KIT and Melanoma: Biological Insights and Clinical Implications

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Melanoma, originating from epidermal melanocytes, is a heterogeneous disease that has the highest mortality rate among all types of skin cancers. Numerous studies have revealed the cause of this cancer as related to various somatic driver mutations, including alterations in *KIT*—a proto-oncogene encoding for a transmembrane receptor tyrosine kinase. Although accounting for only 3% of all melanomas, mutations in c-KIT are mostly derived from acral, mucosal, and chronically sun-damaged melanomas. As an important factor for cell differentiation, proliferation, and survival, inhibition of c-KIT has been exploited for clinical trials in advanced melanoma. Here, apart from the molecular background of c-KIT and its cellular functions, we will review the wide distribution of alterations in *KIT* with a catalogue of more than 40 mutations reported in various articles and case studies. Additionally, we will summarize the association of *KIT* mutations with clinicopathologic features (age, sex, melanoma subtypes, anatomic location, etc.), and the differences of mutation rate among subgroups. Finally, several therapeutic trials of c-KIT inhibitors, including imatinib, dasatinib, nilotinib, and sunitinib, will be analyzed for their success rates and limitations in advanced melanoma treatment. These not only emphasize c-KIT as an attractive target for personalized melanoma therapy but also propose the requirement for additional investigational studies to develop novel therapeutic trials co-targeting c-KIT and other cytokines such as members of signaling pathways and immune systems.

Key Words: c-KIT protein, melanoma, mutation, therapeutics, clinical trial

OVERVIEW OF c-KIT AND ITS RTKs FAMILY

c-KIT or CD117 is a member of class III transmembrane receptor tyrosine kinases (RTKs) along with platelet-derived growth factor receptors (PDGFRs), fms like tyrosine kinase 3 (FLT3)/ CD135, and macrophage colony stimulating factor receptors (M-CSFRs). It was discovered in 1987 as a cellular homologue of viral oncogene *v-kit*, which was isolated from a feline retro-virus.[1,2] A variety of cell types were identified to express c-KIT including hematopoietic cells, germ cells, gastrointestinal (GI) tract Cajal cells, melanoma cells, B cell progenitors, and mast cells.

Wild-type c-KIT protein contains 976 amino acids (aa) divided into three main regions including an extracellular ligand-binding domain with 519 aa, a hydrophobic transmembrane domain with 23 aa, and an intracellular tail (Fig. 1).[3,4] The extracellular domain consists of five immunoglobulin-like domains D1–D5, in which D1–D3 is responsible for stem cell factor (SCF) binding while D4–D5 contains motif for receptor dimerization. The 433 aa cytoplasmic region includes a juxta-membrane domain and a tyrosine kinase domain with an insertion of approximately 80 residues. Most of phosphorylation sites on c-KIT are located at the juxta-membrane region, the kinase insertion domain, and the C-terminal tail. Human c-KIT is encoded by a proto-oncogene located on the chromosome 4 at position of q11–12.[5] This 90 kb gene is transcribed and translated into a core protein of 110 kDa, which is subsequently heterogeneously N-linked glycosylated, mainly in the extra-

Fig. 1. Structure of c-KIT receptor tyrosine kinase.

Fig. 2. c-KIT mediated signaling pathways.

cellular domain closest to the plasma membrane, before maturing to a size of 145−160 kDa.[2,6] c-KIT has four isoforms generated by alternative splicing mechanism.[7-9] The first two isoforms differ in the presence of a glycine-asparagine-asparagine-lysine (GNNK) tetra-peptide adjacent to the extracellular transmembrane domain. The other two relate to the presence or absence of a serine amino acid at position 715 (Ser715) in the kinase insertion region.

The ligand SCF of c-KIT is a hematopoietic cytokine, which signals to maintain survival of hematopoietic cells as well as to promote cell proliferation, differentiation and regulation of growth and development.[10] Upon binding to D1−D3 region of c-KIT, a homodimer of SCF induces a conformational change that enables a homotypic interaction between D4−D5 regions of two adjacent c-KIT molecules.[11,12] This dimerization allows a trans-phosphorylation of tyrosine residues in the intracellular region of each c-KIT monomer by the other, leading to signal transduction through plasma membrane. Many mutations in c-KIT have been found to perturb these characteristics. For example, a mutation in D4 at key residues disrupts the transmembrane regions of each monomer, thereby blocking the subsequent trans-phosphorylation of tyrosine kinase domains.[13] However, this kind of mutation dramatically reduces tyrosine phosphorylation but does not influence the dimerization. A comprehensive summary of *KIT* mutations and their respective clinical implications will be further discussed in detail later.

