REVIEW

The Role of MET in Melanoma and Melanocytic Lesions

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Melanoma is the leading cause of death due to cutaneous malignancy and its incidence is on the rise. Several signaling pathways, including receptor tyrosine kinases, have been recognized to have an etio-pathogenetic role in the development and progression of precursor melanocytic lesions and malignant melanoma. Among those, the hepatocyte growth factor/MET (HGF/MET) axis is emerging as a critical player not only in the tumor itself but also in the immune microenvironment in which the tumor grows and advances in its development. Moreover, the activation of this pathway has emerged as a paradigm of tumor resistance to modern targeted therapies, and the assessment of its expression in patients' samples may be a valuable biomarker of tumor progression and response to targeted therapy. Here we summarize our current understanding of this important receptor tyrosine kinase in normal melanocyte proliferation/motility, in tumor progression and metastasis, its genetic alterations in certain subtype of melanocytic lesions, and how its pathway has been explored for the development of selective inhibitors. (*Am J Pathol* 2019; 189: 2138–2148; <https://doi.org/10.1016/j.ajpath.2019.08.002>)

Melanoma is the most common lethal cancer among all skin malignancies, with a high propensity for metastasis.¹ The 5-year survival rate drops from about 98% in patients with early, localized disease to only 20% in those with metastatic melanoma.¹ The estimated 5-year overall survival is 34% even in the era of immunotherapy such as the PD-1 inhibitor pembrolizumab. The annual incidence of malignant melanoma has increased by approximately 50% over the last decade.^{1,2}

A variety of pathogenic mutations are associated with the initiation, progression, and metastasis of melanoma. Of these, the *BRAFV600E* mutation has been found in approximately half of malignant melanomas and tend to be more frequent in low-cumulative sun-induced damage melanomas.^{3,4} On the other hand, *NRAS*, *NFI*, and other *BRAF* mutations are more frequently present in high-chronic sun-induced damage melanomas.^{4,5} Therapies targeting these mutations and relevant pathways have led to improved patient survival. However, the treatment of locally advanced or metastatic melanomas often requires systemic or combination approaches, including immunotherapy (the checkpoint inhibitors anti-programmed cell death protein 1, anti-programmed cell death protein ligand 1, or cytotoxic T lymphocyte-associated antigen 4 antibodies), targeted

therapy [BRAF and/or mitogen-activated protein kinase kinase (MEK) inhibitors], and chemotherapy.^{6,7} The absolute survival rate remains quite low.⁸ Furthermore, immunotherapy and targeted therapy are often limited by high rates of resistance.^{9,10} Therefore, a better understanding of the molecular events involved in the progression and therapeutic resistance of melanoma is necessary.

Increasing attention has been drawn to the critical role of the hepatocyte growth factor (HGF)/MET pathway in melanoma development, progression, and therapeutic resistance.^{10,11} MET receptor, also known as HGF receptor, is expressed in the epithelial cells of many tissues, including skin, and the tumorigenic effect of the HGF/MET pathway has long been observed in malignancies of various organs. Therapies targeted toward this pathway have yielded improved clinical outcomes, especially in renal cell and lung carcinomas.^{12,13} Therefore, the observation of MET activation in melanoma may open up a new possibility of aid in

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melanoma treatment. MET signaling aberrations have been found in melanomas at both sun-exposed and sun-shielded sites. Commonly found *MET* alterations include *MET* amplifications in desmoplastic melanoma, a high—chronic sun-induced damage melanoma, and *MET* rearrangements in Spitz melanoma as well as in its benign/intermediate precursor lesions.⁴ In the most recent large-scale whole-genome sequencing analysis of melanoma, which included 183 patient samples of cutaneous, mucosal, and acral subtypes, frequent *MET* aberrations were demonstrated, with 24% gene amplifications, 9% single-nucleotide variations/deletions, and 1% structural variants.¹⁴ Therapies targeting the HGF/MET pathway have shown promising results in inhibiting melanoma growth and metastasis in preclinical studies. However, translations of MET inhibitors into clinical studies as single-therapy agents in melanoma, as in other cancers, have been largely unfruitful, possibly due to the complex crosstalk of the HGF/MET pathway with other oncogenic pathways. Recent ongoing efforts include the investigation of synergistic therapeutic effects of combination therapies involving MET inhibitors, and mechanistic studies of MET targeting to overcome therapeutic resistance. These studies promise to better define the roles of this pathway in melanoma and other malignancies and to more precisely guide clinical applications of its targeted therapy.

