ISSN: 2643-4512

Kim. Int Arch Public Health Community Med 2024, 8:095
DOI: 10.23937/2643-4512/1710095
Volume 8 | Issue 1
Open Access

International Archives of
Public Health and Community Medicine

REVIEW ARTICLE

Personalized Therapy in Oncology: Melanoma as a Paradigm for Molecular-Targeted Treatment Approaches

Kevin B. Kim*

California Pacific Medical Center Research Institute, USA

***Corresponding author:** *Kevin B. Kim, California Pacific Medical Center Research Institute, 2333 Buchanan St. San Francisco, CA 94115, USA, Tel: 1-415-885-8600, Fax: 1-415-885-8680*

Abstract

Over recent decades, systemic cancer therapy has undergone significant transformations due to breakthroughs in understanding cancer biology, immunology, and genetics. Consequently, patients with advanced-stage cancers are experiencing unprecedented survival rates. Personalized cancer therapy aims to optimize clinical outcomes by tailoring drug therapies to individual patients based on their tumor genetics and/or epigenetics, thereby minimizing the toxicity associated with ineffective treatments. Progress in genetic sequencing and molecular cytogenetics has revealed oncogenic driver mutations and epigenetic anomalies, paving the way for the development of targeted molecular therapies. This review article elucidates the successful advancement of molecular targeted therapies in malignant melanoma, showcasing the paradigm of personalized cancer therapy.

Keywords

Molecular targeted therapy, Genomic, Mutation, Signal transduction pathways, Drug resistance mechanisms

Introduction

In recent decades, cancer treatment has evolved significantly, driven by advances in cancer genetics and immunology. While chemotherapy remains vital for many metastatic cancers, molecular targeted therapies and checkpoint inhibitors have revolutionized treatment, improving tumor control and extending survival in advanced malignancies. These targeted therapies inhibit key molecules and proteins crucial for tumor growth, resulting in cell death, tumor regression, and prolonged patient survival.

Effective targeted therapy depends on the presence of specific oncogenic molecules in tumor cells. For example, HER2 gene amplification is found in 15-20% of breast cancers, resulting in a functional HER2 receptor that promotes cell growth and inhibits apoptosis [1,2]. Trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2 receptor, is effective in breast cancer with HER2 overexpression and/or amplification but not in patients without HER2-positive breast cancer.

In chronic myelogenous leukemia (CML), the BCR-ABL gene translocation leads to an overactive tyrosine kinase, driving proliferation and survival [3]. Imatinib, an inhibitor of BCR-ABL, KIT, and PDGF receptor-alpha, is effective in treating CML [4].

In advanced renal cell carcinoma (RCC), drugs targeting VEGF or VEGF receptor are used due to Von Hippel Lindau (VHL) gene deficiency, activating the VEGFR pathway in most RCCs [5].

This article will review molecular targeted therapies in malignant melanoma, exemplifying personalized cancer therapy.

Melanoma

Skin cancer represents the most prevalent form of malignancy in the United States, with melanoma being the most lethal variant among skin cancers. Over recent decades, there has been a significant and steady increase in melanoma incidence [6]. In 2023, it is estimated that approximately 97,610 individuals will be diagnosed with melanoma in the United States,

Citation: Kim KB (2024) Personalized Therapy in Oncology: Melanoma as a Paradigm for Molecular-Targeted Treatment Approaches. Int Arch Public Health Community Med 8:095. doi.org/10.23937/2643-4512/1710095

Accepted: January 23, 2024; **Published:** January 25, 2024

and 7,990 are projected to succumb to the disease [7]. However, there has been a notable decline in mortality since 2016, when over 10,000 deaths were anticipated. This decrease in mortality is largely attributable to the introduction of novel therapeutic agents, including checkpoint inhibitors and molecular targeted drugs.

Substantial evidence from numerous large-scale randomized clinical trials has demonstrated that the overall survival (OS) of patients with advanced, metastatic melanoma has improved with these innovative treatments compared to traditional cytotoxic chemotherapy. Notably, a significantly higher proportion of patients are now achieving a 5-year survival in the unresectable metastatic setting. For instance, the 5-year survival rate for patients with advanced, metastatic melanoma was approximately 10% in 2009 [8]. In contrast, the 5-year survival rates with checkpoint inhibitors and/or inhibitors of BRAF and MEK kinases currently range between 34% and 52% [9-11]. These statistics underscore the profound impact of recent advances in melanoma therapy, marking a significant milestone in the management of this aggressive cancer.

