COLD SPRING HARBOR
Molecular Case Studies

RESEARCH REPORT

Complete response to chemoimmunotherapy with bevacizumab in synchronous multiple primary cancers: pulmonary adenocarcinoma and sarcomatoid carcinoma

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Abstract A small percentage of patients have multiple synchronous primary cancers at presentation. In the last five years, many regimens associated with immunotherapy and chemotherapy were approved for first-line metastatic non-small-cell lung cancer (NSCLC) and other solid tumors, but the study of immunotherapy when multiple cancers are present in one patient remains incomplete. Next-generation sequencing biomarkers and immunotherapy markers including PD-L1 can be effectively utilized in the diagnosis and treatment plan for multiple synchronous primary cancers. Immune biomarkers and PD-L1 expression warrant individualized treatments in synchronous primary adenocarcinoma and pulmonary sarcomatoid carcinoma. We describe the case of a patient with pulmonary sarcomatoid carcinoma and lung adenocarcinoma, metastatic to brain de novo. The patient achieved a complete response after only three cycles of carboplatin, paclitaxel, bevacizumab, and atezolizumab and remains free of any evidence of disease after 18 mo of maintenance therapy.

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Ontology terms: lung adenocarcinoma; neoplasm of the lung

Published by Cold Spring Harbor Laboratory Press

doi:10.1101/mcs.a006262

INTRODUCTION

For both men and women, lung cancer continues to be the leading cause of cancer-related deaths; reportedly up to 21% of lung cancer patients develop multiple synchronous primary cancers; and there has been an increase in the number of patients diagnosed with double primary cancers (Ferguson 1993; Noh et al. 2008; Lee et al. 2010; Weir et al. 2013). These rates of multiple primary cancers vary across tumor subtypes, age, exposure such as smoking history, and underlying germline factors and mutations (Travis et al. 2013). The reported increase in these rates is not yet completely defined, and factors such as improved diagnostic tests and more sophisticated treatment could be a potential cause (Coyte et al. 2014).

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However, occurrence of synchronous multiple primary cancers at presentation, with involvement in the lung, have been reported at higher rates, with one study showing 47% of lung patients diagnosed with multiple cancers (Kim et al. 2015b). Since the rapid adoption of next-generation sequencing of tumor tissue and circulating tumor DNA, it has become more common to study the genomic mutations associated with multiple primary cancers and understand the tumor heterogeneity associated with individual tumor subtypes (Whitworth et al. 2018; Mandelker and Ceyhan-Birsoy 2020). This advent has helped not only identify the individual tumor sites but also identify potential treatment options for these patients (Vogt et al. 2017).

In our case, we identify a patient who was diagnosed with lung adenocarcinoma and synchronous pulmonary sarcomatoid carcinoma found in the liver. Pulmonary sarcomatoid carcinomas (PSC) are a spectrum of histologically poorly differentiated carcinomas, accounting for <1% of all non-small-cell lung carcinoma (NSCLC) (Brambilla et al. 2001; Huang et al. 2013; Ung et al. 2016). PSC is well associated with a history of heavy smoking, chemotherapy resistance, and poor prognosis (Ishida et al. 1990; Yendamuri et al. 2012; Ouziane et al. 2014; Lin et al. 2016). The advent of tyrosine kinase inhibitors (TKIs) has shown that a certain subpopulation of PSC patients with molecular targets, including EGFR mutations, ALK fusions, and MET exon 14 skipping, responds well to TKIs, but the overall incidence rate of actionable mutations in PSC is relatively low (Schrock et al. 2017; Li et al. 2020; Yang et al. 2020). Concurrently, PSC tumors have a high incidence of *KRAS* mutations and PD-L1 expression, which makes them ideal candidates for immunotherapy (Vieira et al. 2016; Pecuchet et al. 2017). Clinical studies demonstrating the efficacy of immunotherapy on multiple primary cancers and PSC are limited, but one study of 37 patients with PSC showed an objective response rate (ORR) of 40.5% with a disease control rate of 64.8% regardless of PD-L1 expression (Deng et al. 2020; Domblides et al. 2020). Furthermore, there is preliminary evidence that immunotherapy efficacy may be high in patients with multiple lung cancer primaries (Asmar et al. 2017; Zhang et al. 2021). Therefore, we describe a case of a patient with dual synchronous primaries of pulmonary sarcomatoid carcinoma and lung adenocarcinoma, metastatic to the brain de novo. The patient achieved a complete response after only three cycles of carboplatin, paclitaxel, bevacizumab, and atezolizumab.

