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ORIGINAL ARTICLE

Southwest Oncology Group S0826: A phase 2 trial of SCH 727965 (NSC 727135, dinaciclib) in patients with stage IV melanoma

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Abstract

Background: Cell cycle inhibition is an established therapeutic approach for some cancers. A multicenter, single-arm, phase 2 trial (ClinicalTrials.gov identifier NCT00937937) of the cyclin-dependent kinase inhibitor SCH 727965 (NSC 747135; dinaciclib) was conducted in patients with metastatic melanoma to determine its clinical activity.

Methods: Patients with metastatic melanoma of cutaneous or mucosal origin were eligible if they had zero to one previous treatments, a Zubrod performance status of 0–1, and adequate organ function. SCH 727965 50 mg/m^2 was given intravenously

every 3 weeks until progression. Co-primary end points were 1-year overall survival (OS) and 6-month progression-free survival (PFS).

Results: Seventy-two patients were enrolled from July 1, 2009, to November 1, 2010, at 24 institutions. Sixty-eight percent of patients had M1c disease, and 43% had elevated lactate dehydrogenase levels. Twenty-eight patients (39%) experienced grade 4 adverse events, including 20 cases of neutropenia. Sixty-seven patients were evaluable for response. There was a response in zero of 67 patients (95% confidence interval [CI], 0%–5%), and stable disease was observed in 21%. The estimated median PFS was 1.4 months (95% CI, 1.4–1.5 months), and the 6-month PFS rate was 6% (2%–13%). The median OS was 8.2 months (95% CI, 5.5–10.5 months), and the 1-year OS rate was 38% (95% CI, 26%–49%).

Conclusions: This multicenter, US National Cancer Institute Cancer Therapy Evaluation Program-sponsored trial of SCH 727965 was conducted at a time when the current generation of effective therapies for melanoma were not available. Although the null hypothesis of 1-year OS was rejected, the minimal PFS impact and substantive toxicity indicated that this regimen lacks justification for further investigation as a single agent.

KEYWORDS
cyclin-dependent kinase (CDK), CDK inhibition, dinaciclib, melanoma

INTRODUCTION

The treatment landscape for metastatic melanoma has changed significantly since 2011. Specifically, four immune checkpoint inhibitors (ipilimumab, pembrolizumab, nivolumab, and relatlimab) and three BRAF plus MEK inhibitor combinations (dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib) have resulted in improvements in progression-free survival (PFS) and overall survival (OS) in trials conducted worldwide.[1] Novel treatments, however, are still needed to continue to improve outcomes for patients who either do not respond to or are not candidates for these treatments.

Cell cycle dysregulation is a hallmark of malignancy, including in melanoma. Cyclin-dependent kinases (CDKs) help govern the cell cycle by signaling cells to progress to the next stage of the cell cycle.[2] In melanoma, multiple CDKs are overexpressed, including CDK1, CDK2, and CDK5.[3] Loss-of-function variants in CDKN2A (a CDK inhibitor) and activating mutations of p16INK4A:CDK4 are associated with a 500-fold increase in melanoma risk.[4] CDK2 inhibitors (including flavopiridol/alvocidib, dinaciclib, and riviclib) have shown promising antitumor activity in pancreatic[5] and neuroblastoma[6] xenograft models and have demonstrated clinical activity in phase 1/2 trials for relapsed chronic lymphocytic leukemia[7] and multiple myeloma.[8]

Overexpression of CDK2 in melanoma and activity of CDK2 inhibitors against various tumors make these compounds promising therapeutic candidates. Dinaciclib (SCH 727965) is a CDK2 inhibitor with additional activity against CDK1, CDK5, and CDK9,[2,4] which has demonstrated activity in xenograft melanoma models.[9] A phase 1 trial of dinaciclib in melanoma was conducted but was terminated because of slow accrual.[10] At the time the current study was developed, there was little available to patients with advanced disease, thus a phase 2 trial of dinaciclib was completed.

MATERIALS AND METHODS

Patient eligibility

Patients with biopsy-proven, stage IV melanoma of cutaneous or mucosal origin or patients with unknown primary were eligible for this trial. Patients with ocular melanoma were excluded, as were patients with any history of brain metastases (treated or untreated). Eligible patients had received, at most, one prior systemic regimen for stage IV melanoma (chemotherapy, biologic/immunotherapy, hormonal therapy, or a combination regimen). Patients who had received any prior CDK inhibitor therapy were excluded.

