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Sargen, M.R.; Kim, J.; Potjer, T.P.; Velthuizen, M.E.; Martir-Negron, A.E.; Odia, Y.; ... ; Goldstein, A.M.

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Estimated Prevalence, Tumor Spectrum, and Neurofibromatosis Type 1–Like Phenotype of *CDKN2A*-Related Melanoma-Astrocytoma Syndrome

Michael R. Sargen, MD; Jung Kim, PhD; Thomas P. Potjer, MD, PhD; Mary E. Velthuizen; Arelis E. Martir-Negron, MD; Yazmin Odia, MD; Hildur Helgadottir, MD, PhD; Jessica N. Hatton, MS, CGC; Jeremy S. Haley, MS; Gretchen Thone, MS, CGC; Brigitte C. Widemann, MD; Andrea M. Gross, MD; Marielle E. Yohe, MD, PhD; Rosandra N. Kaplan, MD; Jack F. Shern, MD; R. Taylor Sundby, MD; Esteban Astiazaran-Symonds, MD; Xiaohong R. Yang, PhD, MPH; David J. Carey, PhD; Margaret A. Tucker, MD; Douglas R. Stewart, MD; Alisa M. Goldstein, PhD

IMPORTANCE Knowledge about the prevalence and tumor types of *CDKN2A*-related melanoma-astrocytoma syndrome (MAS) is limited and could improve disease recognition.

OBJECTIVE To estimate the prevalence and describe the tumor types of MAS.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study analyzed all available MAS cases from medical centers in the US (2 sites) and Europe (2 sites) and from biomedical population genomic databases (UK Biobank [United Kingdom], Geisinger MyCode [US]) between January 1, 1976, and December 31, 2020. Patients with MAS with *CDKN2A* germline pathogenic variants and 1 or more neural tumors were included. Data were analyzed from June 1, 2022, to January 31, 2023.

MAIN OUTCOMES AND MEASURES Disease prevalence and tumor frequency.

RESULTS Prevalence of MAS ranged from 1 in 170 503 (n = 1 case; 95% CI, 1:30 098-1: 965 887) in Geisinger MyCode (n = 170 503; mean [SD] age, 58.9 [19.1] years; 60.6% women; 96.2% White) to 1 in 39 149 (n = 12 cases; 95% CI, 1:22 396-1:68 434) in UK Biobank (n = 469 789; mean [SD] age, 70.0 [8.0] years; 54.2% women; 94.8% White). Among UK Biobank patients with MAS (n = 12) identified using an unbiased genomic ascertainment approach, brain neoplasms (4 of 12, 33%; 1 glioblastoma, 1 gliosarcoma, 1 astrocytoma, 1 unspecified type) and schwannomas (3 of 12, 25%) were the most common malignant and benign neural tumors, while cutaneous melanoma (2 of 12, 17%) and head and neck squamous cell carcinoma (2 of 12, 17%) were the most common nonneural malignant neoplasms. In a separate case series of 14 patients with MAS from the US and Europe, brain neoplasms (4 of 14, 29%; 2 glioblastomas, 2 unspecified type) and malignant peripheral nerve sheath tumor (2 of 14, 14%) were the most common neural cancers, while cutaneous melanoma (4 of 14, 29%) and sarcomas (2 of 14, 14%; 1 liposarcoma, 1 unspecified type) were the most common nonneural cancers. Cutaneous neurofibromas (7 of 14, 50%) and schwannomas (2 of 14, 14%) were also common. In 1 US family, a father and son with MAS had clinical diagnoses of neurofibromatosis type 1 (NF1). Genetic testing of the son detected a pathogenic *CDKN2A* splicing variant (c.151-1G>C) and was negative for *NF1* genetic alterations. In UK Biobank, 2 in 150 (1.3%) individuals with clinical NF1 diagnoses had likely pathogenic variants in *CDKN2A*, including 1 individual with no detected variants in the *NF1* gene.

CONCLUSIONS AND RELEVANCE This cohort study estimates the prevalence and describes the tumors of MAS. Additional studies are needed in genetically diverse populations to further define population prevalence and disease phenotypes.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Michael R. Sargen, MD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Dr, Room 6E-542, Rockville, MD 20850 (michael.sargen@nih.gov).

