PRZESTRZELSKA, Magda, ŚLESICKA, Iga, ZOZULA, Natalia, TOMCZEWSKA, Zuzanna, RYKUCKA, Aleksandra, WĄS, Marcin, LATAŁA, Aleksandra, KIEŁBASA, Justyna, KOWALCZYK, Agata and BIL, Katarzyna. Advances in Targeted Therapies and Combination Approaches for Melanoma: A Comprehensive Review. Quality in Sport. 2024;23:54869. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.23.54869
https://apcz.umk.pl/QS/article/view/54869

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 03.09.2024. Revised: 25.09.2024. Accepted: 03.10.2024. Published: 04.10.2024.

Advances in Targeted Therapies and Combination Approaches for Melanoma: A Comprehensive Review

Magda Przestrzelska [MP]

Faculty of Medicine Collegium Medicum Uniwersytet Kardynała Stefana Wyszyńskiego w Warszawie

Wóycickiego 1/3, 01-938 Warszawa

Poland

https://orcid.org/0009-0009-8688-7047

magda.przestrzelska123@gmail.com

Iga Ślesicka [IŚ]

Mazovian Specialized Hospital in Ostrołęka of Józef Psarski, Jana Pawła II 120A, 07-410 Ostrołęka

Poland

https://orcid.org/0000-0001-7282-4875

igaslesicka@gmail.com

Natalia Zozula [NZ]
District Medical Center in Grójec Piotra Skargi 10 street, 05-600 Grójec
Poland
https://orcid.org/0009-0009-9741-5061
nataliazozula0@gmail.com
Zuzanna Tomczewska [ZT]
Provincial Specialist Hospital named after Blessed Father Jerzy Popiełuszko in Włocławek, Wieniecka 49, 87-800 Włocławek
Poland
https://orcid.org/0000-0002-4327-3311
ztomczewska@gmail.com
Aleksandra Rykucka [AR]
Rear Admiral Professor Wiesław Łasiński 7th Military Navy Hospital with Outpatient Clinic named after in Gdańsk Polanki 117 street, 80-305 Gdańsk
Poland
https://orcid.org/0009-0003-0171-8647
aleksandra.rykucka@wp.pl
Marcin Wąs [MW]
District Medical Center in Grójec Piotra Skargi 10 street, 05-600 Grójec
Poland
https://orcid.org/0009-0004-8645-0121
mos1@vp.pl
Aleksandra Latała [AL]
District Medical Center in Grójec Piotra Skargi 10 street, 05-600 Grójec
Poland
https://orcid.org/0009-0007-1701-2728
aleksandra.latala10@gmail.com
Justyna Kiełbasa [JK]
Independent Public Healthcare Complex in Pruszków 2/4 Armii Krajowej Avenue, 05-800 Pruszków
Poland
https://orcid.org/0009-0002-0616-7402
justynakielbasa1b@gmail.com

Agata Kowalczyk [AK]
Mazovian Specialized Hospital in Ostrołęka of Józef Psarski, Jana Pawła II 120A, 07-410 Ostrołęka
Poland
https://orcid.org/0009-0007-9497-0970
agata.kowalczyk95@gmail.com
Katarzyna Bil [KB]
Independent Public Specialist Western Hospital named after St John Paul II,
Daleka 11, 05-825 Grodzisk Mazowiecki
Poland
https://orcid.org/0009-0003-6518-1711
katarzynabil2503@gmail.com

Abstract

Introduction and Purpose: Melanoma, an aggressive malignancy from melanocytes, has a poor prognosis. Despite advances in targeted therapies and immunotherapies, drug resistance remains a challenge. This review examines the molecular pathways involved in melanoma and therapeutic strategies targeting them, aiming to improve patient outcomes and overcome treatment resistance by understanding genetic alterations and signaling cascades driving melanoma progression.

State of Knowledge: Melanoma arises from genetic predisposition and UV radiation exposure, involving mutations in pathways like RAS/RAF/MAPK and PI3K/AKT. Targeted therapies, such as BRAF and MEK inhibitors, are effective, especially in BRAF-mutant patients. However, resistance mechanisms, including alternative pathway activation and immune evasion, limit their long-term success. Combination therapies with immunotherapies show promise in overcoming resistance. Emerging targets like NRAS, c-KIT, and c-MET offer new treatment possibilities. Ongoing challenges include identifying biomarkers for patient stratification and managing treatment-related toxicity.

