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Case Report

Entrectinib for NTRK Fusion-Positive Metastatic Melanoma Progressing on Combined PD-1 and CTLA-4 Inhibition: A Case Report

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Case report · Metastatic melanoma · Entrectinib · NTRK3 gene fusion

Abstract

Introduction: The burden of melanoma is increasing globally. Despite the use of immunotherapy and targeted therapy, the prognosis of metastatic melanoma remains relatively poor. The integration of comprehensive molecular profiling can lead to the detection of actionable biomarkers and the expansion of treatment options, thereby prolonging cancer patient survival. ***Case Presentation:*** We herein present the case of a female 54-year-old patient diagnosed with melanoma of the right knee, for which she underwent surgery. Patient showed progression of disease after 10 cycles of adjuvant nivolumab. Ipilimumab (1 mg/kg every 3 weeks) was added to the treatment regimen but no clinical improvement was observed. Molecular profiling was conducted based on patient tissue, and an *ANXA2-NTRK3* fusion was detected in the tumor. This specific fusion has not been previously reported; however, it is in-frame and similar to other known oncogenic *NTRK* fusions. At the time of entrectinib initiation, the patient had clear disease progression on the right leg on standard of care immunotherapy. She was commenced on entrectinib 200 mg once daily for 2 weeks. Dose escalation was attempted, and treatment intensity was managed based on drug tolerability. Good treatment response was observed on laboratory and radiologic parameters. As of September 2023, i.e., 2.5 years after treatment initiation, patient disease continues to be controlled with entrectinib. ***Conclusion:*** Profiling of advanced tumors is important to determine the presence of agnostic markers that can be targeted and ultimately improve the prognostic outcome of patients after the failure of standard of care.

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Introduction

The burden of melanoma is increasing globally. The incidence of this malignancy rose by 170% in 3 decades, while its mortality almost doubled in the same time frame [1]. 57,000 deaths were attributed to melanoma in 2020 and a 68% increase in mortality is projected by 2040 [2].

Historically relying on interleukin 2 (IL-2)-based approaches, the management of metastatic melanoma has dramatically changed in the past decade. This shift was driven by the advancement of immunobiology and cancel cell biology and the subsequent integration of targeted therapies and immunotherapy. This in turn introduced striking responses and real-world improvements in survival that were previously unattainable especially in advanced/metastatic melanoma cases [3, 4]. Clinical evidence clearly shows the survival advantage afforded by immunotherapy in advanced/metastatic melanoma [5, 6]. Based on this, current international guidelines recommend the immunotherapeutic anti-Programmed cell death protein 1 (PD-1) drugs nivolumab or pembrolizumab as preferred choices for first-line systemic treatment in cutaneous melanoma. International guidelines recommend the use of immunotherapy as monotherapy with nivolumab, pembrolizumab, or combination of nivolumab and the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor ipilimumab [7]. The guidelines also recognize the need for targeted therapy, alone or in combination with systemic immunotherapy, for the management of tumors with known oncogenic mutations. For example, mono or combination targeted therapy is recommended in case of *BRAF* V600 activating mutation, neurotrophic tyrosine receptor kinase (NTRK) fusion-positive tumors, and *NRAS*-mutated tumors, among others [7].

However, the prognosis of metastatic melanoma remains relatively poor. Disease recurrence can be expected for at least 13.4% of patients with advanced/metastatic melanoma within 2 years, even after prior immunotherapy exposure [8, 9]. Overall 5-year survival rates of advanced melanoma treated with pembrolizumab are around 34%, with only 21% of patients remaining free of disease after 5 years [5]. While nivolumab seems to offer higher 5-year overall survival rates as monotherapy (44%) or combination therapy (52% in combination with ipilimumab) [6], the fact remains that more than half of patients will die within 5 years of diagnosis with advanced/metastatic melanoma. It is therefore clear that significant improvements are needed in both preventative and therapeutic efforts. Meaningful changes in melanoma incidence and mortality trends could be achieved through intensive awareness campaigns, better screening, and increased treatment access [10]. The integration of comprehensive molecular profiling is also important as it can prolong survival among cancer patients through the detection of actionable biomarkers and the expansion of treatment options [11, 12].

In this report, we present the case of a female 54-year-old patient with previously resected metastatic melanoma. This case report details the successful management of advanced disease with molecular profiling-guided targeted therapy after progression on both mono and combination immunotherapy.