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Pathogenic germline variants in *CDKN2A* predispose to cancer by disrupting cell cycle regulatory pathways p16/Rb and p14ARF/p53.[1] Disease-causing variants of *CDKN2A* increase risk for melanoma most significantly, and to a lesser degree, increase risk for pancreatic cancer, lung cancer, and head and neck squamous cell carcinoma.[2-5]

Melanoma-astrocytoma syndrome (MAS; OMIM 155755) is an uncommon phenotype featuring tumors of the central and peripheral nervous system in individuals who harbor germline pathogenic *CDKN2A* variants.[6,7] The spectrum of tumor risk in MAS is poorly understood, with fewer than 15 families with this syndrome described in the medical literature (eTable 1 in Supplement 1). In this cohort study, we estimate the prevalence and describe the tumor types of MAS to inform disease recognition and management strategies.

Key Points

Question What is the prevalence and tumor spectrum of *CDKN2A*-related melanoma-astrocytoma syndrome?

Findings In this cohort study of 640 292 individuals in 2 population genomic databases, melanoma-astrocytoma syndrome prevalence ranged from 1 in 170 503 to 1 in 39 149, and patients had a diverse spectrum of neural and nonneural tumors. Multiple patients had clinical diagnoses of neurofibromatosis type 1 without genetic alterations of the *NF1* gene.

Meaning This study estimates prevalence and describes the tumor types of melanoma-astrocytoma syndrome, although additional studies are needed in genetically diverse populations to further define population prevalence and the spectrum of skin and nonskin phenotypes.

Methods

Case Series

Investigators from the National Cancer Institute, Miami Cancer Institute, Karolinska University Hospital, and University Medical Center Utrecht provided for analysis deidentified clinical data for all available cases of MAS seen between January 1, 1976, and December 31, 2020. Patients with *CDKN2A* germline pathogenic variants identified through clinical or research genetic testing, or first-degree relatives of variant carriers, were classified as having MAS if they had 1 or more neural tumors (eTable 2 in Supplement 1). All neural and nonneural neoplasms in patients with MAS were identified using medical records (ie, pathology reports, physician notes) or tumor registry data. Patients from the National Cancer Institute, Sweden, and the Netherlands initially presented for genetic evaluation because they were part of families with 2 or more individuals with cutaneous melanoma. The proband of a Florida family presented to the Miami Cancer Institute for evaluation of neurofibromatosis type 1 (NF1) because of a personal history of multiple neural tumors.

Genomic-Based Ascertainment

The UK Biobank (United Kingdom) and Geisinger MyCode (Pennsylvania, US) are biomedical population genomic databases that link germline exome data with electronic health records.[8,9] We identified all study participants in both cohorts with *CDKN2A* variants that were predicted to be pathogenic or likely pathogenic by ClinVar or InterVar and that met American College of Medical Genetics and Genomics and Association for Molecular Pathology criteria for these classifications. We used *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes and histology codes to identify tumor diagnoses.

This investigation followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. This study was determined by study investigators and the Geisinger Institutional Review Board not to be human participants research based on 45 CFR 46 (Common Rule) since it involved the analysis of deidentified data. Additional information about each database, variant calling, and study approvals is available in the eMethods of Supplement 1. Data were analyzed using R, version 4.1.0 (R Foundation for Statistical Computing), and SAS Enterprise Guide, version 8.3.0.103 (SAS Institute).

Results

In Geisinger MyCode (170 503 individuals; mean [SD] age, 58.9 [19.1] years; 60.6% women; 2.2% Black; 96.2% White; 1.6% unknown or other race) and UK Biobank (469 789 individuals; mean [SD] age, 70.0 [8.0] years; 54.2% women; 3.7% Black; 94.8% White; 1.5% unknown or other race), MAS prevalence was 1 in 170 503 (n = 1 case; 95% CI, 1:30 098-1:965 887) and 1 in 39 149 (n = 12 cases; 95% CI, 1:22 396-1:68 434), respectively (**Table 1**). The prevalence of individuals with *CDKN2A* germline pathogenic variants was 2-fold higher in UK Biobank (295 individuals, 0.06%) compared with Geisinger (47 individuals, 0.03%).

