined with other cytostatic agents, such as temozolomide, carboplatin, or paclitaxel. However, no improvements were observed in the outcomes. In these trials, the response was not correlated with the presence of BRAF V600E mutation. It is believed that sorafenib actually targets VEGFR-2 or PDGFR-β more strongly than BRAF in these patients. At present, its main indications are for the treatment of clear cell renal carcinoma and unresectable HCC, where angiogenesis seems to play a more important role [32]. Some preclinical studies suggest that sorafenib would be more effective in the small group of melanomas with BRAF mutations, rather than in melanomas with V600E mutation [33].

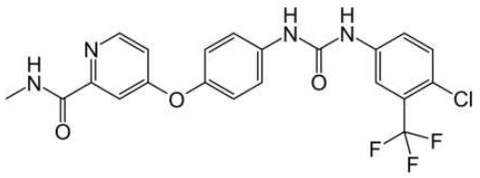

Figure 3. Chemical structure of sorafenib.

4.2. RAF265

RAF265 (Figure 4) is an orally bioavailable small molecule with preclinical antitumor activity that is currently being tested in phase I clinical trials for locally advanced or metastatic melanoma. RAF265 is a novel, orally dosed, small-molecule BRAF kinase and VEGFR-2 inhibitor with potent preclinical antitumor activity in mutant BRAF tumor models. The preclinical effectiveness of RAF265 for the treatment of melanoma has been evaluated. Advanced metastatic melanoma tumors from 34 patients were orthotopically implanted into nude mice. The tumors that grew in mice (17 of 34) were evaluated to determine their response to RAF265 (40 mg/kg/daily) for 30 days. Nine of the 17 successfully implanted (53%) tumors had mutant BRAF, whereas 8 (47%) tumors had wild-type BRAF. Tumor implants from 7 of 17 patients (41%) responded to RAF265 treatment with a >50% reduction in tumor growth [34]. In 2011, the clinical data of this first human study were presented at the 47th ASCO meeting. The first in human study, and RAF-265 was shown to be effective in patients with mutated and wild-type BRAF melanomas. The observed 11-day mean half-life of RAF-265 indicated that an intermittent dosing schedule should be investigated. At the 42nd ACSO meeting, the MTD of oral RAF-265 was reported as 48 mg with a continuous daily dosing schedule. Dose-

limiting hematological toxicities following qd dosing (67 mg) highlighted the need to explore intermittent dosing. RAF265 is also a multitargeted small molecule inhibitor of the BRAF V600E mutant and VEGFR. A phase I trial that treated advanced melanoma patients with RAF265 demonstrated an overall response rate of 16% for patients with BRAF mutation-positive melanoma and 13% for patients with wild-type BRAF or unknown status of BRAF mutation [35].

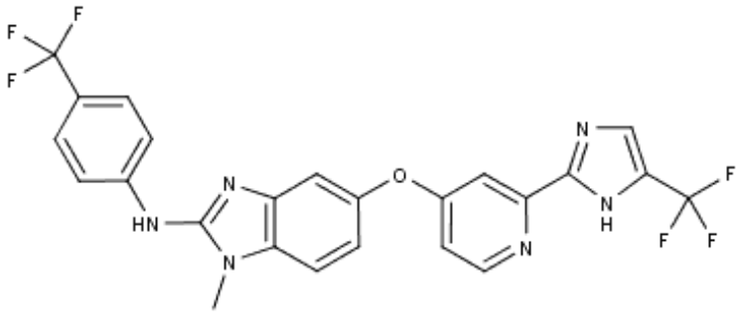

Figure 4. Chemical structure of RAF265.