Downstream signaling pathways of c-KIT

Many studies have been done on various cell lines to describe different downstream signaling cascades of c-KIT, including mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway, PI3K/AKT pathway, Src family kinases pathway, phospholipases PLC-γ pathway, and JAK/STAT pathway.[14-18] These signaling pathways can be activated independently or concomitantly by c-KIT and they are inte-
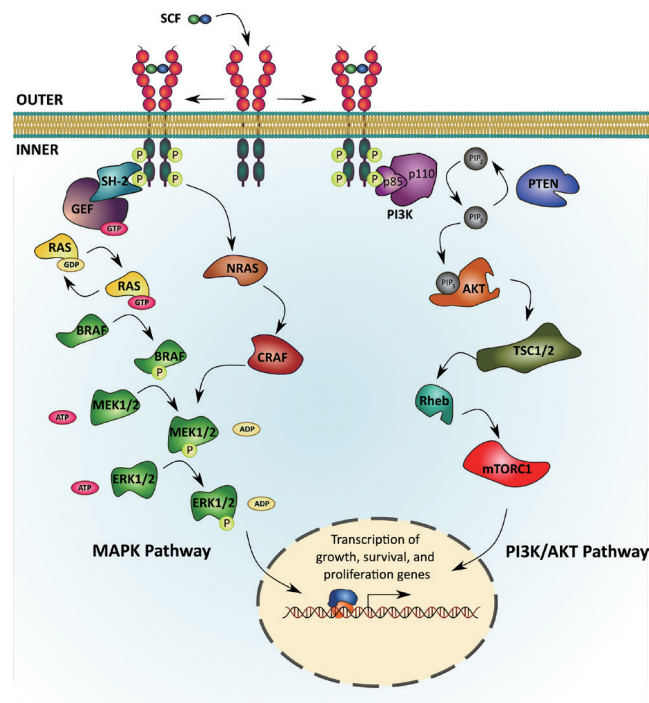
grated into a signaling circuit. Since different pathways relate to different cell types as well as cancer types, we will review in detail only pathways that are mostly well-known and researched on in c-KIT derived melanoma, which are MAPK/ERK pathway and PI3K/AKT pathway (Fig. 2).

MAPK/ERK pathway

Through trans-phosphorylation by SCF binding, c-KIT is activated and recruits adaptor proteins containing a Src homology 2 (SH-2) domain. This SH-2 protein will then associate with a guanine nucleotide exchange factor (GEF) that exchanges guanosine triphosphate (GTP) and guanosine diphosphate (GDP). This SH-2/GEF complex activates the G-protein RAS by transferring its GTP.[19] Activation of RAS leads to the activation of a serine/threonine protein kinase BRAF, which subsequently phosphorylates mitogen-activated protein kinase kinase1/2 (MAP2K1/2 or MEK1/2). MEK1/2, in turn, phosphorylates and activates ERK1/2. Several ERK1/2-activated transcription factors (TFs) induce the expression of genes related to cell proliferation, apoptosis, differentiation, adhesion, and mobility.[20,21]

PI3K/AKT pathway

PI3K/AKT pathway is responsible for cell survival and regulation of apoptosis. This signaling pathway can be activated via two mechanisms: either directly through interaction with c-KIT at position Tyr721 or indirectly through scaffold protein Gab2 and adapter protein Grb2.[22,23] The p85 subunit of PI3K interacts with autophosphorylated c-KIT through its SH2 domain, changes conformation, and associates with the enzymatic p110 subunit to fully activate PI3K. That activation step also recruits

PI3K to plasma membrane, placing it in close proximity of its lipid substrate, phosphatidylinositol 4,5-biphosphate (PIP2), which converts PIP2 to phosphatidylinositol 3,4,5-triphosphate (PIP3). The PIP3 then activates the pleckstrin homology (PH) domain, which contains proteins such as the serine/threonine kinase AKT.

AKT can activate several downstream proteins such as Bad, Foxo, and nuclear factor kappa-light chain enhancer of activated B cells (NF-κB) to interfere with the initiation of apoptosis and promote cell survival.[24-27] AKT also activates mTORC1 or mTor complex 1 (mTor, Raptor, GβL, PRAS40, and Deptor) through downstream pathway members like TSC1/2 and Rheb. This mTORC1 relates to melanocyte proliferation and migration.[28] The PI3K/AKT pathway can be inhibited by the phosphatase and tensin homolog (PTEN) gene. The PTEN protein removes one inorganic phosphate group from PIP_3 to regenerate PIP_2, which prevents the activation of AKT.