RESULTS

Clinical Presentation

The patient is a 78-yr-old male with Eastern Cooperative Oncology Group (ECOG) performance status 1, a former smoker, and a history of abdominal pain prior to diagnosis. A computed tomography (CT) scan demonstrated multiple liver lesions, retroperitoneal lymph nodes, and two right lung nodules. Subsequent positron emission tomography (PET) CT showed a right upper lobe spiculate nodule measuring 22 mm × 15 mm, a right lower lobe irregular nodule, measuring 14 mm × 8 mm, and multiple lesions in the liver with largest mass in the anterior right hepatic lobe measuring 71 mm × 49 mm (Fig. 1A). A brain magnetic resonance imaging (MRI) also revealed two enhancing right frontal lobe lesions measured at 12 and 2 mm (Fig. 2A). The patient underwent a core biopsy of the right lung which demonstrated poor differentiated adenocarcinoma consistent with lung primary (Table 1). The liver mass was also biopsied and showed poorly differentiated carcinoma with sarcomatoid features (Table 1). The lung and liver lesions demonstrated different morphologies and immunohistochemical profiles, and a site of origin could not be confidently assigned for the liver lesion.

Molecular testing was performed to understand tumor origin. *Guardant360* liquid biopsy resulted in KRAS G12V mutation, TP53 I254S mutation, TP53 G154fs mutation, and a tumor

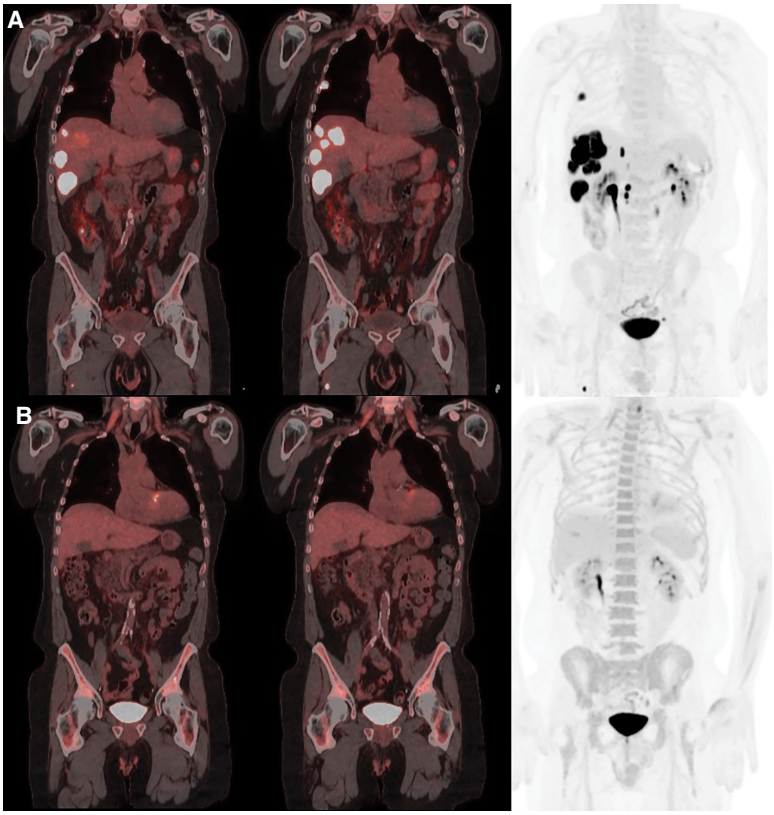

Figure 1. Positron emission tomography (PET) computed tomography (CT) of the whole body in coronal plane displaying the treatment response of the FDG-avid liver lesions. (*A*) At diagnosis. (*B*) After three cycles of therapy.

mutational burden (TMB) at 16.43 mut/Mb along with other mutations (Table 2). Solid tumor tissue panel *HopeSeq Lung* was performed on the pulmonary nodule and showed KRAS G12C mutation at an allele frequency of 12%, TP53 R306* mutation at an allele frequency of 6% and PD-L1 (22C3) tumor proportion score (TPS) of 95%. The same tissue panel was performed on the liver biopsy and showed KRAS G12V mutation at an allele frequency of 15%, TP53 I254S mutation at an allele frequency of 6%, TP53 G154Afs*16 mutation at an allele frequency of 8% and PD-L1 (22C3) TPS of 95% along with other alterations (Table 1). Because both samples and the liquid biopsy had the same driver mutations (*KRAS* and *TP53*), the diagnosis of synchronous primary pulmonary sarcomatoid carcinoma, variant pleomorphic, alongside lung adenocarcinoma, metastatic to the liver, retroperitoneal lymph nodes, and brain was made with the staging of IVB (T1cNxM1c).

