

Sustained Response to the Mitogen-Activated Extracellular Kinase Inhibitor Trametinib in a Spindle Cell Sarcoma Harboring a QKI-RAF1 Gene Fusion

François Panet, MD, MSc¹; Sungmi Jung, MD¹; and Thierry Alcindor, MD, MSc¹

JCO Precis Oncol 6:e2100303. © 2022 by American Society of Clinical Oncology

Introduction

The advent of molecular pathology tools such as next-generation sequencing (NGS) has helped refine the classification of sarcomas and may help find new therapeutic targets.¹ Recently, a new group of soft-tissue sarcomas was described as harboring a distinct immunohistochemistry profile of S100 and CD34 coexpression and recurrent gene fusions involving *RAF1*, *BRAF*, or *NTRK1/2*.² In this paper, we report a case of recently described spindle cell tumor displaying a *QKI-RAF1* gene fusion resistant to standard cytotoxic chemotherapy. The use of the mitogen-activated extracellular kinase (MEK) 1 and 2 inhibitor trametinib yielded clinical benefit and an absence of progression for 10 months.

Case Presentation

The patient, a 27-year-old woman without significant medical history, sought medical attention in May 2019 in a hospital outside Canada for a spinal cord compression syndrome with severe pain and paraparesis. A laminectomy encompassing T12-L3 vertebrae was performed with an initial improvement in symptoms. She presented again 1 month later in June with cauda equina syndrome with recurrent severe pain and sphincter dysfunction. The magnetic resonance imaging (MRI) showed conus medullaris compression by a dural lesion and she underwent a second T12-L3 laminectomy. The pathology reports from surgery showed intradural high-grade round to spindle cell sarcoma suggestive of Ewing sarcoma.

At that point, the patient transferred her care to the McGill University Health Centre (MUHC) located in Montreal, Canada. A fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) performed in July 2019 showed a metabolically active spinal lesion at the L3-L4 level without distant metastases. In the spine MRI, the presence of an extensive intradural and extramedullary mass occupying the spinal canal completely from T12-L4 and encasing the conus medullaris was noted. Given her initial diagnosis of Ewing sarcoma, while transfer of her

tumor blocks and pathologic review of the case were pending, she was treated with eight cycles of alternating vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide plus definitive radiation therapy to the thoracic and lumbar spine. She completed this treatment in February 2020. The patient improved neurologically with a decrease in pain and the ability to walk with a walker. An FDG PET-CT done in March 2020 showed no residual metabolically active lesion, although the mass had remained stable in size. The decision to stop chemotherapy was because of the progressively worsening hematologic toxicity of the regimen and rising uncertainty about the accurateness of the diagnosis of Ewing sarcoma, given the lack of radiologic response.

At the same time, the tumor specimens were reviewed at the MUHC and another institution. Given the absence of *EWSR1* and *SS18* gene rearrangement, the diagnoses of Ewing sarcoma and synovial sarcoma, respectively, were ruled out. On Archer NGS performed in an outside institution, a *QKI-RAF1* gene fusion was identified, and a diagnosis of the newly described spindle cell tumor defined by S100 and CD34 coexpression with recurrent gene fusion was made.

The patient re-presented in April 2020, < 3 months after the end of her treatment, with recurrent cauda equina. The FDG PET-CT and MRI showed a hypermetabolic intradural relapse at T11-L1 causing conus medullaris compression. The patient was treated with temozolomide-irinotecan as second-line chemotherapy. This treatment was poorly tolerated, and the tumor size increased on MRI after one cycle.

In June 2020, after informed consent for participation to a special-access program, the patient was prescribed single-agent trametinib, a highly selective MEK1/2 reversible antagonist. This treatment was chosen to block the oncogenic effect of the *RAF1* gene fusion. After the start of trametinib, her pain was significantly lower. Furthermore, there was a sustained complete metabolic response on FDG PET-CT.

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 22, 2021 and published at ascopubs.org/journal/po on January 20, 2022; DOI <https://doi.org/10.1200/P0.21.00303>

Creative Commons Attribution Non-Commercial No Derivatives 4.0 License



Throughout her illness, the patient had multiple antibiotic courses for recurrent urosepsis secondary to compression of the urinary tract by tumor. She ultimately died of septic shock from multidrug-resistant bacteria in May 2021. No relapse from her sarcoma was observed during the 10 months of trametinib treatment.