Case Presentation

This report describes the case of a 54-year-old married woman with four children. Other than a history of diabetes mellitus, the patient had no known allergies, was a non-smoker who does not engage in alcohol consumption, and had no family history of cancer.

The patient was diagnosed with melanoma of the right knee in November 2019, for which she underwent surgery in January 2020. No spitzoid melanoma components were identified upon histological examination. Shortly after, she was commenced on adjuvant nivolumab

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(240 mg every 2 weeks) in March 2020 and completed 10 cycles by November 2020. Due to progression of disease on the leg, ipilimumab (1 mg/kg every 3 weeks) was added to the treatment regimen. No clinical improvement was observed even after three cycles of therapy. She then suffered from Coronavirus Disease 2019 (COVID-19), from which she had a lengthy recovery. In the interim period, patient tissue samples were sent for molecular profiling (results shown in Table 1). Tissue was obtained from the new biopsy that was performed to determine the diagnosis. This is due to the unavailability of the original pathology report from the two previous excisional biopsies that were performed in the patient's native country. Molecular profiling showed that tumor mutational burden was low and an *ANXA2-NTRK3* fusion was detected in this tumor. This specific fusion has not been previously reported; however, it is in-frame and similar to other known oncogenic *NTRK* fusions.

The patient underwent a clinical review prior to enrollment in the entrectinib special access program. A comprehensive discussion was carried out with the patient and supporting family member, detailing entrectinib's side effects profile and that response to therapy cannot be guaranteed. Supporting family was also fully aware that limb perfusion therapy should be considered at some point in the management. However, limb perfusion therapy was not immediately accessible to the patient. At the time of entrectinib initiation, the patient has clear cut disease progression on the right leg. Examination revealed multiple nodules fungating from the right knee to the ankle: clear signs of progression on immunotherapy (Fig. 1a, b). In March 2021, she was commenced on entrectinib 200 mg once daily for 2 weeks. Good treatment response was observed with unremarkable laboratory test results. The patient developed Bell's palsy (right side) that was observed to be resolving gradually and was determined to be unrelated to entrectinib. Due to this, entrectinib was administered at the same dose for another 2 weeks. Entrectinib was well tolerated and Bell's palsy resolved, which led to the increase of entrectinib dose to 400 mg once daily for 2 weeks. Patient response to treatment and laboratory test results were good with the exception of elevated blood sugar. She was referred to the treating diabetologist to explore options for restoring glycemic control. The only concomitant medications taken by the patient were diabetic medications. After a thorough check with pharmacists, these medications were not found to have any interaction with entrectinib. Entrectinib dose was escalated again, with the patient taking entrectinib 600 mg once daily for 3 weeks. On May 25, 2021, she presented with complaints of shortness of breath. She was found to be clinically unwell and had a bilateral pleural effusion that was then drained. Following this, patient symptoms improved. Pathology report revealed no disease and the patient was restarted on entrectinib 200 mg once daily. Once again, she responded well to entrectinib and had good laboratory test results. The chest remained clear, while the lesions on the leg showed notable improvement. Entrectinib dose was increased to 400 mg on June 2021. However, upon patient follow-up on the August 1, 2021, the patient revealed that daily entrectinib 400 mg was not well tolerated. Instead, the patient was only taking entrectinib 400 mg once daily for 2 days each week, alternating it with entrectinib 200 mg once daily.

Radiologic imaging was conducted on the November 29, 2021. Computed tomography with contrast of the neck, chest, abdomen, and pelvis showed multiple mild to moderate enlarged retroperitoneal and iliac lymph nodes. Observations remained unchanged as compared to the previous study, with no newly developed evidence of disease. There was also no change in existing bilateral multiple tiny pulmonary nodules. Magnetic resonance imaging with contrast of the brain was unremarkable. Eastern Cooperative Oncology Group (ECOG) score was 0 and leg lesions showed further improvement. As of September 2023 (approx. 2.5 years of treatment with entrectinib), the patient was alive and well and continued to be in

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Table 1. Molecular profiling results with therapy associations