MET Structure, HGF/MET Signaling, and Biological Functions

The proto-oncogene *MET* on the 7q31 locus encodes MET, alias HGF receptor.¹⁵ HGF, a pleiotropic heparin-binding protein, binds to MET and elicits multiple biological activities such as mitogenic, motogenic, and morphogenic responses in various cell types, including melanocytes.¹⁶ HGF is produced as an inactive single-chain precursor that is processed to yield an active heterodimer of one α and one β chain linked by a disulfide bond.¹⁷ MET is a transmembrane receptor composed of a glycosylated, extracellular α subunit and a transmembrane β subunit.¹⁸ The α and the first 212 residues of the β subunit serve as the extracellular binding site for HGF.¹⁹ The intracellular portion of the β subunit contains three major domains: the juxta-membrane domain, the kinase domain, and the C-terminal docking site.¹⁶ Upon ligand binding, two tyrosine residues in the kinase domain, Y1234 and Y1235, are phosphorylated. Phosphorylation of two critical tyrosine residues, Y1349 and Y1356, within the C-terminal docking site recruits multiple intracellular molecules, including GRB2—associated-binding protein 1 (GAB1), growth factor receptor—bound protein 2 (GRB2), phosphatidylinositol 3 kinase (PI3K), phospholipase C γ , Src, and Shc, via binding to a Src homology 2 domain or other recognition motifs.^{11,16} Consequently, multiple signaling pathways controlling cell survival, cell cycle progression, motility, and migration, including the PI3K/Akt, Ras/mitogen-activated

protein kinase (MAPK), Rac1/cell division control protein 42 pathways, are activated (Figure 1).¹⁶

Under normal physiologic conditions, HGF produced by cells of mesenchymal origin acts in a paracrine manner to stimulate MET during embryonic development and throughout adulthood.¹⁶

Role of MET and HGF in Melanocytes

Normal human melanocytes do not secrete HGF but are receptive to HGF through the expression of MET.²⁰ HGF functions as a mitogen, stimulating melanocyte proliferation, in synergy with basic fibroblast growth factor and mast cell growth factor.²¹ HGF/MET signaling also promotes melanocyte motility and maintains high levels of tyrosinase activity and melanin content.^{20,21} Ubiquitous overexpression of HGF in transgenic mice leads to hyperpigmentation in neonatal and adult skin and hyperproliferation of melanocytes in ectopic tissues.²² In addition, the up-regulation of MET expression via melanocyte-inducing transcription factor has been found to protect melanocytes from apoptosis.²³ Under certain insults such as UV radiation, melanocyte-inducing transcription factor could directly bind to the MET promoter in response to the increased level of α -melanocyte—stimulating hormone,²³ further emphasizing the complexity of the interplay of different pathways.

Other studies have also revealed the regulatory roles of HGF/MET signaling in the development of melanocytes from neural crest.²⁴ HGF promotes melanoblast survival and differentiation into pigmented melanocytes *in vitro*. Both *in vitro* and *in vivo* studies in mouse transgenic embryos have shown that the HGF/MET signaling can influence the initial development of neural crest—derived melanocytes.²⁴ These studies not only offer a window on the role of this signaling pathway on physiologic melanocyte functions, but also highlight our incomplete understating and the need for additional studies.

Role of RTKs in Melanoma and Melanocytic Lesions

In malignancies, the HGF/MET pathway is aberrantly activated through several mechanisms, including paracrine signaling, activating mutations, overexpression, or autocrine loop formation.²⁵ Abnormalities in receptor tyrosine kinase (RTK) expression have been demonstrated to contribute to melanoma development and progression.²⁶ In transgenic mice, Ret overexpression or MET activation could lead to melanoma development.²⁷ With advancement in technologies such as whole-genome sequencing, multiple forms of RTK aberrations have been discovered in melanoma cell lines and patient-derived samples.^{1,14} More than 20 RTK families, including epidermal growth factor receptor, extracellular region binding proteins 2 and 4, Kit, fibroblast growth factor receptor, MET, and platelet-derived growth factor receptor, are involved in melanoma tumorigenesis.¹⁴ RTK alterations