Among UK Biobank patients with MAS (n = 12), brain neoplasms (4 of 12, 33%; 1 glioblastoma, 1 gliosarcoma, 1 astrocytoma, 1 unspecified brain tumor) and schwannomas (3 of 12, 25%) were the most common malignant and benign neural tumors, while cutaneous melanoma (2 of 12, 17%) and head and neck squamous cell carcinoma (2 of 12, 17%) were the most common nonneural malignant neoplasms (Table 1). Three (25%) patients with MAS developed 2 or more malignant tumors.

In a case series of 14 patients with MAS (9 [64%] men and 5 [36%] women) from 7 families, brain neoplasms (4 of 14, 29%; 2 glioblastomas, 2 unspecified brain tumors) and malignant peripheral nerve sheath tumor (2 of 14, 14%) were the most common neural malignant neoplasms, while cutaneous melanoma (4 of 14, 29%) and sarcomas (2 of 14, 14%; 1 liposarcoma, 1 unspecified sarcoma) were the most common nonneural cancers (**Table 2**). Six (43%) patients developed 2 or more malignant tumors, and 7 (50%) patients died from cancer, including 4 (29%) deaths attributable to brain neoplasms. Benign neural tumors were also common, including cutaneous neurofibromas (7 of 14, 50%) and schwannomas (2 of 14, 14%). Additionally, a pituitary adenoma was diagnosed in patient 4 (1

Table 1. Clinical Characteristics of Melanoma-Astrocytoma Syndrome (MAS) Cases in UK Biobank and Geisinger MyCode

Characteristic	Individuals, No. (%)	
	UK Biobank	Geisinger MyCode
Total	469 789 (100)	170 503 (100)
Female	254 626 (54.2)	103 365 (60.6)
Male	215 163 (45.8)	67 138 (39.4)
Current age, mean (SD), y	70.0 (8.0)	58.9 (19.1)
Median (IQR) age, y	71 (12.3)	60.9 (28.1)
Race and ethnicity[a]		
Black or African	17 188 (3.7)	3695 (2.2)
White	445 337 (94.8)	164 078 (96.2)
Unknown or other	7264 (1.5)	2730 (1.6)
Pathogenic or likely pathogenic variants in *CDKN2A*[b]	295 (0.06)	47 (0.03)
MAS[c]	12 (0.003)	1 (0.001)
Clinical phenotypes of individuals with MAS[d]	**n = 12 (100)**	**n = 1 (100)**
Clinical diagnosis of neurofibromatosis type 1	2 (17)[e]	0
Epilepsy	1 (8)	0
Cancers		
Basal cell carcinoma	1 (8)	0
Central nervous system	4 (33)	0
Glioblastoma	1 (8)	0
Gliosarcoma	1 (8)	0
Astrocytoma	1 (8)	0
Unspecified malignant brain tumor	1 (8)	0
Cutaneous melanoma	2 (17)	0
Head and neck squamous cell carcinoma	2 (17)	0
Lung adenocarcinoma	1 (8)	0
Testicular seminoma	1 (8)	0
Benign neural tumors		
Benign neoplasm of peripheral nerves and autonomic nervous system	1 (8)	0
Benign tumor of cranial nerves	1 (8)	0
Benign tumor of pituitary gland	1 (8)	1 (100)
Benign tumor of spinal meninges	1 (8)	0
Meningioma	1 (8)[f]	1 (100)
Schwannoma	3 (25)	0

[a] Geisinger patients self-reported race and ethnicity. The unknown category for Geisinger includes individuals from the following groups: Other (n = 771 Asian or Asian Pacific Islander; n = 322 Native Hawaiian or Other Pacific Islander; n = 300 American Indian or Alaska Native), Patient Declined to Provide, Unable to Obtain, Missing, and Two or More. UK Biobank data field 1717 ("skin color") was used to group individuals as White (includes codes for very fair, fair, light olive, and dark olive skin), Black or African (includes codes for Brown and Black skin), or unknown.

[b] All variants were filtered for genotype quality greater than 30 and ABHet greater than 0.2 and less than 0.8. Variants were classified as pathogenic if they were predicted to be likely pathogenic or pathogenic in ClinVar (version August 16, 2022) or InterVar and met American College of Medical Genetics and Genomics and Association for Molecular Pathology criteria for these classifications.