Conclusions: Understanding the molecular mechanisms of melanoma is crucial for advancing therapies. Targeted therapies and combination approaches have improved outcomes, especially in advanced cases. However, challenges like treatment resistance and toxicity require ongoing research. By exploring signaling pathways and new targets, treatment efficacy and durability can be enhanced. Continued research and clinical trials are essential to translate these advancements into practice, improving survival rates and quality of life for melanoma patients.

Key words: Melanoma, Targeted therapy, Immunotherapy

1. Introduction

Melanoma is a type of cancer with a steadily rising incidence rate. While it represents just 4% of all malignant skin cancers, it is responsible for 79% of the fatalities associated with these cancers [1]. Melanoma arises from DNA damage caused by UV or radiation exposure, leading to the malignant transformation of melanocytes [2]. Most melanomas have mutations in the RAS/RAF/MAPK and PI3K/AKT cellular regulatory pathways [3,4]. Currently, melanoma is among the most common cancers in fair-skinned individuals, particularly those with blonde or red hair and light-colored eyes. Unlike other solid tumors, it primarily affects young and middle-aged people [5-7]. Host risk factors, including the number of congenital or acquired nevi, genetic predisposition, and a family history of melanoma, are significant for the development of melanoma. Approximately 25% of cutaneous melanomas originate from a nevus [8]. Although dacarbazine and surgical resection can effectively manage early stages of melanoma, they prove ineffective in treating metastatic melanoma, leading to poor survival rates among patients [9]. However, the treatment options for unresectable stage III and IV melanoma have been transformed by immunotherapies and targeted therapies, leading to significantly enhanced survival rates compared to traditional chemotherapy regimens [10]. Molecularly targeted tyrosine kinase inhibitors (TKIs) that target specific components of the RAS/RAF/MAPK and PI3K/AKT pathways demonstrate efficacy in treating metastatic melanoma [3, 11]. The combination of tyrosine kinase inhibitors (TKIs) and immunotherapies aimed at key proteins within the oncogenic RAS/RAF/MAPK or PI3K/AKT pathways has demonstrated the ability to postpone the development of resistance, leading to enhanced progression-free survival in patients with metastatic melanoma [12, 13]. In this review, we will describe the specific therapeutic efficacy and the combinatory potential of agents targeting BRAF, MEK, NRAS, KRAS, HRAS, c-Kit, c-MET, and PI3K/AKT in detail

2. BRAF

BRAF serine/threonine kinase (BRAF) is a cellular controller of growth and survival, with mutations occurring in over 60% of cases of cutaneous melanoma. The BRAF V600E missense mutation, involving a substitution of valine with glutamic acid, is responsible for over 80% of all BRAF mutations. The V600K and V600D mutations

constitute the majority of the remaining 20% [14]. Dabrafenib, a BRAF inhibitor, received FDA approval in 2013 and has been widely employed as a primary treatment for advanced melanoma harboring the BRAF V600E mutation, both on its own and in combination with other therapies [15]. . Dabrafenib, combined with trametinib, a MEK inhibitor, is one of the main therapeutic options. The combination of dabrafenib and trametinib led to 11.4 months of progression-free survival without added toxicity compared to 7.3 months in the monotherapy cohort [16]. In 2014, the FDA granted approval for the utilization of this combination therapy in metastatic and unresectable melanoma with BRAF V600E/K mutations, and in 2018, this approval was expanded to include stage III melanoma [17]. The FDA granted approval for encorafenib, the latest BRAF inhibitor designed for advanced V600-mutated melanoma, in June 2018 [18]. Analyzed trial data evaluated the combination of encorafenib with binimetinib, an MEK inhibitor, and demonstrated that this combination enhanced overall survival rates in melanoma patients when compared to encorafenib alone [19]. In particular, incorporating binimetinib into the treatment regimen enables the administration of higher doses of encorafenib, leading to a more pronounced improvement in response rates. However, this escalation in efficacy is also linked with an elevated occurrence of adverse events [19-20]. The selected molecularly targeted treatment methods described above, correlated with immunotherapy, offer new therapeutic opportunities for melanoma. These methods require more detailed research regarding patient profiles for whom such therapy could be directed.