Based on the molecular testing results and the pathological diagnosis confirmation, the patient was started on carboplatin AUC5, paclitaxel 175 mg/m^2, bevacizumab 15 mg/kg, and atezolizumab 1200 mg/dose (ABCP) every 3 wk. The two brain lesions were treated with stereotactic radiosurgery (SRS) at a dose of 20 Gray in one fraction. After three cycles, with a dose reduction due to neuropathy after the first cycle to carboplatin AUC 4 and paclitaxel 150 mg/m^2, follow-up scans showed both morphologic and metabolic partial response of all lesions, including in the central nervous system (CVS) (Figs. 1B, 2B,C). With the patient's consent and wishes, a robotically assisted liver resection was performed, and the patient recovered brilliantly and was discharged the following day. A pathology report showed extensive hyalinization, necrosis, and an old hemorrhage, which were all suggestive

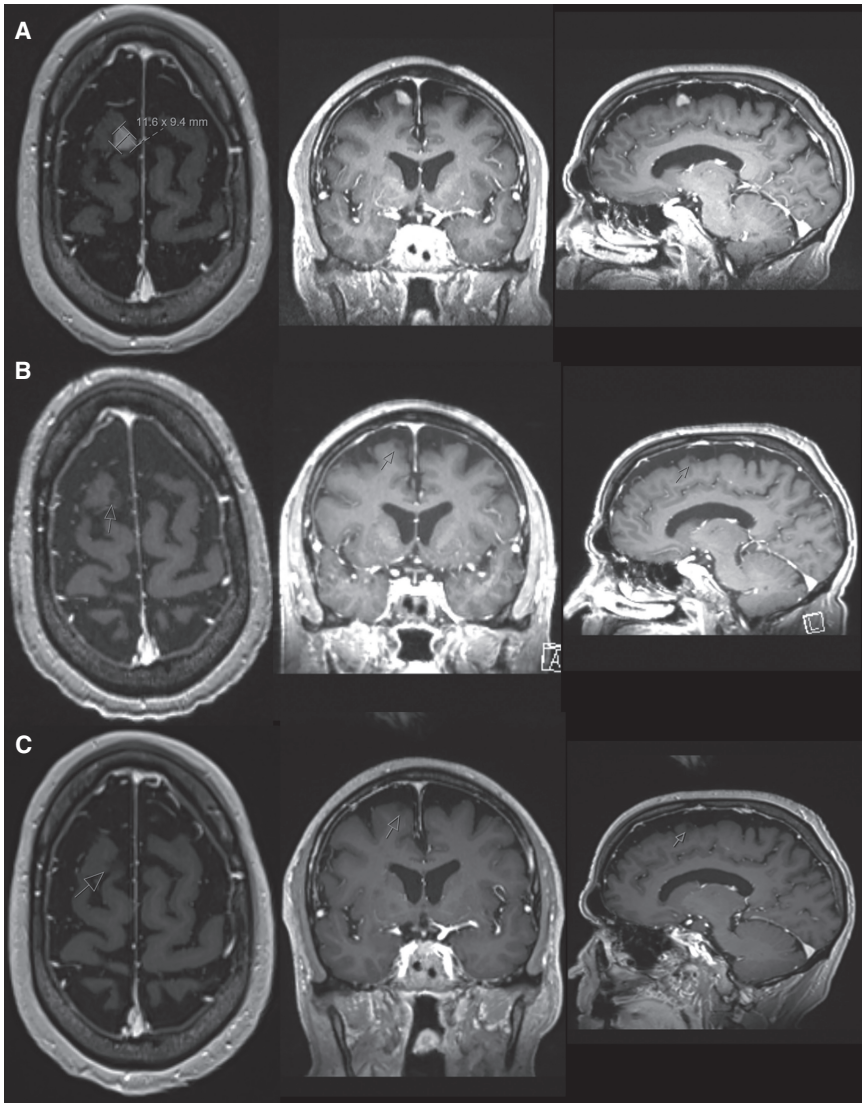

Figure 2. Magnetic resonance imaging (MRI) of the brain scans in transverse, coronal, and sagittal planes displaying the treatment response in of the largest brain lesion. (*A*) At diagnosis. (*B*) 3 mo after treatment. (*C*) 9 mo after treatment.

of treatment effect. The patient achieved a complete response after only 15 wk upon initiation of systemic therapy. Eighteen months later, he continues maintenance monotherapy with atezolizumab 1200 mg every 3 wk and has no evidence of disease.