[c] Individuals were classified as having MAS if they had a pathogenic or likely pathogenic variant in *CDKN2A* plus a benign or malignant tumor of the central or peripheral nervous system. One UK Biobank study participant with diagnosis code C71.9 (Brain, unspecified) had metastatic cancer (C78.0 Secondary malignant neoplasm of lung), and this individual was excluded from the analysis since the possibility of a brain metastasis being miscoded as a primary cancer could not be ruled out.

[d] The percentage of patients with MAS (12 in UK Biobank and 1 in Geisinger MyCode) with each clinical phenotype is reported in parentheses.

[e] These unrelated patients had a diagnosis code for neurofibromatosis (Q85.0) and the same likely pathogenic variant in *CDKN2A* (NM_058195.4:c.97dup; NP_478102.2:p.Glu33fs; ClinVar ID 571028). One individual was detected to have a germline *NF1* pathogenic variant (NM_001042492.3:c.4084C>T; NP_001035957.1:p.Arg1362*; ClinVar ID 344). Germline pathogenic variants and copy number alterations of *NF1* were not detected in the second individual with neurofibromatosis, who also had a diagnosis of epilepsy (G40.9 Epilepsy, unspecified).

[f] Psammomatous meningioma.

of 14, 7%), and this same rare tumor was also diagnosed in 1 patient with MAS in Geisinger and 1 patient with MAS in UK Biobank (Tables 1 and 2). Thirteen (93%) patients had *CDKN2A* variants that altered p14ARF (Table 2).

Patient 1 (≥6 café au lait macules, bilateral neurofibromas) and his son, patient 2 (parent with NF1, >2 neurofibromas), both had clinical diagnoses of NF1. Patient 2 also had a malignant peripheral nerve sheath tumor, an established NF1-associated malignant neoplasm (Table 2).[10] Genetic testing of patient 2 was negative for *NF1* variants and copy number alterations but revealed a pathogenic variant in *CDKN2A* predicted to alter splicing of p16 (c.151-1G>C) and p14ARF

Table 2. Clinical Characteristics of Melanoma-Astrocytoma Syndrome in Case Series

Patient/sex	Cancer diagnoses (age range, y)[a]	Benign tumor diagnoses (age range, y)[a]	Clinical diagnosis of NF1[b]	NF1-related manifestations[b]	Vital status[c]	Cause of death[c]	Age range at death, y[c]	Identified *CDKN2A* variants (ClinVar ID)	Transcripts altered	Additional genetic testing information
US										
Family 1										
1/Male	Malignant peripheral nerve sheath tumor (30-39); pancreas (50-59)	Multiple neurofibromas involving the axilla bilaterally, shoulders, neck, and back (starting at 30-39)	Yes	>6 Café au lait macules in bilateral distribution, widespread cutaneous neurofibromas	Dead	Pancreatic cancer	50-59	c.151-1G>C (182416)[d]	p16, p14ARF	Genetic testing was negative for germline pathogenic variants or copy number alterations of *NF1* in patient 2, who had a clinical diagnosis of NF1
2/Male	Cutaneous melanoma (30-39); malignant peripheral nerve sheath tumor (40-49); lung cancer (60-69)	Multiple neurofibromas including right supra-adrenal (40-49), left inner thigh (40-49), right rib (60-69), and right intercostal chest (60-69)	Yes	Parent (patient 1) with clinical diagnosis of NF1, >2 neurofibromas	Dead	Lung cancer	60-69			
Family 2[e]										
3/Female	Glioblastoma (60-69)	None	No	None	Dead	Glioblastoma	60-69	c.212A>G; p.Asn71Ser (418121)[d]	p16	None
Family 3										
4/Male	Liposarcoma (40-49); cutaneous melanoma (40-49)	Left psoas muscle neurofibroma (40-49); neurofibromas of C-spine, T-spine, chest, retroperitoneum, and pelvis; schwannomas; pituitary adenoma; pancreatic cyst	No	>2 Neurofibromas	Alive	NA	NA	5′UTR-3′UTR pathogenic deletion of *CDKN2A*	p16, p14ARF	Multigene panel testing was negative for germline pathogenic variants of *NF1* and *NF2* in patient 4
5/Female	Cutaneous melanoma (20-29, 30-39)	Neurofibromas of left lower quadrant of abdomen (20-29) and left posterior axilla (20-29)	No	>2 Neurofibromas	Alive	NA	NA			
Netherlands										
Family 1										
6/Female	None	Neurofibromas of vertebra C1 and C2 (20-29) and sacrum (30-39)	No	>2 Neurofibromas	Alive	NA	NA	c.193 + 1G>A (406708)[f]	p14ARF	Genetic testing was negative for germline pathogenic variants of *NF1* and *NF2* in patient 6
7/Male	None	Neurofibromas of brachial plexus (50-59), and multiple additional cutaneous neurofibromas diagnosed thereafter	No	>2 Neurofibromas	Alive	NA	NA			
8/Male[g]	None	Neurofibroma (20-29)	No	None	Alive	NA	NA			
9/Female[g]	Brain tumor (10-19)	None	No	None	Dead	Brain tumor, unspecified	10-19			