4.3. Dabrafenib

Dabrafenib (Figure 5, GlaxoSmithKline PLC), a 4-(3-aminosulfonylphenyl)-5-(pyrimidin-3-yl) thiazole, is a highly selective and potent adenosine triphosphate-competitive BRAF inhibitor with >100-fold selectivity for mutant BRAF over wild-type BRAF in cell lines. In addition, dabrafenib leads to dose-dependent inhibition of MEK and ERK phosphorylation in BRAF mutant cell lines, and it induces tumor regression in melanoma xenografts. Dabrafenib was first clinically tested in study BRF112680, which was the first phase I human dose escalation study designed to evaluate its clinical efficacy, safety, and pharmacokinetics. Preliminary analysis of the initial phase I trial and an extended phase II cohort indicated that dabrafenib was active in the treatment of intracerebral melanoma metastases, with commensurate extracranial activity. In 21 of 34 subjects with BRAF V600E mutant melanoma, the clinical activity at dosages of 150 mg twice daily was determined on the basis of the objective tumor responses, judged using RECIST criteria, observed as soon as 8 weeks after treatment initiation, although the corresponding response rate in melanomas harboring V600K mutation was considerably lower at 19% [36]. In August 2012, GSK applied for the US and EU approval of dabrafenib for unresectable or metastatic melanoma with BRAF V600 mutations.

4.4. Vemurafenib

Recently, the highly specific and potent BRAF V600E inhibitor, designated as vemurafenib (Figure 6, RO5185426, RG7204, PLX4032; Plexxikon Inc.), has delivered highly promising results. It was launched in the US after FDA approval for BRAF V600E mutation-positive unresectable or metastatic melanoma in 2011 and in the UK in 2012. In a phase III randomized, controlled trial, patients with metastatic melanoma and BRAF mutation received first-line

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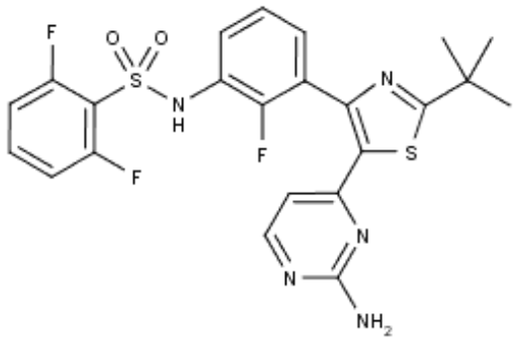

Figure 5. Chemical structure of dabrafenib.

treatment with vemurafenib or dacarbazine, and the primary endpoint was OS. These results showed that in addition to improved OS, vemurafenib significantly reduced the risks of death and disease progression by 63% and 74%, respectively, compared with dacarbazine. The response rate in patients who received vemurafenib was 48.4%, which was almost 9 times higher than that in patients who received chemotreatment (5.5%). Furthermore, 84% of the patients who received vemurafenib were alive after 6 months compared with 64% who received chemotreatment, i.e., the median OS with vemurafenib (10.5 months) was longer than that with dacarbazine [37]. Vemurafenib produced improved OS and PFS rates in patients. Thus, it offers a novel, first-line, personalized treatment for patients with mutated BRAF [38].

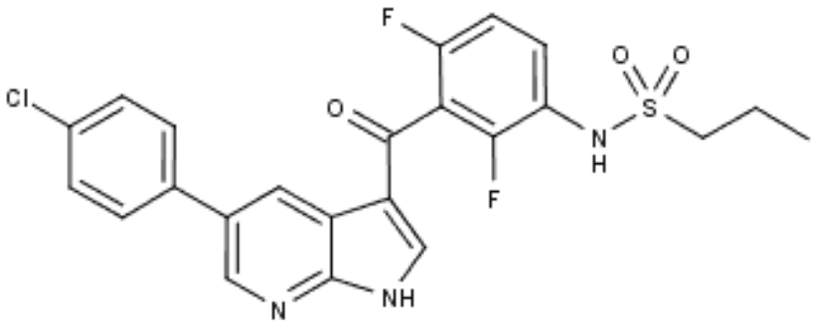

Figure 6. Chemical structure of vemurafenib.