Melanoma's genetic underpinnings, particularly in cutaneous melanoma, predominantly involve mutations in the mitogen-activated protein (MAP) kinase signal transduction pathway. This pathway activates the extracellular signal-regulated kinase (ERK), which plays a crucial role in the proliferation, survival, invasion, and metastasis of melanoma cells. Notably, approximately 50% of cutaneous melanomas exhibit a single base substitution mutation in the BRAF gene, and around 20% possess a mutation in the NRAS gene [12-14]. These mutations in the BRAF and NRAS genes are predominantly mutually exclusive and lead to the activation of the MAP kinase pathway.

Contrastingly, non-cutaneous melanomas present a distinct genetic profile. In acral lentiginous and mucosal melanoma, the frequency of BRAF and NRAS mutations is significantly lower. However, oncogenic mutations in the KIT gene are more prevalent, occurring in 11-21% of cases [15]. In uveal melanoma, mutations in the GNAQ or GNA11 gene are present in about 80% of cases, while mutations in the BRAF and NRAS genes are rare [16,17].

These genetic alterations, primarily the kinase-activating mutations, present substantial opportunities for the development of molecularly targeted therapeutic drugs. Currently, effective targeted drugs are available for treating patients with cutaneous melanoma harboring a BRAF mutation and those with acral or mucosal melanoma exhibiting KIT mutations.

BRAF-Mutant Melanoma

BRAF inhibitors

BRAF, a serine-threonine kinase in the MAP kinase pathway, is critically involved in melanoma cell biology. Approximately 50% of melanomas exhibit oncogenic mutations in BRAF, predominantly at codon 600, with V600E and V600K mutations constituting 80% and 15% of these, respectively [14]. These V600 BRAF mutations lead to continuous activation of the MEK and ERK proteins in the MAP kinase pathway, fostering melanoma cell proliferation, invasion, and survival [14].

Inhibition of the V600 BRAF kinase disrupts MEK and ERK activation, suppressing the MAP kinase pathway and inducing cell growth arrest. Initial attempts to target the BRAF kinase in melanoma with sorafenib, an RAF kinase inhibitor, were unsuccessful [18]. Likewise, a phase III study combining sorafenib with carboplatin and paclitaxel did not demonstrate improvement in progression-free survival (PFS) or overall survival (OS) compared to chemotherapy alone [19]. This was attributed to sorafenib's inability to adequately inhibit the mutated BRAF-driven MAP kinase pathway, as it more effectively inhibits wild type BRAF and CRAF proteins, causing significant toxicity in patients with V600 BRAF-mutant melanoma.

The ineffectiveness of sorafenib in treating melanoma led to intensified efforts to develop more specific inhibitors targeting mutant BRAF kinase. Vemurafenib emerged as the inaugural selective inhibitor for V600 BRAF mutant melanoma in clinical trials. It was specifically engineered to target the V600E BRAF mutation more effectively than the wild type, using a scaffold-based crystallographic approach, resulting in a higher affinity for V600 BRAF (IC50 31 nM/L) compared to wild type BRAF (IC50 100 nM/L) [20,21]. In a phase I study, 32 advanced melanoma patients with the V600E BRAF mutation treated with vemurafenib showed an 81% overall response rate [22]. Rapid metabolic responses were detected within two weeks in many patients.

In a phase III trial involving 675 treatment-naive patients with advanced melanoma carrying the V600E BRAF mutation, including 19 patients with the V600K mutation, the group receiving vemurafenib exhibited a marked improvement in progression-free survival (PFS) and overall survival (OS) compared to those treated with dacarbazine (HR 0.26 [95% CI, 0.20-0.33, $p < 0.001$] for PFS; HR 0.37 [95% CI, 0.26-0.55, $p < 0.001$] for OS) [23]. The median PFS durations were 5.3 months for vemurafenib and 1.6 months for dacarbazine, with response rates of 48% and 5%, respectively. Due to these substantial PFS and OS benefits, vemurafenib received FDA approval in the United States in 2011.