KIT interactions with other cytokines

It is well established that c-KIT interacts with various families of adaptor proteins, which contain multiple interaction domains, including SH2 and PH. Among growth factor receptor-bound proteins, c-KIT was shown to interact with Grb7 at Tyr-936 position in the downstream signaling of cell migration.[29,30] Another member in this family, Grb10, was found to interact with c-KIT to facilitate its PI3K-kinase-dependent activation and following association with AKT.[31] CrkL, a member of Crk family, has its phosphorylation induced by c-KIT and can interact with the ubiquitin E3 ligase c-Cbl.[32] Activation of c-KIT can also trigger the binding to its juxta-membrane region of Dok1, an adaptor that can interact with many signaling proteins such as Abl, SHIP, PLCγ1, and CrkL.[33] Another interactor of c-KIT, Lnk, may negatively regulate function of c-KIT as $lnk^{-/-}$ mice had an enhanced hematopoiesis.[34]

Apart from adaptor proteins, c-KIT can interact with and facilitate functions of many different cytokines. For examples, in primary mast cells, SCF-induced activation of c-KIT is required to evoke optimal IL-33-induced cytokine production.[35] c-KIT can also affect erythropoiesis as it can replace erythropoietin (Epo) to activate its receptor (Epo-R) by tyrosine phosphorylation and induce maturation of progenitors.[36] Similar with the interaction between c-KIT and Epo-R, the interaction with IL-7 of c-KIT can indirectly stimulate Jak-Stat pathway in T-lymphoid cells under the absence of Stat5 activation.[37] In myeloid cell line, interestingly, members of the transmembrane 4 superfamily (TM4SF), including CD9, CD63, and CD81, show their physical association and serve as negative modulators of c-KIT, thus, regulating its sensitivity to Steel factor (SLF) in hematopoietic progenitors.[38]

KIT mutations in melanoma

Dysregulation of c-KIT can affect cell proliferation, tumor growth, and metastasis in various cancer types such as gastrointestinal stromal tumors (GIST), leukemia (the first tumor found linked to KIT mutation), lung cancer, acute myeloid leukemia, and melanoma.[3,7,39,40] In fact, KIT mutations (mainly in-frame deletions of exon 11) are found in 80% of GIST tumors.[41,42] Apart from gene amplifications, KIT mutations in melanoma are almost all missense substitutions and widely distributed (Fig. 3). Table 1 shows a catalogue of 47 recorded KIT mutations based on data collected from a pooled analysis of 1635 patients samples from 12 recent melanoma genomics studies using cBioPortal (www.cbioportal.org) and several separate studies.[43-54] KIT mutations are identified in 3% of all melanomas and more specifically in 36% of acral melanomas, 39% of mucosal melanomas, and 28% of melanomas on chronically sun-damaged (CSD) skin but none in melanomas on skin without CSD or non-CSD (NCSD).[46] About 70% of KIT mutations in melanoma are localized to exon 11, most often a lysine-to-proline mutation at codon 576 (L576P), and to exon 13, most often a methionine-to-glutamic acid mutation at codon 642 (K642E). L576P affects the juxta-membrane domain and K642E affects a kinase domain. Both mutations lead to constitutive activation of c-KIT tyrosine kinase activity and subsequent induction of both MAPK and PI3K/AKT pathways.[55] Interestingly, mutations in KIT almost never occur in conjunction with BRAF (V600E) and NRAS (G12/Q61) mutations thereby suggesting an epistatic relationship.[56] Melanomas without these recurrent alterations in BRAF and NRAS have a significant enrichment for either KIT mutations or alterations in NF1, a downstream modulator in c-KIT/MITF signaling axis.[48]
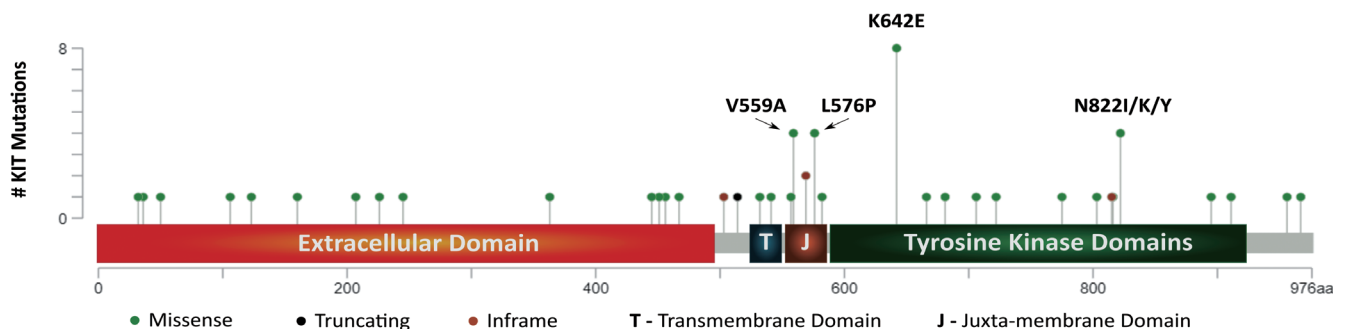