Figure 1 Summary of hepatocyte growth factor (HGF)/MET signaling and functions in tumor cells and microenvironment. **A:** HGF-induced activation of MET signaling cascade by either paracrine or autocrine manner. Phosphorylation of critical tyrosine residues triggers the recruitment of multiple effector molecules inside tumor cells, thus activating several downstream signaling pathways responsible for cell migration, proliferation, and survival. **B:** Endogenous HGF/MET axis can also be activated in neutrophils and cytotoxic T cells in the tumor microenvironment. MET-dependent neutrophils may also indirectly affect the functions of T cells. APC, adenomatous polyposis coli; EMT, epithelial–mesenchymal transition; FAK, focal adhesion kinase; GAB, GRB2–associated-binding protein; GRB, growth factor receptor–bound protein; MEK, marker extraction kernel; mTOR, mammalian target of rapamycin; PAK, p21-activated kinase; PD-L, programmed cell death protein ligand; PI3K, phosphatidylinositol 3-kinase; PLC, phospholipase C; SHP, small heterodimer partner; SLUG, human embryonic protein SNAI 2; Snai1, zinc finger protein SNA 1; SOS, son of sevenless protein; Twist, Twist family bHLH transcription factor.

are frequently identified in cutaneous, acral, and mucosal melanomas, and may represent promising therapeutic targets.

In a subset of melanocytic neoplasms, recurrent rearrangements of kinases, have been described as a mechanism of oncogenic activation.^{28,29} The resulting chimeric proteins are constitutively active, stimulating oncogenic signaling pathways. In particular, gene rearrangements of *MET* resulting in in-frame *MET* kinase fusions are found in Spitz tumors and Spitzoid melanomas.³⁰ *MET* fusions tend to occur in younger patients (with an average age of onset of 20 years), and are present across benign, atypical, to malignant lesions, suggesting early occurrence of the *MET* fusions during tumor progression.³⁰ Common mutations in melanomas involving *NRAS*, *NFI*, or *BRAF* are usually not present in Spitzoid neoplasms. However, some of them can become aggressive and metastasize. These lesions may require systemic therapy, but targeted therapeutic options for these melanocytic lesions do not currently exist. Since *MET* fusions occur in a mutually exclusive pattern with activating mutations in known melanoma oncogenes, they may represent a unique therapeutic target in those lesions.^{29,30} Additional functional studies in mouse models and larger cohorts of patients with specific mutations or other genetic alterations will be required to evaluate the effects of each of these genetic alterations in melanoma, and to further develop tailored therapeutic strategies.

Role of MET and HGF in Primary Melanoma

Multiple mechanisms that confer oncogenic potential to HGF and MET in a wide variety of human cancers have been described, including autocrine or paracrine loop formation, MET-activating mutations, structural variants, and gene amplification.²⁵ For example, a study showed that the HGF/MET autocrine loop stimulated the aberrant growth of melanocytes with endogenous MET overexpression and drove tumorigenesis in a transgenic mouse model.³¹ Several other studies have also shown that some melanomas in humans can express both MET and HGF, in contrast to normal melanocytes, which rarely produce HGF, further confirming the formation of an autocrine loop in melanoma development.^{5,32–34}

Various *MET* mutations have been identified in melanoma.³⁵ Among these, activating mutations in the *MET* kinase domain are most closely associated with its oncogenic capacity.^{25,36,37} Mutations within the *MET* juxtamembrane domain also have a role in tumorigenesis, cell motility, and migration. In lung cancer (eg, juxtamembrane), domain mutations result in alternative splicing of *MET* and production of more stable MET proteins.^{7,9,38} New missense *MET* mutations in the juxtamembrane domain, contributing to melanoma growth and progression, have been identified in a cell line (N948S) and tumor tissue (R988C).³¹ Other studies have questioned the association of *MET* mutations with adverse prognosis in malignant melanoma.^{6,16}