Dabrafenib, another selective V600 BRAF inhibitor, was evaluated in a phase III study with 250 treatment-naive patients with unresectable metastatic melanoma. Compared to dacarbazine, dabrafenib significantly improved PFS (HR 0.30 [95% CI 0.18-0.51; $p < 0.0001$]), and had a higher response rate (50% versus 6%) [24].

Median PFS was 5.1 months for dabrafenib versus 2.7 months for dacarbazine. In addition, there was substantial prolongation of overall survival in the dabrafenib arm (HR of 0.77 [95% CI 0.52-1.13]) [25]. This led to its FDA approval in 2013 for advanced V600E/K BRAF-mutant melanoma.

Encorafenib, distinct for its longer dissociation half-life from V600E-mutant BRAF, directly compared against vemurafenib in the COLUMBUS trial. This randomized phase III trial, which also assessed a combination of encorafenib and binimetinib, a selective MEK inhibitor, showed superior PFS (HR 0.68 (95% CI, 0.52-0.88, 2-sided p = 0.0038)) and OS (HR 0.76 (95% CI 0.58-0.98, two-sided p = 0.033)) for encorafenib compared to vemurafenib [26,27].

MEK inhibitors

An alternative strategy to direct inhibition of mutant BRAF kinasein the MAP kinase pathway is the targeting of its downstream substrate. MEK kinase, the only known substrate downstream of BRAF, was also extensively tested for the treatment of V600 BRAF mutant melanoma. Initial efforts with early MEK inhibitors like CI-1040 and PD0325901 were unsuccessful due to intolerable toxicity and/or lack of clinical efficacy [28]. However, the development of trametinib, a specific inhibitor of MEK1 and MEK2 proteins, marked a turning point. Promising clinical activity of trametinib was observed in phase I and II studies [29,30].

In a pivotal phase III study involving 322 patients with metastatic V600E or V600K BRAF-mutant melanoma, participants were randomized to receive either trametinib or cytotoxic chemotherapy [31]. The study's primary and secondary endpoints were progression-free survival (PFS) and overall survival (OS), respectively. Results showed that patients in the trametinib arm experienced significantly longer PFS (HR 0.45 [95% CI, 0.33-0.63] P < 0.001) and higher response rates (22% versus 8%) compared to those receiving cytotoxic chemotherapy. The median PFS was 4.8 months for trametinib versus 1.5 months for chemotherapy. Additionally, trametinib was associated with a superior OS, with a hazard ratio of 0.54 (95% CI 0.32-0.92, p 0.01). The 1-year and 2-year OS rates were 60.9% and 32.0%, respectively, in the trametinib arm, compared to 49.6% and 29.4% in the chemotherapy arm [32]. Based on these findings, trametinib received FDA approval in 2013 for the treatment of V600E or K BRAF-mutant advanced melanoma.

It is noteworthy that trametinib exhibits limited clinical activity in patients with V600 BRAF mutant melanoma who have experienced disease progression on prior BRAF inhibitor therapy. A phase II study of trametinib in this patient cohort revealed no responses among 40 participants previously treated with a selective BRAF inhibitor [30]. These results suggest a preference for selective BRAF inhibitors over trametinib as the initial targeted therapy for V600 BRAF mutant melanoma, despite the absence of a direct head-to-head comparison between these two drug classes.

Combination of BRAF inhibitor and MEK inhibitor

While selective BRAF inhibitors have substantially improved clinical responses and overall survival in melanoma patients, most individuals eventually experience disease progression. This resistance arises from various mechanisms, including the development of new kinase-activating mutations in the NRAS gene, alternative splicing of BRAF, amplification of BRAF and/or CRAF, acquisition of new MEK mutations, or overexpression of COT protein [33-37]. These alterations can circumvent the inhibitory effects of BRAF inhibitors on V600 BRAF kinase.

Interestingly, about 70% of resistance mechanisms involve reactivation of the MAP kinase pathway despite ongoing BRAF inhibitor treatment. No new BRAF gene mutations have been reported in the context of treatment resistance. Preclinical studies have shown that combining a MEK inhibitor with a BRAF inhibitor delays resistance in V600E BRAF-mutant melanoma cells.