Fig. 3. Wide distribution of KIT genetic alterations in melanoma (from cBioPortal).[43-54]

Table 1. Catalogue of *KIT* Mutations in Melanomas

No	KIT mutation	Mutation type	Variation type	Copy number	Exon location	Corresponding region	Cancer type
1	G32V	Missense	G → T	ShallowDel	2	Extracellular domain	Cutaneous melanoma
2	P36Q	Missense	C → A	Gain	2	Extracellular domain	Cutaneous melanoma
3	V50L	Missense	G → C	-	2	Extracellular domain	Desmoplastic melanoma
4	S106F	Missense	C → T	Diploid	2	Extracellular domain	Cutaneous melanoma
5	S123F	Missense	C → T	Diploid	3	Extracellular domain	Cutaneous melanoma
6	L160V	Missense	T → G	-	3	Extracellular domain	Cutaneous melanoma
7	A207S	Missense	G → T	Diploid	3	Extracellular domain	Cutaneous melanoma
8	G226W	Missense	G → T	Gain	4	Extracellular domain	Cutaneous melanoma
9	T245M	Missense	C → T	Diploid	4	Extracellular domain	Cutaneous melanoma
10	P363S	Missense	C → T	Diploid	6	Extracellular domain	Cutaneous melanoma
11	G445E	Missense	G → A	-	8	Extracellular dimerization motif	Cutaneous melanoma
12	S451C	Missense	C → G	Gain	9	Extracellular dimerization motif	Cutaneous melanoma
13	P456Q	Missense	C → A	-	9	Extracellular dimerization motif	Cutaneous melanoma
14	P467Q	Missense	C → A	Diploid	9	Extracellular dimerization motif	Cutaneous melanoma
15	N463S	Missense	-	-	9	Extracellular dimerization motif	Mucosal melanoma
16	Y503del_insFAH	In-frame Ins	- → TTGCCC	Amp	9	Extracellular dimerization motif	Cutaneous melanoma
17	V532I	Missense	G → A	Diploid	10	Transmembrane domain	Melanoma
18	M541L	Missense	A → C	ShallowDel	10	Transmembrane domain	Melanoma of unknown primary
19	W557R	Missense	T → A/C	Amp	11	Juxta-membrane domain	Acral, mucosal, cutaneous melanoma
20	V559A	Missense	T → C	Diploid/ ShallowDel	11	Juxta-membrane domain	Acral, mucosal, cutaneous melanoma
21	V559D	Missense	T → A	-	11	Juxta-membrane domain	Acral, mucosal melanoma
22	V569A	Missense	T → C	-	11	Juxta-membrane domain	Cutaneous melanoma
23	Y570H	Missense	-	-	11	Juxta-membrane domain	CSD melanoma
24	Y570_L576del	In-frame Del	TT → -	-	11	Juxta-membrane domain	Cutaneous melanoma
25	L576P	Missense	T → C	Amp	11	Juxta-membrane domain	Acral, mucosal melanoma
26	W582L	Missense	G → T	ShallowDel	11	Juxta-membrane domain	Cutaneous melanoma
27	K642E	Missense	A → G	Amp/Gain/ Diploid	13	TKI domain/ATP-binding pocket	Acral, mucosal, cutaneous melanoma
28	V654A	Missense	-	-	13	TKI domain/ATP-binding pocket	Mucosal melanoma
29	T666I	Missense	C → T	-	14	Kinase insertion domain	Cutaneous melanoma, lentigo maligna melanoma
30	F681I	Missense	T → A	-	14	Kinase insertion domain	Desmoplastic Melanoma
31	L706F	Missense	C → T	Diploid	14	Kinase insertion domain	Cutaneous melanoma
32	M722I	Missense	G → T	Diploid	15	Kinase insertion domain	Cutaneous melanoma
33	Q775K	Missense	C → A	Diploid	16	Kinase domain	Cutaneous melanoma
34	G803C	Missense	G → T	Diploid	17	Kinase domain	Cutaneous melanoma
35	R815_D816delinsS	IF del		Diploid	17	Kinase domain	Cutaneous melanoma
36	D816N	Missense	G → A	Amp	17	Kinase domain	Cutaneous melanoma
37	D820Y	Missense	-	-	17	Kinase domain	Mucosal melanoma
38	N822I	Missense	A → T	Amp	17	Kinase domain	Cutaneous melanoma
39	N822K	Missense	T → G	Gain	17	Kinase domain	Cutaneous melanoma
40	N822Y	Missense	A → T	Amp	17	Kinase domain	Cutaneous melanoma
41	A829P	Missense	-	-	18	Kinase domain	Mucosal melanoma
42	P838L	Missense	-	-	18	Kinase domain	Acral melanoma
43	V8521	Missense	-	-	18	Kinase domain	Mucosal melanoma
44	A895T	Missense	G → A	-	19	Kinase domain	Cutaneous melanoma
45	P911L	Missense	C → T	-	20	Kinase domain	Cutaneous melanoma
46	R956Q	Missense	G → A	-	21	C-terminal tail	Melanoma
47	S967F	Missense	CC → TT	-	21	C-terminal tail	Cutaneous melanoma