DISCUSSION

Multiple primary tumors involve one or more tumors in an individual at the same time after it has been ruled out that one of the lesions is a metastasis of others (Vogt et al. 2017). In lung cancer, it has been reported that incidence of multiple primaries varies from 13.4% to 22% with high variability based on study populations (Rosso et al. 2009; Sánchez de Cos Escuín

Table 1. Immunohistochemistry and molecular characterization

Pathology		
Diagnosis	Poorly differentiated adenocarcinoma consistent with lung primary	Poorly differentiated carcinoma with sarcomatoid features
Specimen Site	Right lung nodule	Liver
Immunostains (+)	AE1/AE3, CK7, Napsin A, TTF-1	CK-oscar, AE1/AE3 (weakly), CK7 (weakly), EMA (weakly), CK-8/18 (weakly), WT-1 (weakly), ERG, Fli-1 (weakly), actin (weakly), P53, Ki-67, vimentin
Immunostains (–)	CK20	CK20, CK5/6, TTF-1, Napsin A, HepPar 1, S100, Mart 1, HMB-45, Calretinin, Factor VIII, CD31, CD34, MOC-31
Tumor markers (% AF)		
KRAS	G12C (12%)	G12V (15%)
TP53	R306* (6%)	I254S (6%), G154Afs*16 (8%)
TERT		c.-146C > T (9%)
PD-L1 expression	95%	95%
TMB	Cannot be determined	Cannot be determined
MSI	Stable	Stable
VUS	RAD50 V683I (51%)	RAD50 V683I (53%), ROS1 E2027K (9%)
Liquid biopsy (% cfDNA)		
KRAS		G12V (1.2%)
TP53		I254S (0.5%), G154fs (0.7%)
TERT		Promoter SNV (0.4%)
TMB		16.43 mut/Mb
MSI		Stable
VUS		ROS1 E2027K (0.7%), PALB2 S270I (0.2%)
SYN		MSH6 G685G (0.7%), VHL P154P (0.3%), PDGFRA Y172Y (0.2%)

(AF) Allelic fraction, (cfDNA) circulating-free DNA, (MSI) microsatellite instability, (PD-L1) programmed death ligand-1, (SYN) synonymous alteration, (TMB) tumor mutational burden, (VUS) variants of unknown significance, (SNV) single-nucleotide variant.

et al. 2016). For many of these patients the secondary cancer type is usually of lung origin, most commonly SCLC, but 19% are reported to be of unspecified origin (Bhaskarla et al. 2010). Pulmonary sarcomatoid carcinomas are extremely rare, accounting for <1% of all NSCLC (Yendamuri et al. 2012). The diagnosis of PSC is mainly based on morphological features, and although immunohistochemical stains can be helpful, molecular testing may be necessary to determine primary site origin (Terra et al. 2016; Huey et al. 2019). PSC often are diagnosed with distant metastases in unusual sites such as pancreas, kidneys, and the digestive tract, which results in a poor prognosis and PSC has historically been shown to be chemoresistant, where up to two-thirds of patients progress on first evaluation (Giroux Leprieur et al. 2013; Vieira et al. 2013). Although not usually seen in NSCLC, metastasis resections have been reported with satisfactory results and were offered based on patient desires (Gomez et al. 2016). However, with the advent of immunotherapy and targeted therapy, deep and long-lasting responses have been seen (Velcheti et al. 2013; Fallet et al. 2015; Schrock et al. 2017; Domblides et al. 2020). Our patient had all the commonly established pathological, radiological, and clinical features of primary sarcomatoid carcinoma and underwent a liver resection during systemic chemotherapy and immunotherapy.

Because of the low incidence of PSC and the relatively new adoption of a comprehensive genomic sequencing to clinical practice, the molecular profile of PSC is widely variable and needs to be refined (Terra et al. 2016; Li et al. 2017; Schrock et al. 2017; Zhou et al. 2021).