4.5. Selumetinib

MEK is a protein that belongs to the MAPK pathway downstream of BRAF. Selumetinib (Figure 7, AZD6244; AstraZeneca), an orally available selective inhibitor of MEK1/2, was developed for the potential treatment of patients with cancers, such as NSCLC, pancreatic cancer, colorectal cancer, biliary cancer, and thyroid carcinoma, in phase II trials [39]. By 2006, a phase II trial was underway to compare selumetinib with temozolomide for unresectable late-stage malignant melanoma. However, disappointing data were reported in December 2007, and Astra Zeneca reported that it did not plan to advance selumetinib as a monotreatment

for melanoma and would investigate other options. In March 2010, the enrollment of 91 patients was completed in a phase II trial of selumetinib in combination with dacarbazine compared with dacarbazine alone for the first-line treatment of melanoma with BRAF mutation. In January 2012, the top-line data were expected in the first half of 2012. By November 2010, AstraZeneca had begun a phase II trial of the drug plus temozolomide in patients with metastatic melanoma of the eye. The trial was ongoing in January 2011. In May 2008, a phase II trial of selumetinib plus chemotreatment for melanoma was planned to start in the second half of 2008. By June 2006, selumetinib had entered a phase II trial for malignant melanoma. The randomized, open-label, multicenter trial compared the drug with temozolomide in 180 patients with unresectable stage III/IV disease. Astra Zeneca began dosing patients in the trial in September 2006. The top-line data reported in December 2007 showed that the drug had failed to improve PFS. At that time, Astra Zeneca did not plan to conduct a phase III trial for this indication and was considering other options. Additional data were presented at the 44th ASCO annual meeting; however, no significant difference was observed in the primary endpoint of PFS in the overall group or mutation subgroup between the two treatment arms. Similar data were also reported in the interim analysis of OS. In February 2010, additional data were presented at the Biomarkers Fifth Annual Congress in Manchester, UK. Patients harboring bRaf gene mutations showed some signs of better clinical responses. In June 2010, similar data were presented at the 46th ASCO meeting in Chicago, IL. A 12% response rate was observed in patients with bRaf mutations. Further results were expected. By November 2010, enrollment was completed.

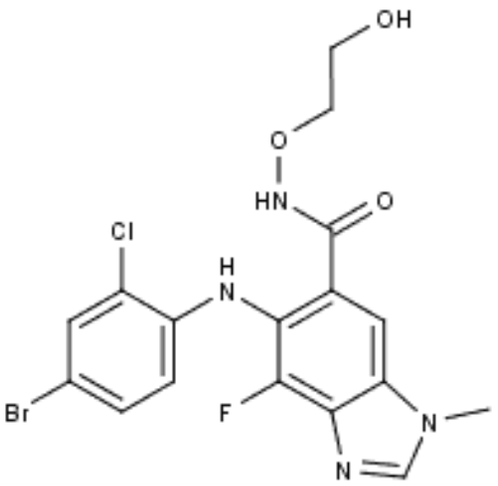

Figure 7. Chemical structure of selumetinib.

5. AKT inhibitors for melanoma treatment

The phosphoinositide 3-kinase (PI3K) pathway is an important driver of cell proliferation and survival, particularly in cells that respond to growth factor receptor engagement. The

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PI3K/AKT/mTOR pathway is another signaling transduction pathway that is aberrantly activated in several cancers, including melanoma [40]. As shown in Table 4, AKT inhibitor such as perifosine is under evaluation for melanoma.