CSD, chronically sun-damaged.

CLINICAL IMPLICATIONS OF *KIT* MUTATIONS

Correlations between clinical features and *KIT* mutations

The *KIT* mutation rate and its association with various clinico-pathological features remains controversial as results of different studies are inconsistent. Here, we summarize the data from Gong, et al's 2018 meta-analysis[57] of the clinical implications of *KIT* mutations (Table 2). In this analysis, selected studies must satisfy three inclusion criteria: 1) *KIT* mutations detected in the tissue samples of human melanoma, but not in cell lines, 2) the incidence of *KIT* mutations according to clinicopathologic parameters was described in detail, and 3) studies were carried out on humans and published in Eng-

Table 2. Associations between *KIT* Mutations and Various Clinicopathological Features/Races of Melanomas

Clinicopathologic characteristics	OR	95% CI	*p* value	Association with *KIT* mutation
Age (≥60 yr)				
Asian	1.349	1.056–1.723	0.017	Positive
White	0.795	0.337–1.879	0.602	None
Overall	1.296	1.025–1.641	0.031	Positive
Sex				
Asian	1.134	0.910–1.412	0.264	None
White	0.860	0.426–1.735	0.674	None
Overall	1.106	0.897–1.364	0.347	None
Mucosal melanoma				
Asian	1.080	0.842–1.386	0.545	None
White	3.003	1.895–4.758	<0.001	Positive
Overall	1.363	1.094–1.697	0.006	Positive
Acral melanoma				
Asian	1.361	1.087–1.702	0.007	Positive
White	1.435	0.901–2.286	0.128	None
Overall	1.374	1.123–1.682	0.002	Positive
Cutaneous melanoma with NCSD				
Asian	0.613	0.424–0.886	0.009	Negative
White	0.094	0.018–0.500	0.006	Negative
Overall	0.562	0.392–0.805	0.002	Negative
Cutaneous melanoma with CSD				
Asian	1.643	0.962–2.806	0.069	None
White	7.791	1.370–44.291	0.021	Positive
Overall	1.880	1.127–3.136	0.016	Positive
Melanoma on the extremities	0.294	0.105–0.820	0.019	Negative
Breslow thickness				
>1 mm	0.910	0.586–1.413	0.674	None
>4 mm	1.177	0.928–1.492	0.179	None
Ulceration	0.968	0.772–1.215	0.781	None

CSD, chronically sun-damaged; NCSD, non-CSD; OR, odds ratio; CI, confidence interval.

lish. This study collected data from 497 out of 5224 patients harboring *KIT* mutations, comprising 360 Asian patients and 137 White patients.