Patients were not excluded for the receipt of prior adjuvant systemic therapies, including interferon α2b, granulocyte-macrophage colony–stimulation factor, chemotherapy, and biochemotherapy. Adjuvant therapies included treatments received after a patient was resected free of stage IV disease, before recurrence. Patients who had measurable and nonmeasurable disease were included because 1-year OS was the primary end point.

Enrolled patients had adequate hematologic function (absolute neutrophil count ≥1500/mcl, platelets ≥100,000/mcl, and

hemoglobin ≥ 9g/dl), hepatic function (serum bilirubin ≤1.5 times the institutional upper limit of normal [IULN] and aspartate and alanine transferase levels ≤2.5 times the IULN [or ≤5 times the IULN with hepatic metastasis), and renal function (serum creatinine ≤1.5 times the IULN), with a Zubrod performance status of 0–1.

Treatment

Patients received SCH 727965 50 mg/m^2 intravenously over 2 hours every 21 days (i.e., one cycle). Cycles were repeated until (1) progression of disease or symptomatic deterioration, (2) unacceptable toxicity, (3) treatment delay >3 weeks for any reason, or (4) patient withdrawal from the study for any reason.

All patients were monitored for infusion reactions, hypotension, nausea, and diarrhea. Blood pressure was monitored before and at the end of each infusion and at home at least weekly for the first 4 weeks of protocol treatment. Unless contraindicated, patients received a 5-HT3 antagonist before each infusion, with dexamethasone given at physician discretion.

Toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events. Dose modifications were made for grade 3–4 dermatologic and nonhematologic toxicities. For the first two occurrences of either neutropenia or thrombocytopenia grade 3 (>7 days) or grade 4, the study drug was held until resolution to grade ≤1 and was resumed at one lower dose level. The patient was removed from the study protocol for a third occurrence. Full dose was defined as 50 mg/m^2 intravenously: −1 level was 40 mg/m^2 intravenously, and −2 level was 30 mg/m^2 intravenously. No dose reductions were made for anemia. Transfusions and epoetin alfa were given at the discretion of the treating investigator, as were granulocyte colony-stimulation factor and granulocyte-macrophage colony–stimulation factor.

All patients provided written informed consent to participate in this study. The trial was conducted in accordance with the provisions of the Declaration of Helsinki and with Good Clinical Practice guidelines as defined by the International Conference on Harmonization. The study protocol, amendments, and patient consent forms were approved by the institutional review board or independent ethics committee at each study site before the start of the trial.

Statistical analysis

It was assumed that the regimen was not of further interest if the true 1-year OS rate was <25% and the 6-month PFS rate was <5%. Conversely, a true 1-year OS rate >40% was defined as indicating considerable interest. With 60 patients accrued over 1 year and an additional year of follow-up, an observed 1-year OS rate ≥34% would be considered evidence that the regimen warranted further study, assuming 6-month PFS and toxicity were also favorable.[11] With this design, the power of a one-sided 0.05 test was >80%. OS was defined as the duration from enrollment to death from any cause. Patients last known to be alive were censored at the date of last contact. PFS was defined as the duration from enrollment to progression, symptomatic deterioration, or death from any cause. Patients last known to be alive and progression free were censored at the date of last contact. OS and PFS estimates were calculated using the Kaplan–Meier method, and 95% confidence intervals (CIs) for the medians were constructed using the Brookmeyer–Crowley method. Response was evaluated in the subset of patients with measurable disease (as defined by Response Evaluation Criteria in Solid Tumors, version 1.1) at baseline. An exact 95% CI for the response rate was calculated using the Clopper–Pearson method. SAS software (version 9.4; SAS Institute Inc.) was used for all statistical analyses.

RESULTS

Patient characteristics

From July 1, 2009, to November 1, 2010, 72 patients were enrolled from 24 institutions. Patient characteristics are listed in Table 1.