Three combination regimens of MEK and BRAF inhibitors have been clinically investigated: Dabrafenib with trametinib, vemurafenib with cobimetinib, and encorafenib with binimetinib. In separate large phase III trials, these combinations demonstrated higher response rates and prolonged PFS and OS compared to vemurafenib alone [38-40]. The hazard ratios (HRs) for PFS with these regimens ranged from 0.51 to 0.61, with median PFS durations of 11 to 14.9 months, versus 7.2 to 7.3 months with vemurafenib. The HRs for OS were between 0.61 to 0.70, with median OS durations of 22.3 to 33.6 months, compared to 16.9 to 18.0 months with vemurafenib.

Following the significant PFS and OS benefits observed, each of these combination regimens received FDA approval for treating advanced V600 BRAF-mutant melanoma: Dabrafenib and trametinib in 2013, vemurafenib and cobimetinib in 2015, and encorafenib and binimetinib in 2018.

BRAF-targeting therapy versus checkpoint inhibitor immunotherapy

Following improvements in clinical outcomes, including overall survival, with targeted combination regimens for melanoma, researchers began to investigate the optimal sequence of targeted therapy and anti-PD1 antibody-based checkpoint immunotherapy in patients with advanced V600 BRAF-mutant melanoma. To explore this, a randomized phase III study was conducted, comparing a combination of dabrafenib and trametinib with nivolumab and ipilimumab in the first-line treatment of patients with unresectable, metastatic

V600 BRAF-mutant melanoma [41-44]. In this study, patients initially receiving targeted therapy were switched to immunotherapy upon disease progression, and vice versa.

Despite slow patient enrollment, likely due to clinician preferences for specific treatment modalities, the study achieved its primary objective. It demonstrated a significant clinical benefit of checkpoint immunotherapy over the targeted therapy regimen, with a 2-year overall survival rate of 71.8% [95% CI, 62.5 to 79.1] compared to 51.5% [95% CI, 41.7 to 60.4; log-rank P = 0.010]. Consequently, the combination checkpoint immunotherapy has become the standard first-line treatment for patients with advanced V600 BRAF-mutant melanoma. However, in patients with comorbidities where immunotherapy is contraindicated, targeted therapy regimens remain the recommended first-line treatment. Additionally, targeted therapy may be considered for patients whose disease recurs during or shortly after completing adjuvant PD1 antibody.

There has been considerable speculation about whether combining targeted therapy with a checkpoint inhibitor could enhance response rates and extend survival compared to each modality alone. A notable phase III study compared a regimen of vemurafenib, cobimetinib, and atezolizumab against targeted therapy alone in 517 patients with advanced V600 BRAF mutant melanoma [45]. The study achieved its primary objective of improving progression-free survival (PFS) (hazard ratio [HR] 0.78; 95% CI 0.63-0.97; p = 0.025), leading to FDA approval in July 2020 for this treatment in advanced BRAF V600-mutant melanoma. However, there were no significant differences in overall response rates or survival durations between the two treatment arms (HR 0.84 [95% CI 0.66-1.06]; p = 0.14), and the triple combination therapy was associated with more severe adverse events.

Another randomized Phase III study, involving 532 patients, compared a combination of spartalizumab (an anti-PD-1 antibody), dabrafenib, and trametinib with a control group receiving dabrafenib, trametinib, and placebo [46]. This study did not meet its primary objective of prolonging PFS (HR 0.82 [95% CI, 0.66 to 1.03]; P = 0.042), although the triple combination showed a slightly higher response rate (69% vs. 64%). The incidence of Grade ≥ 3 adverse events was significantly higher in the triple combination group [47].

Additionally, a smaller phase II study evaluating a combination of dabrafenib and trametinib, with or without pembrolizumab, demonstrated an improved PFS with the targeted therapy-checkpoint inhibitor combination, albeit without reaching statistical significance for the planned improvement [48].

KIT-mutant melanoma

While BRAF mutations are predominant in cutaneous melanomas, other subtypes of melanoma are characterized by different genetic aberrations. In acral lentiginous and mucosal melanomas, mutations in the KIT receptor kinase are more prevalent than BRAF mutations. Specifically, KIT mutations are identified in 15-21% of mucosal melanomas and 11% of acral lentiginous melanomas [15,49]. In contrast, V600 BRAF mutations are found in only about 3% of mucosal melanomas, though a higher incidence (13%) of non-V600 BRAF mutations has been reported [49].