The authors reported that *KIT* mutations are more commonly found in older patients (≥60 years old) [odds ratio (OR)= 1.296, 95% confidence interval (CI): 1.025–1.641; *p*=0.031] and are positively associated with both mucosal melanomas (OR= 1.363, 95% CI: 1.094–1.697; *p*=0.006) and acral melanomas (OR=1.374, 95% CI: 1.123–1.682; *p*=0.002). When stratified by race, KIT was significantly associated with mucosal melanoma in White patients and acral melanoma in Asian patients. Additionally, a negative association was detected between *KIT* mutations and NCSD melanomas in both populations. However, there was a positive association between *KIT* mutations and CSD melanomas overall (OR=1.880, 95% CI: 1.127–3.136; *p*=0.016). *KIT* mutations are usually not found in melanomas that develop on the extremities and not correlated with melanoma on head/neck or trunk. Analyses also showed no significant relationship between *KIT* mutations and sex, Breslow thickness (either >1 mm or >4 mm), histological types, ulceration, mitotic rate, and tumor stages.

Overall, this meta-analysis documented a close association between *KIT* mutations and older age, acral mucosal subtypes of melanoma, and CSD sites, but did not find an association with histological subtypes or tumor stage. However, the results of this study are limited by the number of published data as well as the wide distribution of *KIT* mutations in various exons. The clinical implications of *KIT* mutations are informative clues for developing individualized therapies for patients, which will be reviewed in the next section.

Therapeutic trials of c-KIT inhibitors and success rates in melanomas

A variety of kinase inhibitors have been developed exploring c-KIT as a therapeutic target in melanoma, but not all drugs have been approved for clinical trials. In this section, we summarize data from 13 studies that reported the success rates of four widely used c-KIT inhibitors in melanoma treatments. Summary of those clinical trials in sample size, objective response rate (ORR), disease control rate (DCR), median progression-free survival (PFS), and median overall survival (OS) is shown in Table 3.

Imatinib

Imatinib, or imatinib mesylate, which was initially developed as an inhibitor of the BCR-ABL fusion protein and PDGFR, was found to also inhibit c-KIT and considered an effective drug for treatment of patients with GIST.[58,59] Clinical experience in four single-arm, open-label phase II trials of imatinib[44,60-62] will be compared. The most recent study among these screened 78 patients for response after continuous treatment with 400 mg/day imatinib until intolerable toxicities or disease progression occurred. Mutations in patients were widely distrib-

Table 3. Summary of Clinical Trials of KIT Inhibitors in *KIT*-Mutation Derived Melanomas

No.	KIT inhibitors (mg)	No. of patients	ORR (%)	DCR (%)	Median PFS (months)	Median OS (months)	Study
1	IMA 400 BID	25	16	36	2.8	10.7	Carvajal, et al.[44]
2	IMA 400 QD or BID	43	23.3	53.5	3.5	12.0	Guo, et al.[60]
3	IMA 400 QD or BID	24	29.2	50	3.7 (TTP)	12.5	Hodi, et al.[61]
4	IMA 400 QD	78	21.8	60.3	4.2	13.1	Wei, et al.[62]
5	NIL 400 BID	9	22.2	77.8	2.5	-	Cho, et al.[64]
6	NIL 400 BID	19	15.8	52.6	3.3 (TTP)	9.1	Carvajal, et al.[56]
7	NIL 400 BID	42	16.7	57.1	3.3	11.9	Lee, et al.[67]
8	NIL 400 BID	42	26.2	73.8	4.2	18.0	Guo, et al.[66]
9	NIL 400 BID	25	16	64	6.0	13.2	Delyon, et al.[65]
10	DAS 70 BID	36	5	-	2.0	13.8	Kluger, et al.[70]
11	DAS 70 BID	22	18.2	50	2.1	7.5	Kalinsky, et al.[69]
12	SUN 50 QD	10	40	50	-	-	Minor, et al.[72]
13	SUN 50 QD	31	13	39	1.3 (TTP)	4.3	Decoster, et al.[71]

ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; BID, twice daily; QD, once daily; IMA, imatinib; NIL, nilotinib; DAS, dasatinib; SUN, sunitinib; TTP, time to progression.