The median patient age was 65.4 years, and 52 patients (72%) were male. Thirty-four patients (47%) had a Zubrod performance status of 1. Fifty-five patients (76%) had cutaneous primary tumors, and the remaining patients had mucosal (eight patients; 11%) and unknown (nine patients; 13%) tumors. The majority of patients had stage M1c (49 patients; 68%), followed by M1b (19 patients; 26%), and M1a (four patients; 6%) according to the American Joint Committee on Cancer 7th edition *AJCC Cancer Staging Manual*. The most common sites of metastatic disease were lung (41 patients; 57%); lymph node, skin, or soft tissue (41 patients; 57%); liver (23 patients; 32%); and bone (18 patients; 25%). Thirty-one patients (43%) had an elevated lactate dehydrogenase level at baseline.

Toxicity

Adverse events were assessed on all 72 patients and are summarized in Table 2. Treatment-related adverse events occurred in 65 patients (90%). The five most commonly reported adverse events, of any grade, were neutropenia (49 patients; 68%), nausea/vomiting (45 patients; 63%), diarrhea (43 patients; 60%), leukopenia (40 patients; 56%), and fatigue (39 patients; 54%). The number of patients who had grade 3–4 adverse events was 51 (71%). Grade 3–4 treatment-related adverse events that occurred in three or more patients were neutropenia (36 patients; 50%), leukopenia (18 patients; 25%), diarrhea (11 patients; 72%), lymphopenia (five patients; 7%), and fatigue (three patients; 4%). The 28 patients (39%) who had treatment-related grade 4 adverse events included 20 cases (28%) of neutropenia, two cases (3%) of leukopenia, and one case (1%) each of cardiac ischemia/infarction, dehydration, abdominal pain, whole-body

TABLE 1 Patient characteristics.

	SCH 727965, *n* = 72: No. (%)
Age: Median [range], years	65 [29–90]
Sex	
Men	52 (72.0)
Women	20 (28.0)
Race	
White	69 (96.0)
Asian	2 (3.0)
Pacific Islander	1 (1.0)
Zubrod performance status	
0	38 (53.0)
1	34 (47.0)
Type of primary	
Cutaneous	55 (76.0)
Mucosal	8 (11.0)
Unknown	9 (13.0)
Stage, AJCC 7th edition	
M1a	4 (6.0)
M1b	19 (26.0)
M1c	49 (68.0)
Site(s) of metastases	
Lymph node, skin, or soft tissue	41 (57.0)
Lung	41 (57.0)
Liver	23 (32.0)
Bone	18 (25.0)
Other visceral	17 (24.0)
Other nonvisceral	14 (19.0)
Elevated LDH	
No	41 (57.0)
Yes	31 (43.0)

Abbreviations: AJCC, American Joint Committee on Cancer; LDH, lactate dehydrogenase.

muscle weakness, headache, syncope, cardiac troponin elevation, and anterior ischemic optic neuropathy. Overall, the most common nonhematologic toxicities were diarrhea (43 patients), fatigue (39 patients), nausea (39 patients), and vomiting (27 patients). Six patients (8%) discontinued treatment because of adverse events. No treatment-related deaths occurred.

Because of safety concerns arising from the current trial and from clinical trials in other diseases with this agent, the trial was placed on temporary hold from February 2010 to June 2010, during which time the Cancer Therapy Evaluation Program reviewed all pertinent adverse data from all dinaciclib trials. It was determined that the cumulative available data did not change the risk–benefit profile for patients, and the trial proceeded to completion of accrual.

Response

Response was analyzed in the subset of patients who had measurable disease at baseline. In total, 67 patients with measurable disease were included in this analysis, including nine patients who could not have their exact response determined because of inadequate follow-up assessments and who were counted in the denominator as nonresponders. Stable disease was observed in 14 patients (21%). There were no responders, and the overall clinical activity is shown in Table 3. The estimated response rate was 0% (95% CI, 0%–5%).

The study was officially closed to follow-up on April 7, 2014. At that time, eight patients were still alive. The median follow-up among these patients was 32.5 months (range, 3.2–40.4 months). The estimated median PFS was 1.4 months (95% CI, 1.4–1.5 months), and the 6-month PFS estimate was 6% (95% CI, 2%–13%). The estimated median OS was 8.2 months (95% CI, 5.5–10.5 months), and the 1-year estimate was 38% (95% CI, 26%–49%). PFS and OS curves are shown in Figures 1 and 2, respectively. Seventeen patients (24%) patients received subsequent systemic therapies, and the most common treatments included chemotherapy (*n* = 7), ipilimumab (*n* = 5), vemurafenib (*n* = 2), and interleukin-2 (*n* = 2).