(continued)

Table 2. Clinical Characteristics of Melanoma-Astrocytoma Syndrome in Case Series (continued)

Patient/sex	Cancer diagnoses (age range, y)[a]	Benign tumor diagnoses (age range, y)[a]	Clinical diagnosis of NF1[b]	NF1-related manifestations[b]	Vital status[c]	Cause of death[c]	Age range at death, y[c]	Identified *CDKN2A* variants (ClinVar ID)	Transcripts altered	Additional genetic testing information
Family 2										
10/Male	None	Neurofibroma of tibial nerve (20-29)	No	None	Alive	NA	NA	c.193 + 1G>A (406708)[f]	p14ARF	None
11/Male	Cutaneous melanoma (30-39, 30-39); sarcoma not otherwise specified in the sacrum (40-49)	Schwannoma (30-39)	No	None	Dead	Sarcoma not otherwise specified	40-49			
Family 3										
12/Male	None	Neurofibromas of left and right ischiadic nerves (40-49)	No	>2 Neurofibromas	Alive	NA	NA	c.193G>C; p.Gly65Arg (1504229)[f]	p14ARF	None
13/Female[g]	Brain tumor (30-39)	None	No	None	Dead	Brain tumor, unspecified	30-39			
Sweden										
Family 1										
14/Male	Glioblastoma (30-39); leukemia (30-39)	None	No	None	Dead	Glioblastoma	30-39	c.335_337dup; p.Arg112dup (183759)[d]	p16, p14ARF	None

Abbreviations: NA, not applicable; NF1, neurofibromatosis type 1.

[a] Information was obtained from medical records (US, Netherlands) and the Swedish Cancer Registry. The age range for each tumor diagnosis was provided if known.

[b] Diagnoses were based on revised diagnostic criteria for NF1.[10]

[c] Death information was obtained from medical records (US, Netherlands) and the Swedish Cause of Death Registry.

[d] Variant annotation to cDNA used transcript NM_000077.5 (*CDKN2A*/p16).

[e] Family 2 was previously reported as family E in a prior publication.[5]

[f] Variant annotation to cDNA used transcript NM_058195.4 (*CDKN2A*/p14ARF).

[g] First-degree relative of family member with pathogenic germline *CDKN2A* variant.

(c.194 – 1G>C) (Table 2). Germline material for *NF1* testing was not available for patient 1.

In UK Biobank, 2 in 150 (1.3%) unrelated individuals with NF1 *ICD-10* code Q85 had a likely pathogenic variant in *CDKN2A* (NM_058195.4:c.97dup; NP_478102.2:p.Glu33fs). One individual with this *CDKN2A* variant also had a pathogenic variant in *NF1* (NM_001042492.3:c.4084C>T; NP_001035957.1:p.Arg1362*), while the second individual had no detected variants in the *NF1* or *SPRED1* genes. The *CDKN2A* variant (p.Glu33fs) identified in individuals with NF1 was detected in 84 UK Biobank study participants, including 2 (2.4%) individuals without NF1 with malignant brain tumors (1 gliosarcoma, 1 astrocytoma) (eTable 3 in Supplement 1). There were 208 individuals in Geisinger with NF1, and none harbored *CDKN2A* disease-causing variants.