Biomarker	Method[γ]	Analyte	Result	Therapy association		Biomarker level*
NTRK3	Seq	RNA-tumor	Pathogenic fusion	Benefit	Entrectinib, larotrectinib	Level 2
BRAF	Seq	DNA-tumor	Mutation not detected	Lack of benefit	Binimetinib, cobimetinib, dabrafenib, encorafenib, trametinib, vemurafenib	Level 2
NTRK1	Seq	RNA-tumor	Mutation not detected	Not clinically relevant		
NTRK2	Seq	RNA-tumor	Mutation not detected	Not clinically relevant		
Tumor mutational burden	Seq	DNA-tumor	Low	Not clinically relevant	Pembrolizumab[a]	Level 2
BRAF	Seq	RNA-tumor	Mutation not detected	None		
KIT	Seq	DNA-tumor	Mutation not detected	Not clinically relevant	Imatinib	Level 2
MAP2K1 (MEK1)	Seq	DNA-tumor	Mutation not detected	None		
MAP2K2 (MEK2)	Seq	DNA-tumor	Mutation not detected	None		
NF1	Seq	DNA-tumor	Mutation not detected	None		
NRAS	Seq	DNA-tumor	Mutation not detected	None		
PD-L1 (SP142)	IHC	Protein	Negative | 0%	Not clinically relevant[b]		
Mismatch repair status	IHC	Protein	Proficient	Not clinically relevant	Dostarlimab[c], pembrolizumab	Level 2
MSI	Seq	DNA-tumor	Stable	Not clinically relevant	Pembrolizumab	Level 2

*Biomarker reporting classification: level 1 – highest level of clinical evidence and/or biomarker association included on the drug label; level 2 – strong evidence of clinical significance and is endorsed by standard clinical guidelines; level 3 – potential clinical significance.

[a]Association based on FDA pan-cancer approval.

[b]Laboratory-developed test not recommended by NCCN.

[c]Dostarlimab was approved for deficient mismatch repair advanced solid tumors in August 2021, after this case was completed (January 8, 2021).

[γ]Next-generation sequencing (NGS) methods: for whole exome sequencing, direct sequence analysis was performed on genomic DNA isolated from a microdissected, formalin-fixed paraffin-embedded tumor sample using the Illumina platform. NGS was used to determine tumor mutational burden (TMB), microsatellite instability (MSI), gene fusion and whole transcriptome sequencing methods: gene fusion and variant transcript detection were performed on mRNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Agilent SureSelectXT Low Input Library prep chemistry, optimized for FFPE tissue, in conjunction with the SureSelect Human All Exon V7 bait panel (48.2 Mb) and the Illumina NovaSeq; IHC Methods: laboratory-developed tests (LDT) immunohistochemistry (IHC) assays (developed and their performance characteristics determined by Caris Life Sciences) were used. Interpretations of all immunohistochemistry (IHC) assays were performed manually by a board certified pathologist using a microscope and/or digital whole slide image(s).

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remission. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534475).

Discussion

We present the management of a previously resected patient with melanoma who progressed on standard of care anti-PD-1 and CTLA-4 inhibitors. The case report demonstrates the role of molecular profiling in detecting oncogenic biomarkers and details the detection of a previously unreported *ANXA2-NTRK3* gene fusion. It also shows the clinical benefit of this approach in halting disease progression and achieving lesion improvement in a refractory malignancy.

As previously mentioned, the use of immune checkpoint inhibitors targeting PD-1 and CTLA-4 and targeted therapies have led to dramatic improvements in survival in patients with metastatic melanoma [3, 4]. Both PD-1 inhibitors nivolumab and pembrolizumab were shown to lead to sustained 5-year overall survival in patients with advanced melanoma [5, 6]. Patients progressing on anti-PD-1 therapy can still benefit from the addition of another immune checkpoint inhibitor (i.e., ipilimumab) or from retreatment/treatment continuation with PD-1 inhibition [13]. Taking the above-mentioned evidence into consideration and based on its promising risk-benefit profile [14], adjuvant nivolumab was used for the management of the presented case, with the addition of ipilimumab upon rapid disease progression. However, tissue-based molecular profiling was requested as treatment failure was evident, and targeted therapy was considered as a next possible option.