Name	Mechanisms
Perifosine	AKT inhibitor

Table 4. Clinical trials of AKT inhibitors for treating melanoma

Aeterna Zentaris is developing perifosine (Figure 8), an oral alkylphosphocholine signal transduction modulator that inhibits Akt activation in the PI3K pathway, for the potential treatment of various cancers, but primarily MM, neuroblastoma, and RCC. In December 2009, a phase III trial began for MM. In May 2012, Aeterna Zentaris stated that it was continuing phase III MM trials in North America. In August 2011, a phase I trial for recurrent pediatric solid tumors was ongoing. In June 2012, data from the phase I/Ib study were presented. Later that month, the results of two RCC phase II trials were reported. The licensees, Handok Pharmaceuticals, Yakult Honsha, and Hikma, are developing the drug for various cancers, including colorectal cancer. In January 2012, Yakult Honsha initiated a phase I/II trial in patients with refractory advanced colorectal cancer in Japan. In June 2012, Yakult Honsha initiated a phase I combination trial for MM in Japan. Keryx previously collaborated with Aeterna Zentaris for producing drugs to treat various cancers. In December 2009, Keryx began a phase III trial for MM. In December 2011, it was reported that the trial was actively recruiting patients in the US and Canada. In April 2012, Keryx and Aeterna Zentaris planned to evaluate whether the phase III trials for MM would continue as planned. In January 2012, the potential launch of the drug was anticipated by the end of the year, with the completion of the phase III MM trial at the beginning of 2013. In July 2009, Keryx initiated a phase I trial in pediatric patients with solid tumors. In June 2010, the data from the trial were reported. By June 2009, Keryx was developing the drug for colorectal cancer. In April 2010, a phase III trial was initiated. In April 2012, the results showed that the trial had failed to meet its primary endpoint. Later that month, the indication was no longer listed in Keryx's future projects, while in June 2012, it was no longer listed in Aeterna Zentaris's future projects. In July 2007, a phase II trial was initiated for RCC. In May 2009, the clinical data were presented. In June 2007, phase II data were reported for macroglobulinemia. In January 2010, additional data were reported. In February 2007, a phase I trial for ovarian cancer was initiated. In October 2011, the trial was ongoing. In December 2006, Keryx started a phase II trial for rare sarcomas. In November 2007, the preliminary results were reported. In October 2011, the trial was completed. In August 2006, a phase II trial was initiated for GIST. The trial was completed in October 2011. In March 2006, Keryx initiated phase II trials for refractory and relapsed leukemia. In October 2009, another phase II trial was initiated, and the data were reported in December 2010. Aeterna Zentaris had previously been developing the drug for NSCLC. In September 2005, a radio-treatment combination trial began for NSCLC. In June 2009, negative data were reported from the trial and the company planned to concentrate on MM and metastatic colon cancer. Aeterna

Zentaris was advised not to pursue trials in pancreatic cancer or head and neck cancer. Trials have also been conducted in prostate cancer, liver cancer, breast cancer, melanoma, and glioma.

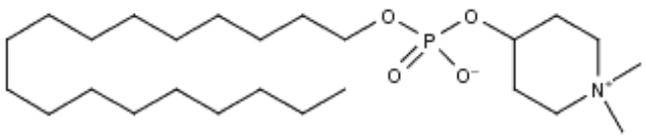

Figure 8. Chemical structure of perifosine.

6. mTOR inhibitors for melanoma treatment

Everolimus (RAD001, Afinitor) is an orally active inhibitor of Mammalian Target of Rapamycin complex 1 (mTORC1), a multifunctional signal transducing protein implicated in cancer [41]. Everolimus possesses antitumor and antiangiogenic/antivascular activities [42]. Previously, it was shown that the antiangiogenic/antivascular activities produced by mTORC1 inhibition using everolimus were partially overlapping, but they were also distinct from those following VEGFR inhibition by the TKI PTK/ZK (PTK787/ZK 222584; vatalanib) [43]. As shown in Table 5, everolimus is under evaluation for melanoma.