3. MEK

The majority of patients diagnosed with melanoma possess mutations in their oncogenes that control signaling pathways within the mitogen-activated protein kinase (MAPK) pathway. Patients with metastatic melanoma harboring the BRAF V600 mutation, which constitutes 40–50% of melanoma cases, receive treatment with MEK inhibitors like trametinib, cobimetinib, selumetinib, and binimetinib. As previously mentioned, various combinations of BRAF/MEK inhibitors, such as dabrafenib/trametinib have demonstrated superior effectiveness compared to BRAF inhibitors alone in the treatment of BRAF V600 mutant melanoma [21]. Another promising treatment regimen is MEK inhibitors in conjunction with cyclin-dependent kinase (CDK) 4/6 inhibitors or MEK inhibitors paired with an anti-PD-1/PD-L1 antibody [22].

4. NRAS

NRAS mutations are frequently observed across various cancers and play a significant role as oncogenic drivers in melanoma [23]. Melanoma characterized by a significant NRAS burden is linked to thicker tumors, increased mitotic activity, and a poorer prognosis [24-26]. As of now, there hasn't been approval for any targeted therapy specifically aimed at NRAS. However, multiple inhibitors targeting the MAPK pathway and several combination therapies have been explored for NRAS-mutant melanoma. For instance, MEK inhibitors combined with other inhibitors are commonly under investigation. A preclinical study demonstrated that concurrent inhibition of both MEK, which is downstream of Ras, and CDK4/6, could trigger tumor regression in NRAS-mutant melanoma [27]. Melanoma cell lines carrying NRAS mutations at codon 61 were subjected to treatment with Amgen Compd A (a pan-RAF inhibitor) and trametinib (a MEK inhibitor) to synergistically inhibit cell growth. Cell lines responsive to this combination exhibited increased phosphorylated MEK levels, suggesting a high reliance on the MAPK pathway for cell proliferation. Cyclin D1, regulated by the MAPK pathway and interacting with CDK4/6 to initiate

G1-to-S phase transition, emerged as a crucial mediator for cell growth in these responsive cell lines. This investigation revealed that targeting RAF and MEK could effectively curb cell growth in NRAS-mutant melanoma cell lines reliant on the MAPK pathway. Furthermore, it underscores the importance of addressing alternative pathways since resistant cell lines may activate pro-survival mechanisms independent of MAPK [28]. In response to drug resistance to MEK inhibitors, recent preclinical studies have explored combination therapies aimed at overcoming resistance to MEK inhibitors (MEKi). One study revealed that concurrent inhibition of MEK and ERK5, an alternative pathway activated as a compensatory response to MEKi, possibly through the receptor tyrosine kinase PDGFRβ, effectively suppressed the growth and progression of NRAS-mutant melanoma cells both in vitro and in xenograft models [29]. These approaches, while still in the early stages of research, have the potential to address resistance and improve the effectiveness of inhibitors directed at the MAPK pathway. There are numerous studies and proposed therapies for melanomas with NRAS mutation. To date, there hasn't been any advancement in combination therapy specifically tailored for NRAS-mutant melanoma.

5. HRAS and KRAS

KRAS stands out as one of the most frequently mutated oncogenes in human cancers. It encodes a GTPase within the RAS/MAPK pathway, which fosters cell growth and proliferation. KRAS mutations are predominantly observed at the G12 position, often involving glycine-to-cysteine alterations. These point mutations tend to favor the active conformation of the KRAS protein (GTP-bound). Elevated KRAS activity prompts uncontrolled cell growth and proliferation in cancer. While KRAS inhibitors are mainly investigated in non-small cell lung cancer and colorectal cancer, some clinical trials are exploring their application in other advanced or metastatic solid tumors. KRAS mutations are detected in about 1% of melanomas [30]. HRAS is the least commonly mutated GTPase compared to the other two Ras isoforms, and its transcriptional regulation varies from that of NRAS and KRAS. Mutations in HRAS are found in only 1.5% of all melanoma cases, and increased HRAS expression is associated with reduced survival rates in patients with cutaneous melanomas [31-32]. HRAS isn't commonly used as a mutation marker in clinical settings for melanoma patients, and its significance in solid tumors has been relatively understudied. In a preclinical study, the effectiveness of ASN007, an ERK1/2 inhibitor, was assessed in cell lines carrying mutated RAS, including HRAS. ASN007 demonstrated strong antitumor activity, which was further potentiated by the addition of the PI3K inhibitor copanlisib [33].