DISCUSSION

This multiinstitutional, Cancer Therapy Evaluation Program-sponsored trial of the CDK2 inhibitor dinaciclib, which was conducted at a time when no approved effective therapies existed, failed to demonstrate meaningful clinical activity. In 2008, at the time of trial development, an observed 1-year OS rate ≥40% was considered sufficient evidence that this agent would warrant further investigation, provided 6-month PFS, response, and toxicity were also favorable. The observed 1-year OS rate of 38% came close to this benchmark, but the 6-month PFS rate (6%) was not favorable, and grade 4 toxicities were prominent (39% of patients), thus lacking justification to further investigate dinaciclib as a single agent. It is plausible the higher than expected OS could be accounted for patients who subsequently went on to experimental studies that later received US Food and Drug Administration approval (i.e., ipilimumab, vemurafenib).

CDK inhibitors, may be classified based on their effects against the cell cycle CDKs as either pan-CDK inhibitors or more selective CDK inhibitors, with varying potency against the transcriptional

TABLE 2 Number of patients with adverse events, including the five most common adverse events of any grade and all grade 3/4 adverse events.[a]

	SCH 727965, *n* = 72					
AE	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any grade**	**%**
Neutropenia	5	8	16	20	49	68.0
Nausea/vomiting	25	19	1	0	45	63.0
Diarrhea	23	9	11	0	43	60.0
Leukopenia	6	16	16	2	40	56.0
Fatigue	26	10	3	0	39	54.0
Hypotension	7	8	2	0	17	24.0
Lymphopenia	5	2	5	0	12	17.0
AST increase	6	1	1	0	8	11.0
Mucositis	4	3	1	0	8	11.0
Abdominal pain	3	2	1	1	7	10.0
Hyponatremia	6	0	1	0	7	10.0
Musculoskeletal pain	3	2	2	0	7	10.0
Dehydration	1	4	0	1	6	8.0
Supraventricular arrhythmia	2	1	2	0	5	7.0
Dyspnea	1	2	1	0	4	6.0
Edema	2	1	1	0	4	6.0
Muscle weakness, whole body	2	0	1	1	4	6.0
Neuropathy	3	0	0	1	4	6.0
Blurred vision	1	1	1	0	3	4.0
Headache	2	0	0	1	3	4.0
Cardiac ischemia/infarction	0	0	1	1	2	3.0
Febrile neutropenia	0	0	2	0	2	3.0
Tumor pain	0	1	1	0	2	3.0
Hypoperfusion	0	0	1	0	1	1.0
Hypoxia	0	0	1	0	1	1.0
Elevated PTT	0	0	1	0	1	1.0
Prolonged QTc	0	0	1	0	1	1.0
Renal injury/failure	0	0	1	0	1	1.0
Somnolence	0	0	1	0	1	1.0
Syncope	0	0	0	1	1	1.0
Thromboembolism	0	0	1	0	1	1.0
Troponin elevation	0	0	0	1	1	1.0
Maximum grade any AE	5	9	23	28	65	90.0

Abbreviations: AE, adverse event; AST, aspartate aminotransferase; PTT, partial thromboplastin time.

[a]No treatment-related deaths (grade 5 AEs) were reported.

CDKs. The CDK inhibitors flavopiridol, seliciclib, and BMS-387032 (SNS-032) have been the most extensively tested in clinical trials. Clinical responses to CDK inhibitors as single-agent therapy, as well as apparent potentiation of cytotoxic chemotherapy, have been most apparent in chronic lymphocytic leukemia, acute leukemias, and mantle cell lymphoma.[12] In contrast to CDKs that govern the transitions between cell cycle phases, transcriptional CDKs, including cyclin H-CDK7, and cyclin T-CDK9, promote initiation and elongation

TABLE 3 Response rates for the study population.[a]

	SCH 727965	
	No.	%
Complete response	0	0.0
Partial response	0	0.0
Stable disease	14	21.0
Progressive disease	43	64.0
Assessment inadequate	9	13.0
Total	67	100.0

[a]Only patients with measurable disease are reported.