The association of MET pathway activation with other well-known melanoma driver genes has also been investigated.^{10,14,39} In primary melanoma-derived cells in humans, Chattopadhyay et al³⁹ observed a higher level of phosphorylation of MET (which leads to more robust pathway activation in response to HGF) in *NRAS*-mutated tumors when compared to *BRAF*-mutated tumors.¹⁰ Concurrently, pharmacologic inhibition of MET resulted in more potent inhibition of melanoma cell proliferation and migration in *NRAS*-mutated tumors compared to *BRAF*-mutated tumors. However, in a recent whole-genome analysis of various subtypes of melanoma, *MET* copy number amplification appeared to be associated with amplification of *BRAF* hotspot mutations, possibly due to the proximity of the *MET* and *BRAF* genes on chromosome 7.¹⁴ Such an association was not observed between *MET* and *NRAS*. Further and better understanding of the association between types and prevalence of *MET* alterations and other common oncogene mutations in melanoma may be needed, in light of the potential benefit of combined targeting for optimal synergistic effects in selected subtypes of melanomas.

Role of MET and HGF in Melanoma Metastasis

Melanomas are highly metastatic tumors. As aforementioned, HGF/MET signaling promotes several critical steps in cancer cell invasion and metastasis, such as cell scattering, migration, extracellular matrix degradation, and angiogenesis.²⁷ Mechanistically, cytoplasmic signaling cascades downstream of MET, including PI3K/Akt and Rac1—cell division control protein 42 pathways, may induce cell cytoskeletal changes and affect cell surface integrin and cadherin expressions, thus controlling cell migration and adhesion processes.⁴⁰

The role of the HGF/MET pathway in metastatic melanoma has been studied in the B16 melanoma cell model, where MET activation was required for metastasis and colonization of melanoma cells in liver, possibly by inducing cell motility and invasion in response to HGF in a paracrine manner.⁴¹ Moreover, MET-induced melanoma cell migration could be completely inhibited by a selective MET inhibitor, indicating the necessity of its pathway in this process.^{42,43} The efficacy of certain MET inhibitors (such as crizotinib) in inhibiting metastasis in preclinical mouse models and patients is currently being evaluated.⁴⁴

Role of MET and HGF in Epithelial–Mesenchymal Transition

Epithelial–mesenchymal transition (EMT) is an essential process contributing to the progression of epithelial cancers from localized disease to invasion and metastasis. Experimental evidence demonstrates the critical roles of phenotype switching (analogous to EMT) in both melanocyte differentiation and melanoma progression to metastatic

disease.^{45,46} As in epithelial cancers, the EMT-like phenotype switching in melanoma is associated with the loss of E-cadherin and the gains of N-cadherin, osteopontin, and osteonectin.⁴⁶ However, with a neural crest derivation, melanocytes and melanoma cells differ from both epithelial and mesenchymal cells phenotypically. A recent review has described the similarities and differences in the expressions and regulations of the common EMT-transcriptional factors between epithelial cancers and melanoma.⁴⁵ For example, zinc finger protein SNA 1 and 2 (SNAIL1 and SNAIL2), human embryonic protein SNAI 2 (SLUG), zinc finger E box–binding homeobox 1 and 2 (ZEB1 and ZEB2), and Twist family bHLH transcription factor (Twist) are all considered as important repressors of E-cadherin in epithelial carcinomas. However, an opposite role of ZEB2, that is, the promotion of differentiation and preservation of E-cadherin expression, was found in melanoma.⁴⁷ Once more, these discrepancies outline our incomplete knowledge and the need for additional studies.

Several studies have demonstrated that the activation of the HGF/MET pathway promotes EMT through the regulation of multiple known repressors of E-cadherin in melanomas (Figure 2).^{33,48,49} In one study, autocrine activation (by adenovirus-induced HGF expression) of MET leads to constitutive activation of MAPK and PI3K and down-regulation of E-cadherin and desmoglein 1 in both normal melanocytes and melanoma cell lines.³³ After exposure to exogenous human recombinant HGF, several melanoma cell lines express up-regulated amounts of SNAIL1, Twist, and human embryonic protein SNAI2 at various time points, mediating the switch from E-cadherin to N-cadherin.⁴⁸ Another study showed that downstream activation of the MAPK/early growth response 1 (Egr-1) pathway is required in HGF/MET–induced SNAIL1 up-regulation.⁴⁹ HGF-induced activation of the MAPK/Egr-1 pathway also exhibits several other functions, including promoting fibronectin matrix synthesis, which mediates melanoma cell migration.⁵⁰

In addition, CD44 isoforms have been found to be critical regulators of EMT.⁵¹ For example, Recio and Merlino⁵² found that in a murine melanoma cell line, transcriptional Egr-1 activation up-regulates CD44v6 expression, facilitating the binding and presentation of Hgf to its receptor.