uted in exons 9, 11, 13, 17, and 18, with 60.2% of mutations occurring in exon 11 or 13. L576P and K642E accounted for 24.3% of all mutations. The median PFS in the evaluable cohort was 4.2 months (95% CI: 1.9–6.4 months), and median OS was 13.1 months (95% CI: 9.6–16.7 months). A range of durability was recorded with 17 partial response (PR) patients, 30 stable disease (SD) patients, and 29 patients showing progressive disease (PD). Differences were found between patients with *KIT* mutations. Patients with *KIT* mutations in exon 11 or 13 had ORR of 24.4% and DCR of 66.7% while those for the group of other alterations had the rate of 19.4% and 54.8% respectively. This study observed generally mild to moderate adverse events (AEs), including edema (50%), rash (18%), fatigue (9%), anorexia (7%), nausea (5%), and neutropenia (2%). The additional three studies showed consistent results. These studies started with high dose of imatinib (400 mg twice a day), which was commonly associated with grades 3–4 AEs such as lymphopenia, anemia, erythema multiforme, and vomiting. Among four studies, complete responses (CRs) were only observed in the earliest study of Carvajal group with two patients durable for 95 and 94 weeks. Both of them had the exon 11 L576P mutation as well as amplification of *KIT*.[44]

Nilotinib

Nilotinib is another small kinase inhibitor with comparable or greater potency than imatinib in targeting *KIT* mutations.[63] Five studies were conducted using this drug, in which all patients received orally nilotinib 400 mg twice a day.[56,64-67] The most recent study was a phase II clinical trial conducted by the

French Skin Cancer Network on 25 patients.[65] At 6 months after nilotinib initiation, only four patients were responsive to nilotinib (ORR: 16%, 90% CI: 5.6–33.0%), including one CR patient and three PR patients. Out of the other 21 patients, six experienced progression and 15 died with an estimated PFS of 6.0 months and a median OS of 13.2 months (95% CI: 5.6–19.9 months). Of note, patients with CR or PR had mutations in exon 11 or 13 with overall response rate of 26%, median PFS of 6 months (95% CI: 3–46.8), and median OS of 14.4 months (95% CI: 9.97–not reached). Among patients, 56% experienced grade 3 drug-related AEs such as fatigue, rash, increased aspartate transaminase/alanine transaminase or cholestasis, and nausea. The author also observed reduced phosphorylated STAT3 in nilotinib treated *KIT*-mutated cell lines, suggesting that the JAK/STAT pathway can be downregulated by c-KIT inhibition and thus, associated with tumor response. However, additional mechanistic studies and molecular profiling are required, as nilotinib also targets PDGFR and ABL, which can both signal through STAT3. Other studies were conducted in patients with or without prior targeted KIT therapy. In the study of 19 patients, patients with L576P mutation showed a 25% ORR and 50% DCR while those for K642E mutation were 25% and 75% respectively.[56] Of note, this study recorded two patients with reduction in size of brain metastases after nilotinib treatment by magnetic resonance imaging scanning.

Dasatinib

Dasatinib is also a c-KIT inhibitor, which also targets Src family kinases (c-Src, YES, LCK, and FYN), BCR-ABL, PDGFR-β, and EPHA2.[68] Two studies of 36 and 22 evaluable patients respectively were conducted to assess clinical efficacy of dasatinib in *KIT*-mutated melanoma treatment.[69,70] Both studies treated patients with various starting doses of dasatinib but eventually fixed at 70 mg twice a day due to toxicity. No CR case was observed in either study. In the first study, only two patients showed PR lasting 64 and 24 weeks, causing an ORR of 5%.[70] Meanwhile, in the second study, four PRs and seven SDs were observed. Common grade 3 AEs were recorded, including fatigue (13%), dyspnea (12%), nausea (11%), anemia (7%), pleural effusion (5%), etc.

Sunitinib

Sunitinib, which targets both c-KIT and vascular endothelial growth factor receptors (VEGFRs), is also approved for treating melanoma. Sunitinib was examined in two studies of 10 and 31 evaluable patients harboring *KIT* mutations in 2012 and 2015, respectively.[71,72] Both of studies started with sunitinib 50 mg daily before reducing to 37.5 and 25 mg per day. One CR with 15 months of durability was observed in the 2012 study. However, the 2015 study recorded no CR but observed 13% PR and 26% SD, which accounted for a DCR of 39%. The median PFS and median OS for the overall population in this study were 1.3 months (95% CI: 1.2–1.4) and 4.3 months (95% CI:

1.0−7.6), respectively. Most commonly recorded grade 3−4 AEs were asthenia (28%), thrombocytopenia (15%), anorexia (10%), and neutropenia (15%).