Consent for Publication

During her illness, the patient provided verbal consent to publication of this case report.

Discussion

Using NGS, *RAF1* gene fusion was recently described in eight soft-tissue sarcomas with various fusion partners including *PDZRN3*, *SLMAP*, and *TMF1*.³ The tumors were found in different organs and usually displayed low-grade features. Only one of the four cases for which follow-up is available developed distant metastases. Our case is the first *RAF1* gene fusion sarcoma to be intradural and fused with *QKI*. Additionally, it was high grade and behaved aggressively, relapsing quickly after definitive chemotherapy and radiation therapy, but did not metastasize. Importantly, it is the first sarcoma case where an *RAF1* gene fusion was successfully targeted by an MEK1/2 inhibitor, resulting in a prolonged clinical benefit and metabolic response on imaging. Successful targeting of *RAF1* gene fusions by MEK1/2 inhibitors has been described in melanoma and anaplastic pleomorphic xanthoastrocytoma.⁴ *RAF1* indeed promotes tumor growth through its interaction with MEK1/2 and the activation of the mitogen-activated protein kinase (MAPK) pathway.

RAF1 is a recently identified oncogene. *RAF1* is part of the *BRAF* gene family and codes for the C-RAF protein. Like *BRAF*, *RAF1* activates the MAPK pathway via its interaction with the MEK 1 and 2 to promote tumor growth and invasion.⁵ Point mutations of *RAF1* in tumor are rarer than *BRAF* because of its lower basal activity.⁶ Nevertheless, multiple oncogenic gene fusions involving *RAF1* have recently been described in melanoma, acinar pancreatic

carcinoma, brain tumors, and sarcoma.⁷⁻⁹ Thus, unlike *BRAF* where somatic mutations are frequent oncogenic drivers, gene rearrangement is thought to be the main event leading to the transformation of *RAF1* into an oncogene. Moreover, identification of *RAF1* rearrangement is essential because there is reported response to MEK inhibitors. For example, patients with melanoma characterized by wild-type *BRAF* but harboring an *RAF1* gene fusion responded to trametinib and cobimetinib.¹⁰⁻¹³ There is also a report of an anaplastic pleomorphic xanthoastrocytoma harboring an *ATG7-RAF1* gene fusion that responded to the MEK inhibitor cobimetinib.⁴

The fusion partner of *RAF1* in our case is *QKI*. The product of *QKI* is an RNA-binding protein implicated in glial development and myelination. Recently, it has been identified in oncogene fusions in pediatric brain tumors with *MYB* and *RAF1* genes.^{14,15} Furthermore, the *QKI-RAF1* fusion gene was shown to be a driver oncogene in cell lines by activating the MAPK and phosphoinositide-3 kinase/mammalian target of rapamycin (PI3K/mTOR) pathways.¹⁵ The use of MEK1/2 reversible antagonist trametinib slowed tumor proliferation. The addition of everolimus, an mTOR inhibitor, to trametinib suppresses tumor growth more effectively and could be considered in case of resistance to single-agent trametinib.¹⁴ In our patient, the use of single-agent trametinib was sufficient to halt cancer proliferation.

In conclusion, we describe here the first case of a *QKI-RAF1* gene fusion in a high-grade soft-tissue sarcoma of intradural location. With secondary resistance to conventional multiagent chemotherapy, the use of the MEK1/2 inhibitor trametinib induced a prolonged metabolic response and clinical benefit. Unfortunately, access to sequencing methods and targeted drugs can be challenging, particularly in rare tumors where good evidence is scarce. Our case illustrates the benefit of NGS in diagnosis accuracy and identification of a therapeutic target, resulting in effective treatment for our patient.

AFFILIATION

¹McGill University Health Centre, Montreal, QC, Canada

CORRESPONDING AUTHOR

Thierry Alcindor, MD, MSc, McGill University Health Centre, Montreal, QC, Canada; e-mail: thierry.alcindor@mcgill.ca.