Together, the findings from these studies unveil the mounting evidence of the role of the HGF/MET pathway in EMT in melanoma, and further confirm the use of MET inhibitors as a viable therapeutic avenue to preventing metastatic disease.

Role of MET and HGF in Immunomodulation in Melanoma

The HGF/MET axis is also involved in the modulation of innate and adaptive immune responses and tissue repair.⁵³ Immune cells in the tumor microenvironment exert both antitumor and protumor effects in several cancers, including

Figure 2 Hepatocyte growth factor (HGF)/MET pathway activation promotes epithelial–mesenchymal transition through up-regulation of multiple E-cadherin repressors and mediating switch from E-cadherin to N-cadherin. Erg, erythroblast transformation-specific transcription factor; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; SLUG, human embryonic protein SNAI2.

melanoma. In this setting, the role in immunomodulation by the HGF/MET pathway in cancer deserves further investigation and may provide valuable therapeutic implications.

Recently HGF/MET signaling has been demonstrated to be required for neutrophil migration to the tumor microenvironment in melanoma.⁵⁴ These antitumor neutrophils exert cytotoxic effects on tumor cells via the production of inducible nitric oxide synthase and nitric oxide (Figure 3). MET deletion in neutrophils, on the other hand, promote cancer growth and metastasis by reducing antitumoral neutrophilic recruitment. These mechanisms may offer in part an explanation for some limited results of selective MET inhibitors in clinical trials.

Glodde et al⁵⁵ also found that HGF/MET signaling mediated the recruitment of reactive neutrophils from bone marrow to tumor and lymph nodes, following immunotherapies such as adoptive T-cell transfer or checkpoint blockade. However, these MET-expressing neutrophils impaired therapeutic T-cell proliferation, thus limiting the efficacy of immunotherapies (Figure 3). Concurrent inhibition of MET successfully potentiated the efficacy of cancer immunotherapy in melanoma-bearing mouse models. Interestingly, patient data mirrored the results in mouse models, showing an increase in serum HGF and blood neutrophil counts in anti-programmed cell death protein 1 therapy nonresponders with advanced melanoma.

A subset of endogenous MET-positive cytotoxic T cells has also been found in melanoma patients, and HGF directly limited the tumor-killing functions of these Met⁺ CD8⁺

tumor-infiltrating lymphocytes in a metastatic melanoma mouse model.⁵⁶ The role of HGF/MET as an immunosuppressive signaling pathway is also put in evidence through the induction of tolerogenic DCs and Langerhans cells, as seen in experimental models of graft-versus-host disease and autoimmune encephalomyelitis.⁵³ Finally, in carcinomas, MET signaling—induced phosphorylation of $\alpha_{6\beta4}$ -integrin possibly contributes to the migration of DCs and Langerhans cells.⁵⁷

Although our current knowledge of the role of the HGF/MET signaling axis is piecemeal at best, overall these pathways appear to be mostly immunosuppressive in cancer immune responses, although additional studies will be necessary to fully understand the therapeutic implications at a time of excitement for the promise of cancer immunotherapy.

Role of MET and HGF in Therapeutic Resistance in Melanoma

The treatment of malignant melanoma has been more recently revolutionized by the introduction of small-molecule targeted therapies and immune checkpoint inhibitors. In particular, B-Raf inhibitors (eg, vemurafenib, the first approved targeted therapy for *BRAFV600E* metastatic melanoma) have achieved significant improvement in PFS and OS, with a response rate of 50% to 60%.^{6,58} The combination of BRAF and MEK inhibitors has further improved the response rate to 70%.⁵⁹ However, almost all patients eventually develop resistance after BRAF or BRAF–MEK combined inhibition.⁵⁸

Resistance to BRAF and/or MEK inhibitors may be acquired via a broad spectrum of both genomic and non-genomic mechanisms.^{10,60} Among these, growth factor–mediated reactivation of MAPK and/or PI3K pathway via RTKs has been found to be an important resistance mechanism,⁶¹ and specifically, HGF/MET pathway activation has been demonstrated recently to elicit both innate and acquired resistance to BRAF inhibitors.