It is increasingly recognized that comprehensive molecular profiling can increase survival among cancer patients through the detection of actionable biomarkers and the expansion of treatment options [11, 12]. In the context of metastatic melanoma, characterization of protein, mRNA, and gene expression can inform on disease prognosis and response to targeted therapy against cancer-driving mutations [15–17]. Common mutations found in melanoma include the *BRAF*, *NRAS*, and *TERT* genes and have all been linked to worse prognosis [18–20]. Regardless of the efficacy and survival advantage afforded by targeted therapy in melanoma [21, 22], BRAF and MEK inhibitors would not have been of benefit in the presented case seeing as no BRAF mutation or other common mutation was found. Gene expression analysis and comprehensive genomic profiling allow the detection of rare mutations such as *RAF1* and *NTRK* gene fusions. Fusions in *NTRK1*, *NTRK2*, and *NTRK3* are generally rare in cancer and observed in 0.31% of adult tumors [23]. When specifically considering most types of melanoma, *NTRK* gene fusions are even more infrequent, occurring in less than 1% of cutaneous or mucosal cases [23]. To note that the frequency of *NTRK* fusions rises considerably in spitzoid melanoma, reaching a prevalence of 21–29%, as well as possibly in cases with low mutation load [24]. While low tumor mutational burden was evident in the presented case, no spitzoid melanoma components were detected in the patient's tissue. That being said, low tumor mutational burden might be indicative of an increased probability of having *NTRK*-positive tumors, although data on melanoma are limited in this regard [23, 24]. The mutual exclusivity of some oncogenic driver genes such as RAS/BRAF alterations and *NTRK* fusions has also been detected and shown to be significant in breast cancer, colorectal cancer, non-small cell lung cancer, with a trend toward mutual exclusivity in melanoma [25]. A study of 751 melanoma cases found *NTRK* fusions in only 4 patients, all of whom had metastatic disease. The researchers detected an *NTRK2-TRAF2* fusion and three *NTRK1* fusions with distinct partners (*TRIM63*, *DDR2*, and *GON4L*) [26]. An *AKAP13-NTRK3* was also described in one case report, leading to the expansion of treatment options for a patient with recurrent melanoma [27].

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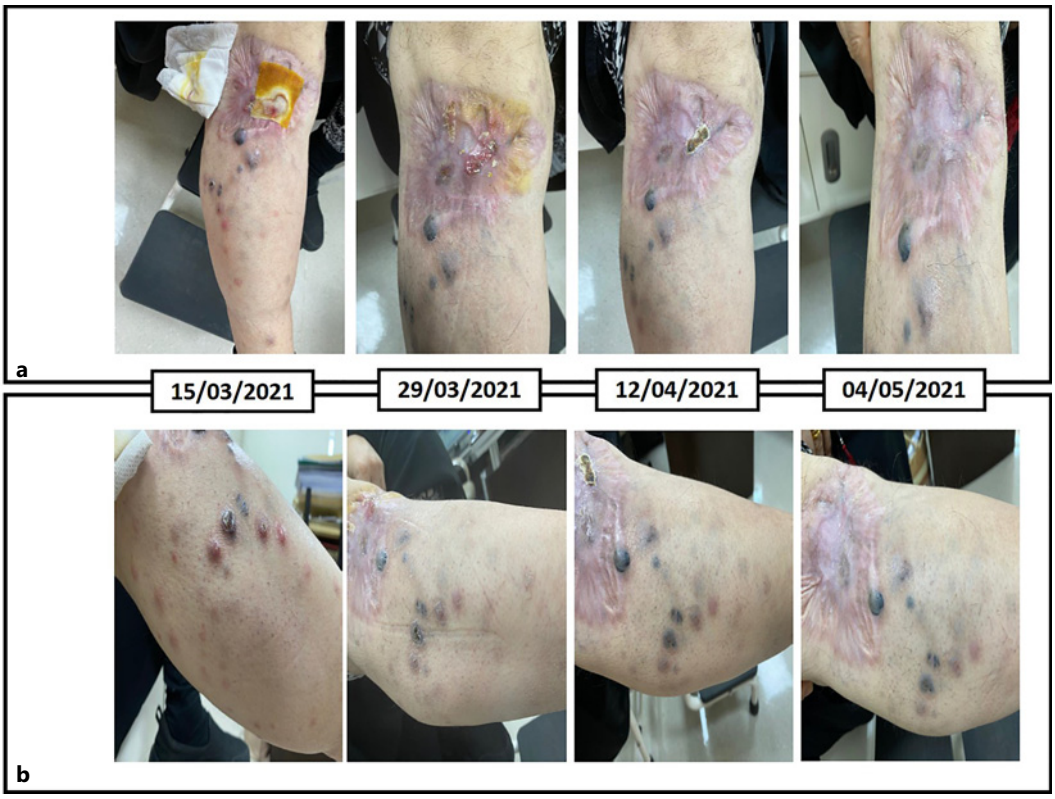

Fig. 1. a, **b** Lesions on the leg before (March 15, 2021) and after starting entrectinib (at different time points; 29 March, 12 April and May 04, 2021). There was a clear improvement in regression of the lesions over time after entrectinib was initiated.