6. c-KIT

Alterations in c-KIT can impact diverse cancer types, affecting processes like metastasis, tumor expansion, and cell proliferation. c-KIT mutations are linked to conditions such as gastrointestinal stromal tumors (GIST), leukemia, lung cancer, and melanoma [34-36]. Additionally, KIT mutations are linked with older age, chronic sun damage, and occur more frequently in mucosal and acral melanomas [37]. Imatinib, a tyrosine kinase inhibitor targeting c-abl, bcr-abl, and platelet-derived growth-factor receptor (PDGFR), has been extensively investigated for its ability to inhibit c-KIT in various malignancies, such as human mast cell leukemia and gastrointestinal stromal tumors (GIST). Its therapeutic efficacy has also demonstrated promising results in treating metastatic melanoma [38-39]. Several other c-KIT inhibitors, including dasatinib, sunitinib, sorafenib, and masitinib, have been investigated as potential therapeutic agents for melanoma. However, additional studies are required to assess

their clinical effectiveness. Numerous clinical trials are evaluating the effectiveness of combining c-KIT inhibitors with other tyrosine kinase inhibitors or immunotherapies, as patients with c-KIT mutant melanoma frequently develop resistance to tyrosine kinase inhibitors alone [40]. The above-mentioned are examples of molecularly targeted therapy combined with immunotherapy or tyrosine kinase inhibitors, these are potential treatment regimens for melanoma with c-KIT mutation, but require thorough research.

7. c-MET

c-MET, a tyrosine kinase receptor encoded by the MET proto-oncogene, binds to hepatocyte growth factor (HGF) and activates the PI3K-AKT, STAT, SRC, and MAPK signaling pathways. This activation leads to tumor cell proliferation, invasion, and metastasis [41, 42]. Therefore, c-MET is a critical target, as its downregulation can silence multiple pathways involved in tumorigenesis [43]. HGF is usually produced by mesenchymal cells when needed and interacts with its receptor, c-MET, in a paracrine manner in skin cells. However, in melanoma cells, there is continuous autocrine production of HGF, leading to the activation of the c-MET receptor beyond mesenchymal cells [44]. Currently, several tyrosine kinase inhibitors (TKIs) targeting c-MET are under investigation. However, their effectiveness against melanoma has been diminished due to the development of resistance, and the mechanisms behind this resistance need further exploration [45]. The c-MET tyrosine kinase inhibitor SU11274 was associated with an elevation in phosphorylation of c-MET, mTOR, p70S6K, and active β-catenin, along with upregulation of GATA-6. Upon developing resistance, upregulation of the mTOR pathway and Wnt signaling was observed, potentially leading to resistance to c-MET inhibitors. However, combining the mTOR inhibitor everolimus and the Wnt inhibitor XAV939 with SU11274 led to a significant 95% reduction in tumors in melanoma cell lines [46]. Uveal melanoma (UM) represents the most prevalent form of eye cancer, comprising approximately 5% of all melanomas. In cultures of uveal melanoma (UM) cells, it was discovered that HGF serves as one of the factors contributing to resistance to treatment [47,48]. Recent in vitro research has demonstrated that LY2801653, a type II kinase inhibitor targeting c-Met, plays a role in overcoming HGF-mediated resistance in uveal melanoma (UM) cell lines treated with trametinib, a MEK1/2 inhibitor. Significant reductions ranging from 64% to 81% in cancer cell survival rates were observed [47]. Moreover, combining MEK inhibitors with AKT inhibitors, PI3K inhibitors, or c-MET inhibitors holds promise for enhancing the clinical effectiveness of these drugs in metastatic uveal melanoma. However, MEK-based treatments are typically associated with toxicity and are not suitable for long-term therapy [49].