During the early 2000s, KIT inhibitors garnered considerable attention for the treatment of advanced melanoma, motivated by the frequent overexpression of KIT in these cancers [50]. However, initial phase II trials in the United States and Europe, testing imatinib-a potent oral inhibitor targeting KIT, BCR-ABL, and PDGFR-yielded limited success. Among these trials, which involved 62 melanoma patients treated with imatinib, only a single patient exhibited a clinical response [51-53]. Notably, these studies enrolled patients regardless of their KIT mutation status, indicating that most participants likely did not have melanomas with KIT mutations.

However, following revelations about the prevalence of KIT mutations in acral and mucosal melanomas [15], interest in using imatinib to treat KIT-mutant advanced melanoma was rekindled. Later single-arm phase II studies demonstrated response rates ranging from 16% to 29%, with a median progression-free survival (PFS) of 3 to 3.7 months in patients with KIT-mutant advanced melanoma [54-56]. It was observed that patients with mutations in exons 9 or 11 of the KIT kinase were more likely to respond to imatinib. Despite these findings, the limited size of the patient groups in these studies has prevented imatinib from undergoing FDA review for this specific treatment, although it has been incorporated into clinical practice.Nevertheless, the limited size of the patient groups in these studies meant that imatinib has not been subjected to FDA review for the treatment of KIT-mutant melanoma, although it is being used in clinical settings.

Conclusions

The advent of selective BRAF and MEK inhibitors marks a significant milestone in the treatment of V600 BRAF-mutant melanoma, yet it also presents new challenges. While these therapies achieve high response rates and extend tumor control and patient survival, the majority of patients eventually face disease progression and mortality. Similarly, KIT inhibitors offer meaningful clinical benefits in KIT-mutant melanoma, but their overall clinical efficacy remains limited.

Advancing targeted melanoma therapies hinges on a deeper understanding of melanoma's molecular biology, which could pave the way for the development of more efficacious and less toxic treatments. Current clinical trials are increasingly incorporating tumor and

blood sample collections for biomarker analyses, aiming to uncover novel mechanisms of drug resistance. These endeavors are expected to contribute to enhanced disease control and improved survival rates in melanoma patients.

Furthermore, discovering new molecular targets via genetic and epigenetic research is essential. Such discoveries may pave the way for novel targeted therapy classes, especially beneficial for melanoma patients without BRAF or KIT mutations or those who have developed resistance to current treatments. Additionally, comprehending how molecular-targeted drugs affect immune cell activation is critical. It is expected that fine-tuning the sequence of targeted therapy and checkpoint immunotherapy will significantly improve melanoma treatment outcomes.