Table 2. Variant table

Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Variant type	Predicted effect	dbSNP/dbVar ID	Genotype
KRAS (c.34G > T, p.G12C)	12p12.1	NM_004985.5:c.34G > T	NP_004976.2: p.Gly12Cys	Missense	Gain, pathogenic	dbSNP: rs121913530	Heterozygous
TP53 (c.916C > T, p.R306*)	17p13.1	NM_000546.6:c.916C > T	NP_000537.3: p.Arg306Ter	Nonsense	Loss, pathogenic	dbSNP: rs121913344	Heterozygous
RAD50 (c.2047G > A, p.V683I)	5q31.1	NM_005732.4: c.2047G > A	NP_005723.2: p.Val683Ile	Missense	Loss, VUS	dbSNP: rs367925756	Heterozygous
KRAS (c.35G > T, p.G12V)	12p12.1	NM_004985.5:c.35G > T	NP_004976.2: p.Gly12Val	Missense	Gain, pathogenic	dbSNP: rs121913529	Heterozygous
TP53 (c.761T > G, p.I254S)	17p13.1	NM_000546.6:c.761T > G	NP_000537.3: p.Ile254Ser	Missense	Gain, pathogenic	dbSNP: rs1330865474	Heterozygous
TP53 (c.461del, p.G154Afs*16)	17p13.1	NM_000546.6: c.460_463del	NP_000537.3: p.Gly154fs	Frameshift, deletion	Loss, pathogenic	dbSNP: rs1567553658	Heterozygous
TERT (c.-146C > T, p.C250T)	5p15.33	NM_198253.3	p.C250T	Missense	Loss, pathogenic	N/A	Heterozygous
RAD50 (c.2047G > A, p.V683I)	5q31.1	NM_005732.4: c.2047G > A	NP_005723.2: p.Val683Ile	Missense	Loss, VUS	dbSNP: rs367925756	Heterozygous
ROS1 (c.6079G > A, p.E2027K)	6q22.1	NM_001378902.1	p.E2027K	Missense	Loss, VUS	dbSNP2/6/ 2023rs1484038087	Heterozygous
TP53 (c.460_463del, p.Gly154fs)	17p13.1	NM_000546.6: c.460_463del	NP_000537.3: p.Gly154fs	Frameshift, deletion	Loss, pathogenic	dbSNP: rs1567553658	Heterozygous
PALB2 (c.809G > T, p.S270I)	16p12.2	NM_024675.4	p.S270I	Missense	Loss, VUS	N/A	Heterozygous
MSH6 (c.2055T > C, p.G685G)	2p16.3	NM_000179.3: c.2055T > C	NP_000170.1: p.Gly685=	Missense, synonymous	Loss, VUS	dbSNP: rs760299985	Heterozygous
VHL (c.462A > G, p.P154P)	3p25.3	NM_000551.4:c.462A > G	NP_000542.1: p.Pro154=	Missense, synonymous	Gain, VUS	dbSNP: rs1060503562	Heterozygous
PDGFRA (c.516C > T, p.Y172Y)	4q12	NM_006206.6:c.516C > T	NP_006197.1: p.Tyr172=	Missense, synonymous	Loss, VUS	dbSNP: rs1046079554	Heterozygous

(VUS) Variant of unknown significance, (N/A) not available.

TP53 mutation frequency in PSC is reported ranging from 22% to 73% and *KRAS* mutations are the second most common in PSC, reports range from 15% to 39%, and frequently cooccur with *TP53* mutations (Schrock et al. 2017; Jiao et al. 2018; Mehrad et al. 2018). Notably, recent findings suggest that PSCs may develop through further undifferentiation of the adenocarcinoma or common tumor cell progenitor through nongenetic mechanisms such as epithelial-to-mesenchymal transition (Pelosi et al. 2003, 2010; Manzotti et al. 2019).