AUTHOR CONTRIBUTIONS

Conception and design: Thierry Alcindor

Provision of study materials or patients: Sungmi Jung, Thierry Alcindor

Collection and assembly of data: Sungmi Jung, Thierry Alcindor

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](http://OpenPayments)).

Thierry Alcindor

Consulting or Advisory Role: Novartis Canada Pharmaceuticals Inc, Taiho Pharmaceutical, Pfizer/EMD Serono, Roche Canada, Merck, Bayer, BMS, AstraZeneca

Research Funding: Epizyme (Inst), EMD Serono (Inst), Karyopharm Therapeutics (Inst), SpringWorks Therapeutics (Inst), Astellas Pharma (Inst), Deciphera (Inst)

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

The authors thank Dr Cristina Antonescu from Memorial Sloan-Kettering Cancer Center for the molecular analysis that led to the accurate diagnosis of this case.

REFERENCES

1. Kallen ME, Hornick JL: The 2020 WHO classification: what's new in soft tissue tumor pathology? *Am J Surg Pathol* 45:e1-e23, 2021
2. Suurmeijer AJ, Dickson BC, Swanson D, et al: A novel group of spindle cell tumors defined by S100 and CD34 co-expression shows recurrent fusions involving RAF1, BRAF, and NTRK1/2 genes. *Genes Chromosomes Cancer* 57:611-621, 2018
3. Antonescu CR: Emerging soft tissue tumors with kinase fusions: An overview of the recent literature with an emphasis on diagnostic criteria. *Genes Chromosomes Cancer* 59:437-444, 2020
4. Touat M, Younan N, Euskirchen P, et al: Successful targeting of an ATG7-RAF1 gene fusion in anaplastic pleomorphic xanthoastrocytoma with leptomeningeal dissemination. *JCO Precis Oncol* 3:1-7, 2019
5. Zebisch A, Troppmair J: Back to the roots: The remarkable RAF oncogene story. *Cell Mol Life Sci* 63:1314-1330, 2006
6. Emuss V, Garnett M, Mason C, et al: Mutations of C-RAF are rare in human cancer because C-RAF has a low basal kinase activity compared with B-RAF. *Cancer Res* 65:9719-9726, 2005
7. Mok Y, Kimpo MS, Chen H, et al: Spindle cell tumour with S100 and CD 34 co-expression showing PDZRN 3-RAF 1 rearrangement—a recently described entity. *Histopathology* 74:1109-1111, 2019
8. Hicks JK, Henderson-Jackson E, Duggan J, et al: Identification of a novel MTAP-RAF1 fusion in a soft tissue sarcoma. *Diagn Pathol* 13:77, 2018
9. Jones D, Kocalkowski S, Liu L, et al: Oncogenic RAF1 rearrangement and a novel BRAF mutation as alternatives to KIAA1549: BRAF fusion in activating the MAPK pathway in pilocytic astrocytoma. *Oncogene* 28:2119-2123, 2009
10. Kim KB, Semrad T, Schrock AB, et al: Significant clinical response to a MEK inhibitor therapy in a patient with metastatic melanoma harboring an RAF1 fusion. *JCO Precis Oncol* 2:1-6, 2018
11. McEvoy CR, Xu H, Smith K, et al: Profound MEK inhibitor response in a cutaneous melanoma harboring a GOLGA4-RAF1 fusion. *J Clin Invest* 129:1940-1945, 2019
12. Williams EA, Shah N, Montesin M, et al: Melanomas with activating RAF1 fusions: Clinical, histopathologic, and molecular profiles. *Mod Pathol* 33:1466-1474, 2020
13. LeBlanc RE, Lefferts JA, Baker ML, et al: Novel LRRFIP2-RAF1 fusion identified in an acral melanoma: A review of the literature on melanocytic proliferations with RAF1 fusions and the potential therapeutic implications. *J Cutan Pathol* 47:1181-1186, 2020
14. Jain P, Fierst T, Han H, et al: CRAF gene fusions in pediatric low-grade gliomas define a distinct drug response based on dimerization profiles. *Oncogene* 36:6348-6358, 2017
15. Jain P, Resnick AC: MYB-QKI drives childhood brain tumors via tripartite mechanism. *Cell Cycle* 16:390, 2017