References

1. King CR, Kraus MH, Aaronson SA (1985) Amplification of a novel v-erbB-related gene in a human mammary carcinoma. Science 229: 974-976.
2. Karunagaran D, Tzahar E, Beerli RR, Chen X, Graus-Porta D, et al. (1996) ErbB-2 is a common auxiliary subunit of NDF and EGF receptors: Implications for breast cancer. EMBO J 15: 254-264.
3. Sawyers CL (1997) Signal transduction pathways involved in BCR-ABL transformation. Baillieres Clin Haematol 10: 223-231.
4. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, et al. (2003) Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 348: 994-1004.
5. Nickerson ML, Jaeger E, Shi Y, Durocher JA, Mahurkar S, et al. (2008) Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. Clin Cancer Res 14: 4726-4734.
6. Guy GP, Thomas CC, Thompson T, Watson M, Massetti GM, et al. (2015)Vital signs: Melanoma incidence and mortality trends and projections - United States, 1982-2030. MMWR Morb Mortal Wkly Rep 64: 591-596.
7. Siegel RL, Miller KD, Wagle NS, Jemal A (2023) Cancer statistics, 2023. CA Cancer J Clin 73: 17-48.
8. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, et al. (2009) Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 27: 6199-6206.
9. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, et al. (2019) Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): Post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol 20: 1239-1251.
10. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, et al. (2019) Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 381: 1535-1546.
11. Robert C, Grob JJ, Stroyakovskiy D, Karaszewska B, Hauschild A, et al. (2019) Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med 381: 626-636.
12. Sensi M, Nicolini G, Petti C, Bersani I, Lozupone F, et al. (2006) Mutually exclusive NRASQ61R and BRAFV600E mutations at the single-cell level in the same human melanoma. Oncogene 25: 3357-3364.
13. Reddy BY, Miller DM, Tsao H (2017) Somatic driver mutations in melanoma. Cancer 123: 2104-2117.
14. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, et al. (2002) Mutations of the BRAF gene in human cancer. Nature 417: 949-954.
15. Curtin JA, Busam K, Pinkel D, Bastian BC (2006) Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol 24: 4340-4346.
16. Van Raamsdonk CD, Bezrookove V, Green G, Bauer J, O'Brien JM, et al. (2009) Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. Nature 457: 599-602.
17. Van Raamsdonk CD, Griewank KG, Crosby MB, Garrido MC, Vemula S, et al. (2010) Mutations in GNA11 in uveal melanoma. N Engl J Med 363: 2191-2199.
18. Eisen T, Ahmad T, Flaherty KT, Gore M, Kaye S, et al. (2006) Sorafenib in advanced melanoma: A Phase II randomised discontinuation trial analysis. Br J Cancer 95: 581-586.
19. Flaherty KT, Lee SJ, Zhao F, Schuchter LM, Flaherty L, et al. (2013) Phase III trial of carboplatin and paclitaxel with or without sorafenib in metastatic melanoma. J Clin Oncol 31: 373-379.
20. Tsai J, Lee JT, Wang W, Zhang J, Cho H, et al. (2008) Discovery of a selective inhibitor of oncogenic B-Raf kinase with potent antimelanoma activity. Proc Natl Acad Sci USA 105: 3041-3046.
21. Bollag G, Hirth P, Tsai J, Zhang J, Ibrahim PN, et al. (2010) Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature 467: 596-599.
22. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, et al. (2010) Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 363: 809-819.
23. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, et al. (2011) Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 364: 2507-2516.
24. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, et al. (2012) Dabrafenib in BRAF-mutated metastatic melanoma: A multicentre, open-label, phase 3 randomised controlled trial. Lancet 380: 358-365.
25. Hauschild A, Grobb J, Demidov L, Jouary T, Gutzmer R, et al. (2014) An update on overall survival (OS) and follow-on therapies in BREAK-3, a phase III, randomized trial: Dabrafenib (D) vs. Dacarbazine (DTIC) in patients (pts) with BRAF V600E mutation-positive metastatic melanoma (MM). Ann Oncol 25: iv374-iv393.
26. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, et al. (2018) Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 19: 1315-1327.
27. Dummer R, Ascierto PA, Gogas H, Arance AM, Mandalà M, et al. (2018) Overall survival in COLUMBUS: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) vs vemurafenib (VEM) or enco in BRAF-mutant melanoma. Journal of Clinical Oncology 36: 9504.
28. Salama AK, Kim KB (2013) MEK inhibition in the treatment of advanced melanoma. Curr Oncol Rep 15: 473-482.

29. Falchook GS, Lewis KD, Infante JR, Gordon MS, Vogelzang NJ, et al. (2012) Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: A phase 1 dose-escalation trial. Lancet Oncol 13: 782-789.

30. Kim KB, Kefford R, Pavlick AC, Infante JR, Ribas A, et al. (2013) Phase II study of the MEK1/MEK2 inhibitor Trametinib in patients with metastatic BRAF-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. J Clin Oncol 31: 482-489.

31. Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, et al. (2012) Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 367: 107-114.

32. Robert C, Flaherty K, Nathan P, Hersey P, Garbe C, et al. (2019) Five-year outcomes from a phase 3 METRIC study in patients with BRAF V600 E/K-mutant advanced or metastatic melanoma. Eur J Cancer 109: 61-69.

33. Nazarian R, Shi H, Wang Q, Kong X, Koya RC, et al. (2010) Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. Nature 468: 973-977.

34. Emery CM, Vijayendran KG, Zipser MC, Sawyer AM, Niu L, et al. (2009) MEK1 mutations confer resistance to MEK and B-RAF inhibition. Proc Natl Acad Sci USA 106: 20411-20416.