Discussion

The prevalence of MAS ranged from 1 in 170 503 (95% CI, 1:30 098-1:965 887) in Geisinger to 1 in 39 149 (95% CI, 1:22 396-1:68 434) in UK Biobank. The Geisinger database had a lower prevalence of individuals with *CDKN2A* germline pathogenic variants and does not capture cancer diagnoses outside of the health system, which may partly explain the lower prevalence of MAS compared with UK Biobank. Affected individuals developed a diverse spectrum of malignant and benign tumors in neural (ie, brain neoplasms, neurofibromas, schwannomas, pituitary adenomas) and nonneural (ie, cutaneous melanoma, head and neck squamous cell carcinoma, sarcomas) tissue.

Interestingly, an NF1-like phenotype (NF1 clinical diagnosis in the absence of *NF1* genetic alterations), which has been reported in 3% of familial and 5% of sporadic NF1 clinical diagnoses, was observed in multiple patients with MAS.[11] This association between MAS and an NF1-like phenotype is further strengthened by our unbiased genomic ascertainment approach. The 2 patients in UK Biobank with clinical NF1 and germline *CDKN2A* alteration were unrelated and harbored the same likely pathogenic variant in *CDKN2A* (p.Glu33fs), which alters p14ARF. Although this variant has conflicting interpretations of pathogenicity in ClinVar (ID: 571028), *CDKN2A* variants altering p14ARF have previously been associated with neural tumors in melanoma-prone families.[3,6] Additionally, 2 of 84 (2.4%) individuals in UK Biobank with the *CDKN2A* variant p.Glu33fs had rare malignant brain tumors, further supporting a role for this specific variant in neural tumor development.

Disease-causing variants of *CDKN2A* are critical for the development of central and peripheral nervous system tumors, which likely explains the MAS phenotype.[12-14] These variants disrupt cell cycle regulatory pathways p16/Rb and p14ARF/p53 that protect cells from dividing until DNA damage has been repaired.[15] Dysregulation of these pathways may predispose to the acquisition of variants in Ras/MAPK pathway genes such as *NF1*, which are associated with the development of café au lait macules, although further studies are needed to investigate whether *NF1* mosaicism is contributing to skin findings in patients with MAS. Our data also suggest that p14ARF alteration might be important for neural tumor development, a hypothesis that needs to be confirmed.

Limitations

Estimates of disease prevalence may not extend beyond the populations studied. Additionally, the possibility of misinterpretation of skin findings leading to NF1 clinical diagnoses cannot be entirely excluded in the absence of clinical images.

Conclusions

This cohort study estimates the prevalence of MAS in 2 large biomedical population genomic databases. Clinicians should be aware of the diverse spectrum of neural and nonneural tumors in this condition and consider *CDKN2A* testing in patients with an NF1-like phenotype who do not harbor germline pathogenic variants or copy number alterations of the *NF1* gene. Additional studies are needed in genetically diverse populations to further define disease prevalence and phenotypes.

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Author Affiliations: Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, Maryland (Sargen, Kim, Hatton, Yang, Tucker, Stewart, Goldstein); Department of Clinical Genetics, Leiden University Medical Center, Leiden, the Netherlands (Potjer); Division Laboratories, Pharmacy and Biomedical Genetics, Department of Genetics, University Medical Center Utrecht, Utrecht, the Netherlands (Velthuizen); Miami Cancer Institute, Baptist Health South Florida, Miami (Martir-Negron, Odia); Department of Oncology and Pathology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden (Helgadottir); Department of Genomic Health, Geisinger Clinic, Geisinger Health System, Danville, Pennsylvania (Haley, Thone, Carey); Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland (Widemann, Gross, Yohe, Kaplan, Shern, Sundby); Laboratory of Cell and Developmental Signaling, Center for Cancer Research, Frederick, Maryland (Yohe); Department of Medicine, University of Arizona College of Medicine, Tucson (Astiazaran-Symonds).

Author Contributions: Drs Sargen and Goldstein had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Co–senior authors: Drs Sargen and Goldstein.
Concept and design: Sargen, Velthuizen, Helgadottir, Tucker, Stewart, Goldstein.
Acquisition, analysis, or interpretation of data: Sargen, Kim, Potjer, Martir-Negron, Odia, Helgadottir, Hatton, Haley, Thone, Widemann, Gross, Yohe, Kaplan, Shern, Sundby, Astiazaran-Symonds, Yang, Carey, Tucker, Stewart, Goldstein.
Drafting of the manuscript: Sargen, Kim, Haley, Stewart.
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