In a recent preclinical study using 12 BRAF inhibitor–resistant patient-derived xenograft models, *MET* amplification was observed at a higher frequency, and it tended to coexist with *BRAF* hotspot mutation.⁶² Moreover, triple combination of BRAF, MEK, and MET inhibitors (capmatinib, encorafenib, binimetinib) leads to complete and sustained tumor regression *in vivo*. On further analysis, both therapy-naïve lesions and post-therapy metastatic samples were found to be MET positive, suggesting that *MET* amplification is a preexisting event contributing to the intrinsic resistance to BRAF inhibitors. In addition, increased HGF secretion in the tumor microenvironment represents another mechanism to induce innate resistance to BRAF inhibitors.⁶³

The mechanisms of MET activation in acquired resistance to BRAF/MEK inhibitors have also been studied.^{10,60,64} Caenepeel et al¹⁰ found that MAPK pathway inhibition after BRAF inhibitor treatment induced rapid increases in MET and growth factor receptor–bound protein 2–associated binder 1 expression; a similar increase in MET also occurred after

Figure 3 Roles of MET signaling in immunomodulation of melanoma microenvironment. MET activation recruits neutrophils to the tumor microenvironment, which may lead to direct cytotoxicity to melanoma cells or may inhibit functions of tumor infiltrating lymphocytes. HGF, hepatocyte growth factor; ICAM, intercellular adhesion molecule; iNOS, inducible nitric oxide synthase; NO, nitric oxide.

MEK pathway inhibition in *NRAS*-mutated melanoma cell lines. Furthermore, *in vivo* experiments have suggested that tumor-derived HGF may be required to rescue melanoma cells from BRAF/MEK inhibitors. An association between MET levels and strength of HGF rescue after vemurafenib treatment has been observed, indicating the potential use of MET levels as a biomarker to identify patients suitable for MET inhibitor combination therapy.¹⁰ Another study identified hypoxia-driven up-regulation of HGF/MET signaling as a major mechanism of resistance to several BRAF inhibitors in melanoma patients and mouse xenografts.⁶⁴ A recent transcriptomic-methylomic analysis revealed recurrently increased *MET* mRNA expression in resistant tumors, possibly due to differential CpG cluster methylation.^{30,60} Further investigations of upstream and downstream components involved in the mechanisms of resistance to BRAF/MEK inhibitors are of paramount importance to understand how to overcome therapeutic resistance in melanoma and ultimately understand the therapeutic potential of MET inhibitors in this setting.

Targeting the HGF/MET Signaling Pathway for the Treatment of Melanoma

Several HGF/MET pathway inhibitors have been developed in the last 2 decades. Promising results have been reported,

especially in papillary renal cell carcinoma and non-small cell lung carcinoma (NSCLC).^{12,13} Table 1 focuses on trials that have evaluated these inhibitors in melanoma. Pharmacologic MET inhibition has been tested in melanoma patients both as single agents or in combination with other anticancer therapies. Most recently combinations with immunotherapy or BRAF/MEK inhibitors have been tested to improve efficacy or to overcome resistance. Analyses of *MET* alteration in several trials have guided the use of these inhibitors.

Capmatinib (INC280) is an oral selective MET inhibitor tested in *MET* fusion-positive patients with wild-type *BRAF/NRAS* metastatic melanomas (NCT02587650), or in patients with advanced *BRAF*-mutated melanoma after progression following standard treatments (NCT01820364, NCT02159066). Genetic analysis of tumor biopsy samples has been used to stratify patients into appropriate targeted therapy groups. One of these Phase II trials (NCT01820364) was terminated early for scientific and business factors, not for safety concerns, and given the small cohort of patients, the results were insufficient for a definitive interpretation. The other trial (NCT02159066) is still ongoing, so no results are available at the moment.