of nascent RNA transcripts by phosphorylating the carboxy-terminal domain of RNA polymerase II. Inhibiting these CDKs can alter the expression of pro-growth and anti-apoptotic proteins, such as D-cyclins, c-MYC, MDM2, MCL-1, p21WAF1/CIP1, NF-κB, and hypoxia-induced VEGF.[13]

Selective inhibition of CDK2 was thought to be of therapeutic value in a subset of patients with melanoma. In melanocytes, CDK2 undergoes transcriptional regulation by the melanocyte lineage transcription factor, microphthalmia-associated transcription factor (MITF).[14] Microarray data sets reveal a tight correlation in expression for MITF and CDK2 in primary human melanomas, but not in other malignancies, defining melanomas with high versus

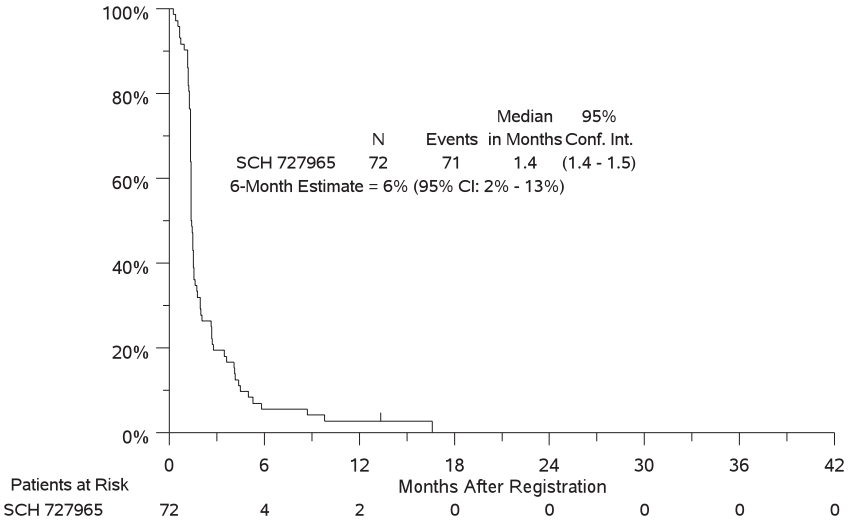

FIGURE 1 Progression-free survival. Kaplan–Meier analysis for progression-free survival of patients with stage IV melanoma treated with SCH 727965 (dinaciclib). CI or Conf. Int. indicates confidence interval.

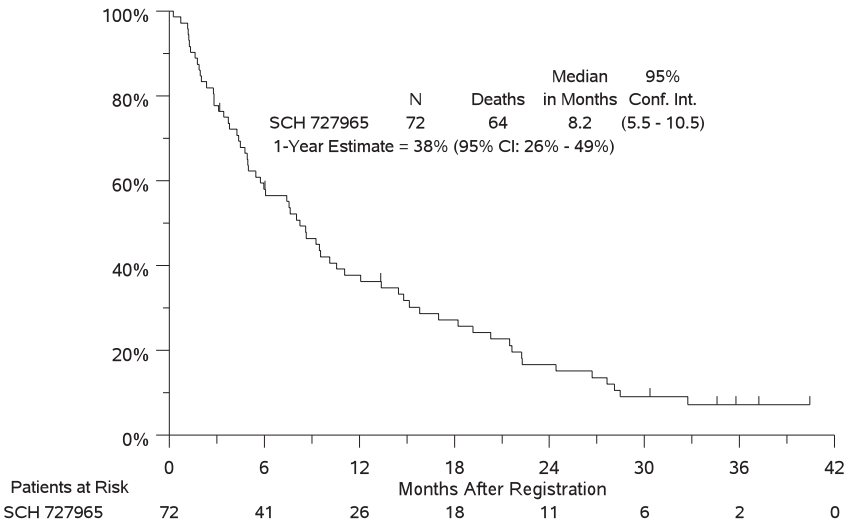

FIGURE 2 Overall survival. Kaplan–Meier analysis for overall survival of patients with stage IV melanoma treated with SCH 727965 (dinaciclib). CI or Conf. Int. indicates confidence interval.

low levels of CDK2s. Low levels of MITF and CDK2 expression in melanoma cell lines accurately predict increased susceptibility to G1 arrest induced by small interfering RNA targeting CDK2 or decreased proliferation in response to roscovitine, a CDK2 inhibitor.[14] Therefore, because subsets of melanomas may be sensitive to a selective CDK2 inhibitor, SCH 727965, a selective and potent CDK inhibitor, was thought to have potential therapeutic benefit in patients with melanoma.