Name	Mechanisms
Everolimus	mTOR inhibitor

Table 5. Clinical trials of mTOR inhibitors for treating melanoma

Novartis has developed and launched everolimus (Figure 9), an oral analog of the mTOR inhibitor sirolimus, as an immunosuppressant to inhibit growth factor-induced cell proliferation and angiogenesis. The product is indicated in Europe and Japan under the trade name Certican for the prophylaxis of organ rejection in adults at low-to-moderate immunological risk of receiving an allogeneic renal or cardiac transplant. This product is also indicated under the trade name Zortress in the US to prevent organ rejection in adult kidney transplant recipients. Under the name Afinitor, everolimus is indicated for the second-line treatment of advanced RCC in Japan, after the failure of treatment with sunitinib or sorafenib in the US, or after the failure of treatment with VEGF-targeted treatment in the EU. It is also indicated for the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection, for the treatment of advanced neuroendocrine tumors (NET) of pancreatic origin, for the treatment of non-cancerous renal angiomyolipoma tumors that do not require immediate surgery in adult patients with TSC (in the US), and for use in combination with exemestane for the treatment of postmenopausal women with advanced hormone-

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receptor positive, HER2-negative breast cancer after the failure of treatment with non-steroidal aromatase inhibitors, including letrozole or anastrozole. In April 2004, everolimus was launched as Certican in Germany for the prevention of heart and kidney transplant rejection and then in EU in 2005. In April 2010, everolimus was launched as Zortress in the US for the prevention of kidney transplant rejection in adults. In March 2007, everolimus was launched for heart transplant rejection in Japan. It was approved for renal transplant rejection in Japan in December 2011. In March 2009, everolimus was launched as Afinitor in the US for the second-line treatment of advanced RCC. In August 2009, the EC approved Afinitor for the second-line treatment of advanced RCC. In April 2010, Afinitor was launched in Japan for RCC. By June 2010, a phase II trial was underway for treatment-naive papillary RCC. In October 2010, Afinitor was approved in the US for the treatment of patients with SEGA associated with TS, while EU approval was granted in September 2011 under the trade name Votubia. In February 2012, a application was submitted in Japan for TS, while an additional dispersible tablet formulation for pediatric use was also applied for at the same time. In May 2011, everolimus was approved by the FDA for pancreatic NET. In September 2011, everolimus was approved in the EU for pancreatic NET. In December 2011, approval was granted in Japan for pancreatic NET. In July 2012, the FDA approved everolimus for use in combination with exemestane for the treatment of postmenopausal women with ER+/HER2− breast cancer after the failure of treatment with letrozole or anastrozole. In July 2012, the EC approved the drug for the treatment of ER+/HER2− advanced breast cancer in postmenopausal women without symptomatic visceral disease after recurrence or progression following treatment with a non-steroidal aromatase inhibitor. In April 2012, everolimus was approved in the US for the treatment of non-cancerous renal angiomyolipoma tumors that do not require immediate surgery in adult patients with TSC. An EU application for angiomyolipoma tumors not requiring immediate surgery in adult patients with TSC was filed in January 2012. The drug is also being developed for other solid tumor indications. By September 2008, phase III trials were underway investigating the use of the drug plus octreotide in the treatment of carcinoid tumors. In February 2009, applications for carcinoid cancer were planned for 2H09. A phase II trial for bladder cancer began in December 2008. In May 2010, a phase III trial began for advanced HCC. In January 2011, an application for HCC was expected in 2013. In June 2010, a phase III program for advanced ER+ and HER2+ breast cancer was ongoing in first- and second-line settings. In July 2009, phase II trials began for head and neck cancer. A phase I trial for colorectal cancer began in June 2010. In October 2010, a phase I trial was planned for cervical cancer. In June 2012, a phase I/II trial for glioma was planned to start in November 2012. A phase II trial for neurofibromas associated with neurofibromatosis was planned for December 2011. A phase I trial for esophageal cancer was planned for January 2012. Drugs are being developed for hematological tumors. A phase I trial for non-Hodgkin's lymphoma (NHL) began in March 2008, while development for NHL was ongoing in January 2012. In June 2009, phase III trials were initiated for diffuse large B-cell lymphoma. In January 2011, Novartis did not expect an application for this indication before 2015. In January 2010, a phase II trial was initiated for Hodgkin's lymphoma. The data were reported in December 2011. In June 2010, the data were reported from a phase I/II trial for multiple myeloma. In February 2008, a phase I trial began using patients with AML. In December 2011, a phase II extension study was