35. Johannessen CM, Boehm JS, Kim SY, Thomas SR, Wardwell L, et al. (2010) COT drives resistance to RAF inhibition through MAP kinase pathway reactivation. Nature 468: 968-972.

36. Poulikakos PI, Persaud Y, Janakiraman M, Kong X, Ng C, et al. (2011) RAF inhibitor resistance is mediated by dimerization of aberrantly spliced BRAF(V600E). Nature 480: 387-390.

37. Trunzer K, Pavlick AC, Schuchter L, Gonzalez R, McArthur GA, et al. (2013) Pharmacodynamic effects and mechanisms of resistance to vemurafenib in patients with metastatic melanoma. J Clin Oncol 31: 1767-7174.

38. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, et al. (2015) Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 372: 30-39.

39. Larkin J, Ascierto PA, Dreno B, Atkinson V, Liszkay G, et al. (2014) Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 371: 1867-1876.

40. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, et al. (2018) Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 19: 603-615.

41. Lacouture ME, Duvic M, Hauschild A, Prieto VG, Robert C, et al. (2013) Analysis of dermatologic events in vemurafenib-treated patients with melanoma. Oncologist 18: 314-322.

42. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, et al. (2014) Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 371: 1877-1888.

43. Su F, Viros A, Milagre C, Trunzer K, Bollag G, et al. (2012) RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. N Engl J Med 366: 207-215.

44. Atkins MB, Lee SJ, Chmielowski B, Tarhini AA, Cohen GI, et al. (2023) Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced braf-mutant melanoma: The DREAMseq Trial-ECOG-ACRIN EA6134. J Clin Oncol 41: 186-197.

45. Gutzmer R, Stroyakovskiy D, Gogas H, Robert C, Lewis K, et al. (2020) Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAF(V600) mutation-positive melanoma (IMspire150): Primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 395: 1835-1844.

46. Dummer R, Long GV, Robert C, Tawbi HA, Flaherty KT, et al. (2022) Randomized phase III trial evaluating spartalizumab plus dabrafenib and trametinib for BRAF V600-mutant unresectable or metastatic melanoma. J Clin Oncol 40: 1428-1438.

47. Ascierto PA, Stroyakovskiy D, Gogas H, Robert C, Lewis K, et al. (2023) Overall survival with first-line atezolizumab in combination with vemurafenib and cobimetinib in BRAF(V600) mutation-positive advanced melanoma (IMspire150): Second interim analysis of a multicentre, randomised, phase 3 study. Lancet Oncol 24: 33-44.

48. Ascierto PA, Ferrucci PF, Fisher R, Del Vecchio M, Atkinson V, et al. (2019) Dabrafenib, trametinib and pembrolizumab or placebo in BRAF-mutant melanoma. Nat Med 25: 941-946.

49. Garrido MC, Bastian BC (2010) KIT as a therapeutic target in melanoma. J Invest Dermatol 130: 20-27.

50. Shen SS, Zhang PS, Eton O, Prieto VG (2003) Analysis of protein tyrosine kinase expression in melanocytic lesions by tissue array. J Cutan Pathol 30: 539-547.

51. Ugurel S, Hildenbrand R, Zimpfer A, La Rosee P, Paschka P, et al. (2005) Lack of clinical efficacy of imatinib in metastatic melanoma. Br J Cancer 92: 1398-1405.

52. Kim KB, Eton O, Davis DW, Frazier ML, McConkey DJ, et al. (2008) Phase II trial of imatinib mesylate in patients with metastatic melanoma. Br J Cancer 99: 734-740.

53. Wyman K, Atkins MB, Prieto V, Eton O, McDermott DF, et al. (2006) Multicenter Phase II trial of high-dose imatinib mesylate in metastatic melanoma: significant toxicity with no clinical efficacy. Cancer 106: 2005-2011.

54. Carvajal RD, Antonescu CR, Wolchok JD, Chapman PB, Roman RA, et al. (2011) KIT as a therapeutic target in metastatic melanoma. JAMA 305: 2327-2334.

55. Guo J, Si L, Kong Y, Flaherty KT, Xu X, et al. (2011) Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. J Clin Oncol 29: 2904-2909.

56. Hodi FS, Corless CL, Giobbie-Hurder A, Fletcher JA, Zhu M, et al. (2013) Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol 31: 3182-3190.