Crizotinib (PF-02341066) is a potent inhibitor of MET, anaplastic lymphoma kinase, and reactive oxygen species 1.⁴⁴ It has received US Food and Drug Administration

Table 1 MET Inhibitors for Malignant Melanoma in Clinical Trials

Drug	Design	Phase	Start date	Status	Patient population	Combinations /comparisons	Clinical trial*
Crizotinib	Efficacy/toxicity	II	March 2015	Active, not recruiting	Uveal melanoma with high risk of recurrence after definitive therapy with surgery or radiation	None	NCT02223819
	Efficacy/genetic aberrations	IV	February 2019	Active, not recruiting	Unresectable Stage III or Stage IV metastatic melanoma with or without <i>BRAF/NRAS</i> mutations	Comparing to standard therapy /clinical trial; matched targeted therapy; trametinib and/or supportive care	NCT02645149
Cabozantinib-s-malate (XL184)	Tolerability/efficacy	I	May 2013	Terminated	Recurrent, Stage III/IV melanoma, Unspecified adult solid tumor, protocol specific	Vemurafenib	NCT01835184
	Efficacy/safety/tolerability/pharmacokinetics /pharmacodynamics	II	August 2009	Completed	Advanced/recurrent/metastatic solid tumors (9 types) including melanoma	None	NCT00940225
	Efficacy/safety	II	July 2013	Completed (no results posted)	Recurrent or Stage III/IV uveal melanoma	Comparing to temozolomide or dacarbazine	NCT01835145
E7050	Safety/efficacy	Ib/II	October 2011	Unknown [†]	Unresectable advanced or metastatic solid tumors (including glioblastoma or Stage III or IV melanoma)	Lenvatinib	NCT01433991
Capmatinib (INC280)	Efficacy	II	September 2018	Recruiting	Previously treated unresectable or metastatic melanoma	Spartalizumab + either capmatinib or LAG525 or canakinumab	NCT03484923
	Efficacy/safety	II	July 2014	Active, not recruiting	Locally advanced or metastatic BRAF V600 melanoma	LGX818 + MEK162 + either capmatinib or LEE011 or BGJ398 or BKM120	NCT02159066
	Efficacy/safety	II	March 2013	Terminated	Advanced BRAF mutant melanoma	LGX818 + either capmatinib or MEK162 or LEE011 or BGJ398 or BKM120	NCT01820364
	Efficacy/safety	II	March 2015	Recruiting	<i>BRAF/NRAS</i> wild-type Stage III-IV melanoma	Either capmatinib or certinib or entrectinib or regorafenib (depending on the fusion kinase status)	NCT02587650

(table continues)

Table 1 (continued)

Drug	Design	Phase	Start date	Status	Patient population	Combinations /comparisons	Clinical trial*
Tivantinib (ARQ197)	Safety/efficacy	I/II	August 2010	Active, not recruiting	Various advanced solid tumors including melanoma, HCC, RCC, NSCLC, breast cancer, and ovarian cancer	Monotherapy or in combination with other drug(s)	NCT01178411
	Safety/preliminary efficacy	I	September 2009	Completed	Adults with advanced solid tumors (HCC, RCC, melanoma, NSCLC, and breast cancer)	Sorafenib	NCT00827177
Met RNA CAR T cells	Safety/efficacy	Early I	December 2016	Recruiting	Advanced melanoma or breast carcinoma	None	NCT03060356

*Available at <http://clinicaltrials.gov>.

†Has passed its completion date and status not been verified in more than 2 years.

CAR, chimeric antigen receptor; HCC, hepatocellular carcinoma; NSCLC, non–small cell lung cancer; RCC, renal cell carcinoma.

(FDA) approval for the treatment of patients with metastatic NSCLC who were anaplastic lymphoma kinase positive or reactive oxygen species 1 positive in 2011 and 2016, respectively (<https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm490391.htm>, last accessed July 2, 2019). Moreover, in May 2018, the FDA granted crizotinib two breakthrough designations, one of which was for patients bearing previously treated metastatic NSCLC with MET exon 14 alterations (Pfizer, New York, NY). The inhibitory effects of crizotinib on MET were also observed in other cancers, including urothelial carcinoma, papillary renal cell carcinoma type 1, and uveal melanoma.^{13,44} In uveal melanoma, crizotinib inhibited cell migration at a concentration sufficient for preventing phosphorylation of the MET receptor but not of ALK or reactive oxygen species 1. Moreover, in a metastatic mouse model of uveal melanoma, crizotinib strongly inhibited the development of metastasis of uveal melanoma.⁴⁴ Its efficacy in prolonging relapse-free survival in patients with high-risk uveal melanoma has been under investigation in an ongoing Phase II clinical trial (NCT02223819).