planned. In December 2008, phase II data were presented for Waldenström's macroglobulinemia. Label extension during transplants was also ongoing. In March 2005, a phase III trial was initiated for lung transplantation. In September 2011, a second phase III trial began for lung transplant rejection. In January 2008, phase III trials for the prevention of liver transplant rejection were ongoing. In October 2011, a US regulatory application for liver transplant rejection was expected later in that year. Development for non-cancer indications was also ongoing. In December 2006, a phase III trial began for autosomal dominant polycystic kidney disease, and the results were published in August 2010. In February 2009, a phase II trial of everolimus in combination with ranibizumab for the potential treatment of age-related macular degeneration began. The drug was previously developed for the treatment of RA, inflammatory bowel disease, and genetic disorders. However, no development has been reported for these indications. In terms of cancer indications, everolimus was also previously developed for Kaposi's sarcoma, although this indication was discontinued by June 2011 because of lack of efficacy in phase II trials. Phase II development was underway by May 2005 for GIST, for hormone-refractory prostate cancer by August 2005, for small cell lung cancer by February 2006, and for NSCLC by June 2007. Phase II data for melanoma were also reported in June 2009.

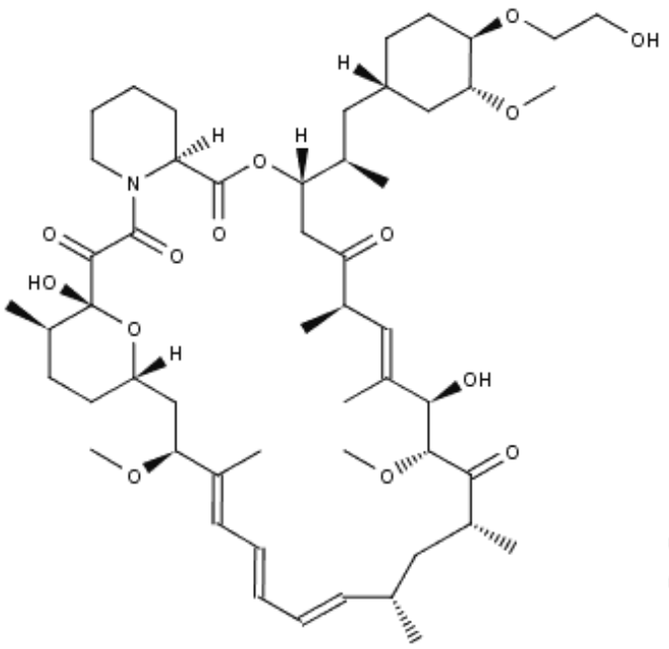

Figure 9. Chemical structure of everolimus.

7. Conclusions

This report reviews the clinical studies of recently developed targeted agents, including immune modulators, c-KIT inhibitors, BRAF/MEK inhibitors, AKT inhibitors, and mTOR

inhibitors, for the treatment of melanoma. Current research is focused on understanding the intrinsic mechanisms of these drugs. This will lead to rationally designed combinations of first- and second-line therapies, which will hopefully improve the efficacy and tolerability in selected groups of patients with melanoma. Understanding the molecular basis of melanoma and translating this knowledge into targeted treatment that improve the survival of patients with advanced melanoma is very important. Immune modulatory antibodies such as tremelimumab, ipilimumab, and BMS-663513 may have a crucial role in initiating and maintaining a melanoma-specific immune response.

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