Several other kinase inhibitors targeting c-KIT were also clinically tested and recorded in case reports. For example, a patient with primary esophageal melanoma harboring *KIT* mutation in exon 11 showed significant response when being treated with oral masitinib.[73] Masitinib treatment caused dysphagia and odynophagia disappeared within 1 week and reduced size of brain metastatic lesions and visceral lesions in the following month. Another example is a 79-year-old man at stage IV M1b metastatic anal mucosal melanoma showing CR upon sorafenib therapy.[74]

Epigenetic regulation of *KIT*

Several up/down regulations of *KIT* expression are caused by epigenetic changes, which includes DNA methylation and histone modifications. For example, in cardiac progenitor cells, *KIT* is upregulated via action of stromal cell-derived factor-1α (SDF-1α). SDF-1α, combined with CXCR4, inhibits expression and global activity of DNA methyltransferase (DNMT), which then leads to demethylation of c-KIT gene.[75] In *KIT*-mutated mast cells, histone deacetylase inhibitors (HDACi) can decrease *KIT* mRNA levels, total c-KIT protein as well as cell surface c-KIT, followed later by major mast cell apoptosis.[76] Some breast cancer cell lines lack the c-KIT expression due to hyperpermethylation of *KIT* promoter and treating these cell lines with methyltransferase inhibitor such as 5Aza-2dC can boost the level of *KIT* mRNA.[77] *KIT* methylation is also recorded in squamous cell carcinoma of uterine cervix that overexpress c-KIT.[78,79] The increased methylation of CpG islands in these skin cancer cells might interfere with the binding of CTCF repressor with *KIT* promoter. In GIST, a repressive complex named PRC [polycomb group (PcG) repressive complex] can reversibly suppress *KIT* expression via various histone modifications such as H3K27me3 and H2AK119ub1.[80] In cutaneous melanoma, intriguingly, the presence of SCF leads to reduced *KIT* expression and increased methylation density at the *KIT* promoter.[81] However, this epigenetic change shows no significant correlations with common genetic drivers such as BRAF, NRAS, and PTEN. This suggests that *KIT* may have a tumor-suppressive function in cutaneous melanoma.[82-84] Supporting this tumor-suppressing role of *KIT* in melanoma, the hypermethylation of *KIT* is also associated with a lower OS rate, even when *BRAF* (*V600E*) is included for the survival risk prediction.[85] Additionally, *KIT* is also found to be inhibited by microRNAs, including miR-221 and miR-222, which leads to differentiation blockade of the melanoma cells and subsequent proliferation.[86] However, these microRNAs are repressed by a TF called promyelocytic leukemia zinc finger (PLZF); therefore, the silencing of PLZF can be a driver of cutaneous melanoma.

On the other hand, considering *KIT* as an oncogene, the epigenetic regulation of *KIT* is related to enhancers, those are dif-ferentially methylated regions (eDMRs) as melanomas progress from normal to primary tumors and then to metastases.[87] Bell, et al.[87] showed that the methylation patterns of eDMRs not only contributes to melanoma progression by overexpressing *KIT* but also distinguishes patient survival rates.

CONCLUSION

Overall, based on data from various studies and case reports, we created a catalogue of *KIT* mutations, though not sufficient, and their mostly associated melanoma subtypes. An understanding of mutational classes in melanoma will facilitate appropriate personalized treatments. Additionally, *KIT* mutations present distinct correlation with a number of different clinicopathologic features. *KIT*-mutated harboring melanomas are closely associated with older age, and acral, mucosal, or CSD sites but not with other histological parameters or tumor stage or sex. Intriguingly, no significant difference is recorded in the clinical association with *KIT* mutations between White populations and Asian populations although *KIT* mutation rate is lower in the latter one.

Upon treatment of melanoma subtypes, clinical efficacy in treating *KIT*-mutated melanoma has been evaluated with various small-molecular inhibitors of c-KIT, including imatinib, nilotinib, dasatinib, and sunitinib. Data collected from studies over 20 years has provided substantially critical insights into the therapeutic trials of these drugs and their success rate. However, in many cases, most patients eventually experience disease progression. One of possible explanation for this drug resistance is the frequent presence of brain and central nervous system metastases in advanced melanoma as the drug penetration is limited in these areas. With this being said, numerous additional investigational studies exploring c-KIT as a therapeutic target in combination therapy against melanoma. For instance, co-targeting c-KIT and its downstream pathways might be a plausible solution to control tumor progression. On the other hand, c-KIT inhibition showed its potential synergy with the immunological checkpoint blockade to develop antitumor effect.[88,89] This is due to the ability of c-KIT inhibitors to enhance immune response such as increased T-cell activation and natural killer cell clonal expansion.[90,91]

AUTHOR CONTRIBUTIONS

Conceptualization: Duc (Daniel) M. Pham and Hensin Tsao. Data

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