The activity of CDK2 inhibitors, however, has not been replicated in vivo.[15,16] A phase 2 trial of flavopiridol, a CDK2 inhibitor with pan-CDK activity similar to that of dinaciclib, did not demonstrate significant clinical activity in melanoma.[17] The development of resistance or an inability to attain therapeutic drug levels without significant toxicity both are possible explanations. Overexpression of ATP-binding proteins[18] and cyclin E[19] have been described in association with flavopiridol resistance in breast and colon cancer lines, respectively, and similar mechanisms may also pertain to the study drug.[17]

Alternative cell cycle inhibitor therapies have shown more promise, including the CDK4 inhibitor palbociclib, which has induced therapeutic senescence in xenograft models of vemurafenib-resistant melanoma.[20] Agents inhibiting a range of other cell cycle targets, including CDK1, CHK1, and MDM2 inhibitors, remain in early stage trials; and exploring the combination of CDK4/6 inhibition and PD-1 inhibition may also hold promise.[4,21]

Our study was conducted at a time when the current generation of therapies were unavailable. The optimal end point in interventional trials has evolved over the years to reflect the preferential use of immune checkpoint inhibitor-based therapies in advanced melanoma. An unprecedented improvement in patient survival since the introduction of PD-1 inhibitors has spurred investigators to explore alternative end points in randomized clinical trials to assess clinical benefit beyond OS, which remains the gold standard. Several immune checkpoint inhibitor-based trials over the years have set the objective response rate and PFS as the primary or coprimary end points. Standard response criteria using Response Evaluation Criteria in Solid Tumors to define progression continue to be used in these studies, lacking an account of variable treatment responses, including pseudoprogression. As immune-related response criteria are being adopted in randomized controlled studies, end points with PFS improvement have been shown to be a valid benchmark for first-line metastatic melanoma studies.[22,23] In the later line setting, in which effective and durable treatment options beyond BRAF/MEK inhibitors and tumor-infiltrating lymphocyte therapy are limited and expected survival outcomes are dismal, arguments favor OS benefit as the standard for novel drug approval. Nevertheless, evolving literature supports the use of PFS as an appropriate surrogate end point for OS in metastatic melanoma.[22–25] As of 2024, effective, later line therapies continue to be an unmet need in melanoma; and promising, novel treatments with robust, early data demonstrate that a PFS benefit compared with standard-of-care options serves as an arguably acceptable endpoint.

CONCLUSION

The treatment landscape for metastatic melanoma has significantly changed since 2011, when the 1-year OS rate was roughly 25%; however, even with all the advances over the past decade, the 5-year OS rate has plateaued at approximately 50%. The current multicenter trial of the CDK2 inhibitor dinaciclib, which was conducted at a time when the current generation of effective therapies were not available, failed to demonstrate sufficient clinical activity to justify further investigation as a single agent. Novel treatments are still needed to continue to improve outcomes for patients with metastatic melanoma.

AUTHOR CONTRIBUTIONS

Christopher D. Lao: Conceptualization; writing–original draft; methodology; investigation; funding acquisition; writing–review and editing; and supervision. **James Moon**: Data curation; formal analysis; writing–original draft; writing–review and editing; methodology; and visualization. **Vincent T. Ma**: Writing–review and editing; formal analysis; and writing–original draft. **John P. Fruehauf**: Investigation and writing–review and editing. **Lawrence E. Flaherty**: Investigation and writing–review and editing. **Martin J. Bury**: Investigation and writing–review and editing. **William G. Martin**: Investigation and writing–review and editing. **Howard Gross**: Investigation and writing–review and editing. **Wallace Akerley**: Investigation and writing–review and editing. **Judith O. Hopkins**: Investigation and writing–review and editing. **Sapna P. Patel**: Writing–review and editing and supervision. **Vernon K. Sondak**: Investigation; writing–review and editing; and supervision; and writing–original draft. **Antoni Ribas**: Investigation; writing–review and editing; supervision; and writing–original draft.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

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