8. PI3K/AKT

While mutations of the phosphatidylinositol 3-kinase (PI3K) itself are uncommon in melanomas, the PI3K/AKT pathway is often implicated through alternative activation mechanisms. One such mechanism involves loss-of-functional mutations in the NF1 tumor suppressor gene, observed in approximately 10–15% of melanoma cases. Consequently, the NRAS protein becomes hyperactive, leading to the activation of both the MAPK and PI3K pathways [50]. Several PI3K inhibitors are currently undergoing investigation in clinical trials. One study aimed to establish the maximum tolerated dose (MTD) of two experimental drugs, pimasertib (MSC1936369B, a mitogen-activated protein extracellular signal-regulated kinase (MEK) inhibitor), and voxtalisib (SAR245409, a PI3K inhibitor), when administered in combination. Both drugs were given orally with escalating doses in 21-day

cycles until the MTD was determined. The MTD was defined as intolerable toxicity, the decision of the investigator to halt treatment, or withdrawal of consent by the subject. Following the determination of the MTD, participants were divided into tumor-specific expansion cohorts, including breast cancer, non-small cell lung cancer (NSCLC), melanoma, and colorectal cancer. In the melanoma cohort, one out of fifteen patients exhibited a complete tumor response to the drugs, while one showed a partial response. Four patients experienced progressive disease, seven had stable disease, and one patient was not evaluated [51]. Other PI3K inhibitors, such as selective PI3K-beta inhibitor GSK2636771 and the PI3K-gamma inhibitor IPI-549 are still under investigation.

9. Conclusions

In this comprehensive review, we've outlined the diverse molecular pathways implicated in melanoma progression and the targeted therapies designed to counteract them. Melanoma, though representing a small fraction of skin cancers, disproportionately accounts for the majority of skin cancer-related fatalities. Its development is intricately linked to mutations in key signaling pathways like RAS/RAF/MAPK and PI3K/AKT, often triggered by UV or radiation exposure. Current therapeutic strategies include both targeted therapies and immunotherapies, offering significant advancements in managing advanced stages of melanoma. Targeted therapies directed at BRAF, MEK, NRAS, c-KIT, and c-MET have shown promising results in clinical trials, often in combination with immunotherapies or other targeted agents. For instance, BRAF inhibitors like dabrafenib, when paired with MEK inhibitors such as trametinib, have demonstrated improved progression-free survival rates in patients harboring BRAF mutations. However, challenges such as drug resistance and toxicity remain significant hurdles in long-term treatment. Strategies like combining MEK inhibitors with AKT inhibitors or PI3K inhibitors aim to enhance therapeutic efficacy while mitigating adverse effects. Additionally, understanding the interplay between different pathways, such as the cross-talk between MAPK and PI3K/AKT pathways, is crucial for developing effective combination therapies. Furthermore, emerging research on less common mutations like HRAS and KRAS highlights the need for tailored therapeutic approaches for specific molecular subtypes of melanoma. Investigational drugs targeting these mutations hold promise but require further validation in clinical trials. In conclusion, the evolving landscape of targeted therapies and combination regimens offers renewed hope for improved outcomes in melanoma patients. Continued research into novel therapeutic targets and optimization of existing treatment strategies are essential for further advancements in melanoma therapy.

Disclosures

Author’scontribution:

Conceptualization: Natalia Zozula, Aleksandra Rykucka, Zuzanna Tomczewska

Methodology: Aleksandra Latała

Software: Marcin Wąs

Check: Justyna Kiełbasa, Magda Przestrzelska

Formal analysis: Iga Ślesicka, Magda Przestrzelska

Investigation: Katarzyna Bil, Agata Kowalczyk

Resources: Zuzanna Tomczewska

Data curation: Aleksandra Rykucka

Writing–rough preparation: Justyna Kiełbasa, Natalia Zozula

Writing–review and editing: Aleksandra Latała, Marcin Wąs, Agata Kowalczyk

Visualization: Katarzyna Bil

Supervision: Iga Ślesicka

Project administration: Natalia Zozula, Aleksandra Rykucka

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This Research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict of Interests: The authors declare no conflict of interest.