The role of comprehensive genomic profiling thus continues to rise in melanoma, as it improves tumor classification in addition to guiding therapy choices [28–30]. This was reflected in the present case report, where molecular profiling allowed the detection of a novel *ANXA2-NTRK3* fusion. To the best of our knowledge, this specific fusion has not been previously reported; however, it is in-frame and similar to other known oncogenic *NTRK* fusions. In over 4,000 whole transcriptome sequencing-tested melanoma cases in Caris Life Sciences (Phoenix, AZ, USA), only 2 *NTRK1* and 5 *NTRK3* fusions have been found. No *NTRK2* fusions have been detected to date. The *ANXA2-NTRK3* fusion described in this case report seems to be the only case of a *NTRK3* fusion with this partner in the Caris Life Sciences database, and no other reports of this fusion could be found in the published literature to the best of our ability. It therefore seems that *ANXA2* is not a common fusion partner with *NTRK3*. Moreover, we could not find evidence of any recurrent fusion partners with *ANXA2*. *NTRK* fusion partners usually contribute a dimerization domain [31]. It is plausible that the annexin repeats retained in the fusion drive localization of the fusion protein to the plasma membrane [32] and promote dimerization to activate the kinase domain of NTRK.

The detection of the *NTRK3* fusion prompted the use of entrectinib in our patient. Data on therapy outcomes in *NTRK* fusion-positive melanoma is as limited as the occurrence of this fusion. Entrectinib is an oral small molecular inhibitor of several receptors, namely, NTRKs (TRKA, TRKB, TRKC), proto-oncogene tyrosine-protein kinase ROS1 and anaplastic lymphoma kinase (ALK). Based on evidence from phase 1 trials, entrectinib was shown to be tolerable and effective against solid tumors harboring *NTRK1/2/3,* in addition to *ROS1*, and *ALK* gene fusions [33]. Another integrated analysis of phase 1 or 2 clinical trials on entrectinib

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supported its safety and tolerability as well as its ability to induce significant durable responses in patients with *NTRK* fusion-positive advanced or metastatic tumors [34]. Based on this, entrectinib was indicated for the treatment of adult or pediatric patients with solid tumors who have neurotrophic tyrosine receptor kinase gene fusions and adult patients with non-small-cell lung cancer harboring *ROS1* rearrangements [35]. It is important to consider that entrectinib could potentially lead to cardiovascular events (consistent with concerns of cardiotoxicity of tyrosine kinase inhibitors in general), although real-world data on this remain rather limited [33, 34, 36, 37]. Entrectinib use has been reported across several tumor types, predominately non-small-cell lung cancer, sarcoma, mammary analog secretory carcinoma (salivary), and breast tumors. Less frequent tumor types included thyroid cancer, colorectal cancer, neuroendocrine cancer, pancreatic cancer, gynecological cancer, ovarian cancer, endometrial cancer, and renal cell carcinoma [33, 34]. That being said, of the 25 patients who received entrectinib in one study, only 1 case of melanoma was included, with the molecular alteration affecting the *ROS1* gene [33].

The present case report thus contributes to the limited body of evidence on the use of entrectinib in *NTRK* fusion-positive metastatic melanoma. It describes the successful use of the drug in halting disease progression and the improvement of existing lesions after failure of standard of care. Response to entrectinib was sustained for approximately 2.5 years of therapy, and the patient continued to be well and in remission.

In conclusion, clinical experience illustrates how molecular profiling can practically expand treatment options for patients with advanced tumors that are refractory to standard of care. By detecting oncogenic biomarkers, molecular profiling offers guidance for the use of targeted therapies to halt disease progression and achieve lesion improvement in a refractory malignancy. The presented case highlights the need to test broadly in clinical practice considering that they can impact prognosis when standard of care fails. Although rare, novel markers can change the natural history of disease when detected.

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Statement of Ethics

Ethical approval is not required for this study in accordance with local and national guidelines in the UAE since this is a case report, and written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

S.D. declares having had consultancies from Newbridge Pharmaceuticals, Caris Life Sciences, Jaansen, BMS, Lilly, MSD, AZ, Pfizer, Novartis, and Ipsen; clinical studies from AZ; and research grants from MSD, AMGEN. Z.A. has no conflicts of interest to declare.

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Author Contributions

S.D. participated in the conception of the manuscript, data generation/follow-up, as well as writing, editing and approval of the final manuscript. Z.A. participated in data generation, writing, editing and approval of the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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