MITF expression in melanoma cells, resulting in decreased invasion and metastasis. Sáez-Ayala and colleagues initiated a multicenter phase II trial of imatinib in patients with KIT-mutated metastatic mucosal, acral, or CSD melanoma. The primary endpoints were response rate and time to progression, and secondary endpoints included overall survival and the association between KIT status and response. Of 24 evaluable patients, 8 had KIT mutations, 11 had KIT amplification, and 5 had both (these patients were classified as having mutations). Surprisingly, the best overall response rate was significantly higher in patients with mutated KIT (54%) compared with patients with amplified KIT (0%), suggesting that KIT mutations and amplifications may act differently in melanoma. Moreover, the disease control rate, including partial responses and stable disease, was significantly higher in KIT-mutated melanomas (77%) than it was in KIT-amplified melanomas (18%). Of note, especially short times to progression were observed in patients with preexisting NRAS mutations, raising the possibility that NRAS mutation contributes to imatinib resistance in melanoma. Although no statistically significant differences were shown in overall survival or time to progression between patients with KIT mutation or amplification, the activity of imatinib in KIT-mutated mucosal, acral, or CSD melanoma provides a rationale for screening such patients for KIT mutations and testing more potent, specific KIT inhibitors in these melanoma subtypes.

**MITF UPREGULATION SENSITIZES MELANOMA CELLS TO ANTIFOLATE TREATMENT**

The presence of distinct subpopulations of differentiated and stem cell–like cells within a tumor contributes to phenotypic heterogeneity and the outgrowth of therapy-resistant cells. Microphthalmia-associated transcription factor (MITF) is a critical regulator of melanocyte differentiation, and decreased MITF expression in melanoma generates tumor-initiating cells with enhanced invasive potential that may contribute to drug resistance and metastasis. Sáez-Ayala and colleagues hypothesized that upregulation of MITF would eliminate these invasive cells and induce melanoma cell differentiation, thereby limiting phenotypic heterogeneity and increasing therapeutic sensitivity. To test this idea, the authors designed a two-step therapeutic strategy consisting of stimulation of MITF expression followed by inhibition of the essential enzyme dihydrofolate reductase (DHFR) using the antifolate prodrug, 3-O-(3,4,5-trimethoxybenzoyl)–(−)-epicatechin (TMECG), which is activated by expression of the melanocyte-specific gene tyrosinase (TYR). Treatment with methotrexate (MTX) stimulated MITF expression in melanoma cells, resulting in decreased invasiveness, increased expression of prodifferentiation genes including TYR, and TYR-driven processing of TMECG. Furthermore, MTX-induced MITF expression enhanced the sensitivity of melanoma cells to TMECG, as combined MTX/TMECG treatment synergistically and selectively induced apoptosis in melanoma cell lines as well as BRAF inhibitor– and MEK inhibitor–resistant patient-derived cells, irrespective of BRAF or TP53 mutation status. In addition, dual MTX/TMECG treatment effectively suppressed melanoma growth and metastasis in vivo without significant toxicity or acquisition of resistance. This cell type–specific antitumor effect was mediated by depletion of dTTP upon DHFR inhibition by MTX/TMECG, which promoted increased S-phase–associated DNA double-strand break formation and subsequent E2F transcription factor 1 (E2F1)–driven, p53–independent cell death. The results of these preclinical studies identify this two-step, directed phenotype-switching approach targets melanoma cells independent of BRAF or TP53 mutations.

**Clinical Trials**

**Major finding:** Imatinib has activity in KIT-mutated mucosal, acral, or chronically sun-damaged melanoma.

**Clinical relevance:** KIT-mutated, but not KIT-amplified, metastatic melanomas respond to imatinib.

**Impact:** Patients with mucosal, acral, or chronically sun-damaged melanoma should be screened for KIT mutations.

**KIT-MUTATED MELANOMAS RESPOND TO IMATINIB**

Mucosal and acral melanomas that develop on sites such as the palms, soles, and nail beds are clinically distinct from cutaneous melanomas of the skin. Furthermore, these types of melanoma infrequently harbor BRAF mutations, suggesting that they are also genetically distinct. Recurrent mutation or amplification of KIT has been found in mucosal and acral melanomas as well as in chronically sun-damaged (CSD) cutaneous melanomas, which also rarely have BRAF mutations. Because the small-molecule kinase inhibitor imatinib has shown efficacy in KIT-mutant gastrointestinal stromal tumors, Hodi and colleagues initiated a multicenter phase II trial of imatinib in patients with KIT-mutated and/or amplified metastatic mucosal, acral, or CSD melanoma. The primary endpoints were response rate and time to progression, and secondary endpoints included overall survival and the association between KIT status and response. Of 24 evaluable patients, 8 had KIT mutations, 11 had KIT amplification, and 5 had both (these patients were classified as having mutations). Surprisingly, the best overall response rate was significantly higher in patients with mutated KIT (54%) compared with patients with amplified KIT (0%), suggesting that KIT mutations and amplifications may act differently in melanoma. Moreover, the disease control rate, including partial responses and stable disease, was significantly higher in KIT-mutated melanomas (77%) than it was in KIT-amplified melanomas (18%). Of note, especially short times to progression were observed in patients with preexisting NRAS mutations, raising the possibility that NRAS mutation contributes to imatinib resistance in melanoma. Although no statistically significant differences were shown in overall survival or time to progression between patients with KIT mutation or amplification, the activity of imatinib in KIT-mutated mucosal, acral, or CSD melanoma provides a rationale for screening such patients for KIT mutations and testing more potent, specific KIT inhibitors in these melanoma subtypes.


**Impact:** This phenotype-switching approach targets melanoma cells independent of BRAF or TP53 mutations.

**Melanoma**

**Major finding:** Treatment with MTX and the antifolate prodrug TMECG is an effective melanoma-specific therapy.

**Mechanism:** MTX induces MITF, leading to TMECG activation by TYR, dTTP depletion, and E2F1–driven apoptosis.

**Impact:** This phenotype-switching approach targets melanoma cells independent of BRAF or TP53 mutations.
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