References

1. Böni R, Schuster C, Nehrhoff B, Burg G. Epidemiology of skin cancer. *Neuro Endocrinol Lett*. 2002;23 Suppl 2:48-51.
2. Khan AQ, Travers JB, Kemp MG. Roles of UVA radiation and DNA damage responses in melanoma pathogenesis. *Environ Mol Mutagen*. 2018;59(5):438-460. doi:10.1002/em.22176

3. Montor, W.R.; Salas, A.; Melo, F.H.M. Receptor tyrosine kinases and downstream pathways as druggable targets for cancer treatment: The current arsenal of inhibitors. Mol. Cancer 2018, 17, 55.
4. Schrank Z, Chhabra G, Lin L, et al. Current Molecular-Targeted Therapies in NSCLC and Their Mechanism of Resistance. *Cancers (Basel)*. 2018;10(7):224. Published 2018 Jul 4. doi:10.3390/cancers10070224
5. Carr S, Smith C, Wernberg J. Epidemiology and Risk Factors of Melanoma. *Surg Clin North Am*. 2020;100(1):1-12. doi:10.1016/j.suc.2019.09.005
6. O'Neill CH, Scoggins CR. Melanoma. *J Surg Oncol*. 2019;120(5):873-881. doi:10.1002/jso.25604
7. Iglesias-Pena N, Paradela S, Tejera-Vaquerizo A, Boada A, Fonseca E. Cutaneous Melanoma in the Elderly: Review of a Growing Problem. *Actas Dermo-Sifiliográficas*. 2019;110(6):434-447. doi:10.1016/j.adengl.2019.05.012
8. Bevona C, Goggins W, Quinn T, Fullerton J, Tsao H. Cutaneous Melanomas Associated With Nevi. *Archives of Dermatology*. 2003;139(12):1620-1624. doi:10.1001/archderm.139.12.1620
9. Davis LE, Shalin SC, Tackett AJ. Current state of melanoma diagnosis and treatment. *Cancer Biology & Therapy*. 2019;20(11):1366-1379. doi:10.1080/15384047.2019.1640032
10. Michielin O, van Akkooi ACJ, Ascierto PA, Dummer R, Keilholz U; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2019;30(12):1884-1901. doi:10.1093/annonc/mdz411
11. Czarnecka AM, Bartnik E, Fiedorowicz M, Rutkowski P. Targeted Therapy in Melanoma and Mechanisms of Resistance. *Int J Mol Sci*. 2020;21(13):4576. Published 2020 Jun 27. doi:10.3390/ijms21134576
12. Luke JJ, Flaherty KT, Ribas A, Long GV. Targeted agents and immunotherapies: optimizing outcomes in melanoma. *Nat Rev Clin Oncol*. 2017;14(8):463-482. doi:10.1038/nrclinonc.2017.43
13. Namikawa K, Yamazaki N. Targeted Therapy and Immunotherapy for Melanoma in Japan. *Curr Treat Options Oncol*. 2019;20(1):7. Published 2019 Jan 24. doi:10.1007/s11864-019-0607-8
14. Smalley KSM. Understanding Melanoma Signaling Networks as the Basis for Molecular Targeted Therapy. *Journal of Investigative Dermatology*. 2010;130(1):28-37. doi:10.1038/jid.2009.177
15. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *The Lancet*. 2012;380(9839):358-365. doi:10.1016/S0140-6736(12)60868-X