Cabozantinib (XL184) is another broad-spectrum, small-molecule kinase inhibitor targeting multiple proteins including MET, vascular endothelial growth factor receptor 2, Ret proto-oncogene, AXL receptor tyrosine kinase protein, Kit, and fms-like tyrosine kinase 3. It was FDA approved for the treatment of metastatic medullary thyroid cancer in 2012 and for the treatment of advanced renal cell carcinoma after failure from prior antiangiogenic therapy in 2016 (<https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm497483.htm>, last accessed July 2, 2019). Due to its potent activity in suppressing tumor growth, angiogenesis, and metastasis in various solid tumors, cabozantinib has been under study for its efficacy in several human malignancies, such as breast, melanoma, and hepatocellular carcinomas; SCLC; NSCLC; and ovarian, pancreatic, and prostate cancers.^{12,65,66}

Specifically, in a cohort of patients with metastatic melanoma (NCT00940225), the median progression-free survival with cabozantinib treatment was 5.7 months, longer than that in patients receiving placebo (3 months). However, the difference was not statistically significant, and further investigation on clinical efficacy may be warranted. That study not only covered patients with cutaneous/mucosal subtypes of melanoma (70%), but also those with uveal melanoma (30%). The median PFS in patients with uveal melanoma was 4.8 months, suggesting antitumor activity regardless of melanoma subtype.⁶⁵

Patients with uveal melanoma are usually excluded from clinical trials in melanoma patients due to resistance to standard therapies, poor prognosis, and high risk for liver metastasis in uveal melanoma.⁶⁵ However, MET represents a rational target for uveal melanoma; its up-regulation and subsequent pro-proliferation/metastasis effects may be associated with mutations in the *GNAQ* and *GNA11* genes, which are present in >80% of cases of uveal melanoma.⁶⁷ A Phase II trial was initiated to assess the efficacy of cabozantinib specifically in patients with recurrent or advanced uveal melanoma (NCT01835145); results are currently under review.

Tivantinib (ARQ 197) is a highly selective oral MET inhibitor that binds to the dephosphorylated MET kinase. Its safety and efficacy have been evaluated in several clinical trials in various advanced solid tumors including hepatocellular carcinoma, renal cell carcinoma, melanoma, NSCLC, breast, and ovarian cancers. The preliminary disease control rate (≥ 8 weeks) was 58% in all patients, 90% in renal cell carcinoma, 65% in hepatocellular carcinoma, and 63% in melanoma.⁶⁸ However, tivantinib failed to improve overall survival over placebo in patients with MET-high advanced hepatocellular carcinoma previously treated with sorafenib in a Phase III clinical trial.⁶⁹ Currently no definitive clinical data on melanoma patients in this trial are available.

Overall, these clinical studies suggest interest in investigating the role of MET inhibitors in treating melanoma, but

the efficacy data are still limited. A better patient stratification based on molecular profile may likely aid in the development of these therapies.

Conclusions

Recent preclinical and clinical studies highlight the important roles of the HGF/MET signaling pathway in melanoma progression, metastasis, and therapeutic resistance. MET exerts these functions through downstream interactions with a multitude of other signaling pathways critical for proliferation, cell survival, and migration, and by acting on both cancer cells and tumor microenvironment. Targeted therapies inhibiting MET signaling have been under active investigation in patients with malignant melanoma, with promising but still limited efficacy data. Ongoing clinical studies suggest that the combination of HGF/MET inhibitors with immunotherapies or targeted therapies may represent an effective therapeutic approach for improving outcomes in melanoma patients. More research investigating the mechanisms contributing to therapy resistance and/or synergistic effect with other currently available therapies may accelerate the development and application of HGF/MET-targeted therapies in melanoma treatment.

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