16. Robert Caroline, Karaszewska Boguslawa, Schachter Jacob, et al. Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. *New England Journal of Medicine*. 2015;372(1):30-39. doi:10.1056/NEJMoa1412690
17. Subbiah V, Baik C, Kirkwood JM. Clinical Development of BRAF plus MEK Inhibitor Combinations. *Trends in Cancer*. 2020;6(9):797-810. doi:10.1016/j.trecan.2020.05.009
18. Yu C, Liu X, Yang J, et al. Combination of Immunotherapy With Targeted Therapy: Theory and Practice in Metastatic Melanoma. *Front Immunol*. 2019;10:990. Published 2019 May 7. doi:10.3389/fimmu.2019.00990
19. Sun J, Zager JS, Eroglu Z. Encorafenib/binimetinib for the treatment of BRAF-mutant advanced, unresectable, or metastatic melanoma: design, development, and potential place in therapy. *Onco Targets Ther*. 2018;11:9081-9089. Published 2018 Dec 14. doi:10.2147/OTT.S171693
20. Koelblinger P, Thuerigen O, Dummer R. Development of encorafenib for BRAF-mutated advanced melanoma. *Curr Opin Oncol*. 2018;30(2):125-133. doi:10.1097/CCO.0000000000000426
21. Sullivan R, LoRusso P, Boerner S, Dummer R. Achievements and Challenges of Molecular Targeted Therapy in Melanoma. *Am Soc Clin Oncol Educ Book*. 2015;(35):177-186. doi:10.14694/EdBook_AM.2015.35.177
22. Dummer R, Long GV, Robert C, et al. Randomized Phase III Trial Evaluating Spartalizumab Plus Dabrafenib and Trametinib for *BRAF* V600-Mutant Unresectable or Metastatic Melanoma. *J Clin Oncol*. 2022;40(13):1428-1438. doi:10.1200/JCO.21.01601
23. Hodis E, Watson IR, Kryukov GV, et al. A landscape of driver mutations in melanoma. *Cell*. 2012;150(2):251-263. doi:10.1016/j.cell.2012.06.024
24. Devitt B, Liu W, Salemi R, et al. Clinical outcome and pathological features associated with NRAS mutation in cutaneous melanoma. *Pigment Cell Melanoma Res*. 2011;24(4):666-672. doi:10.1111/j.1755-148X.2011.00873.x
25. Thomas NE, Edmiston SN, Alexander A, et al. Association Between NRAS and BRAF Mutational Status and Melanoma-Specific Survival Among Patients With Higher-Risk Primary Melanoma [published correction appears in JAMA Oncol. 2015 Jun;1(3):285]. *JAMA Oncol*. 2015;1(3):359-368. doi:10.1001/jamaoncol.2015.0493
26. Kelleher FC, McArthur GA. Targeting NRAS in melanoma. *Cancer J*. 2012;18(2):132-136. doi:10.1097/PPO.0b013e31824ba4df
27. Sosman JA, Kittaneh M, Lolkema MPJK, et al. A phase 1b/2 study of LEE011 in combination with binimetinib (MEK162) in patients with NRAS-mutant melanoma: Early encouraging clinical activity. *JCO*. 2014;32(15_suppl):9009-9009. doi:10.1200/jco.2014.32.15_suppl.9009

28. Atefi M, Titz B, Avramis E, et al. Combination of pan-RAF and MEK inhibitors in NRAS mutant melanoma. *Mol Cancer*. 2015;14(1):27. Published 2015 Feb 3. doi:10.1186/s12943-015-0293-5
29. Adam C, Fusi L, Weiss N, et al. Efficient Suppression of NRAS-Driven Melanoma by Co-Inhibition of ERK1/2 and ERK5 MAPK Pathways. *J Invest Dermatol*. 2020;140(12):2455-2465.e10. doi:10.1016/j.jid.2020.03.972
30. Hong David S., Fakih Marwan G., Strickler John H., et al. KRASG12C Inhibition with Sotorasib in Advanced Solid Tumors. *New England Journal of Medicine*. 2020;383(13):1207-1217. doi:10.1056/NEJMoa1917239
31. Vanni I, Tanda ET, Dalmasso B, et al. Non-BRAF Mutant Melanoma: Molecular Features and Therapeutical Implications. *Front Mol Biosci*. 2020;7:172. Published 2020 Jul 24. doi:10.3389/fmolb.2020.00172
32. Wan X, Liu R, Li Z. The Prognostic Value of HRAS mRNA Expression in Cutaneous Melanoma. *Biomed Res Int*. 2017;2017:5356737. doi:10.1155/2017/5356737
33. Portelinha A, Thompson S, Smith RA, et al. ASN007 is a selective ERK1/2 inhibitor with preferential activity against RAS-and RAF-mutant tumors. *Cell Rep Med*. 2021;2(7):100350. Published 2021 Jul 21. doi:10.1016/j.xcrm.2021.100350
34. Crosier PS, Ricciardi ST, Hall LR, Vitas MR, Clark SC, Crosier KE. Expression of isoforms of the human receptor tyrosine kinase c-kit in leukemic cell lines and acute myeloid leukemia. *Blood*. 1993;82(4):1151-1158.
35. Maulik G, Bharti A, Khan E, Broderick RJ, Kijima T, Salgia R. Modulation of c-Kit/SCF pathway leads to alterations in topoisomerase-I activity in small cell lung cancer. *J Environ Pathol Toxicol Oncol*. 2004;23(4):237-251. doi:10.1615/jenvpathtoxoncol.v23.i4.10
36. Crosier PS, Ricciardi ST, Hall LR, Vitas MR, Clark SC, Crosier KE. Expression of isoforms of the human receptor tyrosine kinase c-kit in leukemic cell lines and acute myeloid leukemia. *Blood*. 1993;82(4):1151-1158.
37. Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. *J Clin Oncol*. 2006;24(26):4340-4346. doi:10.1200/JCO.2006.06.2984
38. Tuveson DA, Willis NA, Jacks T, et al. STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications. *Oncogene*. 2001;20(36):5054-5058. doi:10.1038/sj.onc.1204704
39. Wei X, Mao L, Chi Z, et al. Efficacy Evaluation of Imatinib for the Treatment of Melanoma: Evidence From a Retrospective Study. *Oncol Res*. 2019;27(4):495-501. doi:10.3727/096504018X15331163433914
40. Meng D, Carvajal RD. KIT as an Oncogenic Driver in Melanoma: An Update on Clinical Development. *Am J Clin Dermatol*. 2019;20(3):315-323. doi:10.1007/s40257-018-0414-1

41. Sierra JR, Tsao MS. c-MET as a potential therapeutic target and biomarker in cancer. *Ther Adv Med Oncol*. 2011;3(1 Suppl):S21-S35. doi:10.1177/1758834011422557
42. Peschard P, Park M. From Tpr-Met to Met, tumorigenesis and tubes. *Oncogene*. 2007;26(9):1276-1285. doi:10.1038/sj.onc.1210201
43. Knudsen BS, Vande Woude G. Showering c-MET-dependent cancers with drugs. *Current Opinion in Genetics & Development*. 2008;18(1):87-96. doi:10.1016/j.gde.2008.02.001
44. Puri N, Ahmed S, Janamanchi V, et al. c-Met Is a Potentially New Therapeutic Target for Treatment of Human Melanoma. *Clinical Cancer Research*. 2007;13(7):2246-2253. doi:10.1158/1078-0432.CCR-06-0776
45. Patel M, Eckburg A, Gantiwala S, Hart Z, Dein J, Lam K, Puri N. Resistance to Molecularly Targeted Therapies in Melanoma. *Cancers*. 2021; 13(5):1115. https://doi.org/10.3390/cancers13051115
46. Etnyre D, Stone AL, Fong JT, et al. Targeting c-Met in melanoma: mechanism of resistance and efficacy of novel combinatorial inhibitor therapy. *Cancer Biol Ther*. 2014;15(9):1129-1141. doi:10.4161/cbt.29451
47. Cheng H, Terai M, Kageyama K, et al. Paracrine Effect of NRG1 and HGF Drives Resistance to MEK Inhibitors in Metastatic Uveal Melanoma. *Cancer Res*. 2015;75(13):2737-2748. doi:10.1158/0008-5472.CAN-15-0370
48. Puri N, Ahmed S, Janamanchi V, et al. c-Met Is a Potentially New Therapeutic Target for Treatment of Human Melanoma. *Clinical Cancer Research*. 2007;13(7):2246-2253. doi:10.1158/1078-0432.CCR-06-0776
49. Ohara M, Saito K, Kageyama K, et al. Dual Targeting of CDK4/6 and cMET in Metastatic Uveal Melanoma. *Cancers (Basel)*. 2021;13(5):1104. Published 2021 Mar 4. doi:10.3390/cancers13051104
50. Leonardi GC, Falzone L, Salemi R, et al. Cutaneous melanoma: From pathogenesis to therapy (Review). *Int J Oncol*. 2018;52(4):1071-1080. doi:10.3892/ijo.2018.4287
51. Schram AM, Gandhi L, Mita MM, et al. A phase Ib dose-escalation and expansion study of the oral MEK inhibitor pimasertib and PI3K/MTOR inhibitor voxtalisib in patients with advanced solid tumours. *Br J Cancer*. 2018;119(12):1471-1476. doi:10.1038/s41416-018-0322-4