Another characteristic of PSC is its immunogenicity, and elevated TMB detected in patients suggests a high amount of tumoral neoantigens, which should induce strong tumor immunogenicity and predict response to immunotherapy (Kowanetz et al. 2016; Reck et al. 2016; Schrock et al. 2017). TMB recently received FDA approval as a predictive biomarker for pembrolizumab in all solid tumors with a TMB ≥10 mutations/Mb based on results of KEYNOTE-158 (Marabelle et al. 2020). Furthermore, a recent Phase IIa multibasket study of atezolizumab in advanced solid tumors showed efficacy of TMB as a predictive biomarker of response with TMB ≥16 mutations/Mb (Friedman et al. 2022). Marie Wislez et al. had published a series of 37 consecutive PSC cases that received immunotherapy in the second and third line and the ORR was 40.5% independent of PD-L1 status, which is larger than historical 8%–16% with chemotherapy in the first-line (Vieira et al. 2016; Maneenil et al. 2018; Domblides et al. 2020). PD-L1 positivity varies widely in PSC cases, from 53%–94%, which may be justified by different methods and cohorts (Velcheti et al. 2013; Kim et al. 2015a; Vieira et al. 2016; Domblides et al. 2020). Even with this heterogeneity, PD-L1 positivity in PSC is routinely higher than the historical 20%–60% in usual NSCLC histologies (Velcheti et al. 2013; Kim et al. 2015a; Yu et al. 2016). Notably, our patient was PD-L1 positive with a score of 95% and achieved a complete response with only three cycles of therapy.

In the past few years, several regimens were approved for first line metastatic NSCLC and other cancer types, which complicates the treatment options for patients with multiple cancers (Antonia et al. 2017; Wolchok et al. 2017; Larkin et al. 2019). The choice of a regimen that includes bevacizumab was based on the poorly differentiated histology and the prognosis of pulmonary sarcomatoid carcinoma. As the patient had pulmonary sarcomatoid carcinoma detected in the liver, it was also supported by the results of the IMpower 150 trial, in which the subgroup with previous liver metastasis had a median overall survival gain of four months, with ABCP (Socinski et al. 2021). The efficacy of immunotherapy in patients with multiple primary cancers is limited but one case series of patients with multiple primary malignancies with advanced melanoma showed that six out of 11 patients had complete response to immunotherapy (Ebia et al. 2021).

In conclusion, this case report confirms the efficacy of immunotherapy in patients with dual synchronous primary tumors and to the best of our knowledge this is the first reported complete response in a patient with both lung adenocarcinoma and pulmonary sarcomatoid carcinoma after treatment. Our report also shows the importance of molecular testing in tumors with differential pathological immunostains to determine the best course of therapy and we advocate that more clinical studies are required that evaluate the efficacy of immunotherapy in patients with multiple primary cancers.

METHODS

The patient's tumor tissue was analyzed with City of Hope's in-house insurance-reimbursable CLIA-certified targeted panel HopeSeq, a broad-based mutation sequencing panel that evaluates full exon of 523 genes, copy-number variations, microsatellite instability, tumor mutation burden, PD-L1 IHC, and a fusion analysis panel of more than 5000 selected rearrangements in 165 genes. The patient's liquid biopsy was analyzed through Guardant360,

a commercial targeted next-generation sequencing service available as an insurance-reimbursable CLIA assay.

ADDITIONAL INFORMATION

Data Deposition and Access

All data presented in the case report was included in the manuscript, and raw sequencing data could not be uploaded as it was sequenced through insurance-reimbursable CLIA-certified commercial panels and consent to upload was not obtained. The variants were submitted to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and can be found under accession numbers SCV003804197, SCV003804198, and SCV003804201–SCV003804209.

Ethics Statement

The City of Hope Institutional Review Board approved this study and informed consent was obtained under IRB# 07047.

Acknowledgments

The authors thank City of Hope nurses and supportive staff for their dedication to their patients.

Author Contributions

All authors participated in the conceptualization, methodology, data curation, original draft preparation, and reviewing and editing the final manuscript. R.S. provided supervision and funding.

Competing Interest Statement

The authors have declared no competing interest.

Received December 22, 2022; accepted in revised form February 9, 2023.

Funding

The work was supported by the National Cancer Institute of the National Institutes of Health under award number P30CA033572.

REFERENCES

Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, Chiappori A, Lee KH, de Wit M, et al. 2017. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* **377:** 1919–1929. doi:10.1056/NEJMoa1709937

Asmar R, Sonett JR, Singh G, Mansukhani MM, Borczuk AC. 2017. Use of oncogenic driver mutations in staging of multiple primary lung carcinomas: a single-center experience. *J Thorac Oncol* **12:** 1524–1535. doi:10.1016/j.jtho.2017.06.012

Bhaskarla A, Tang PC, Mashtare T, Nwogu CE, Demmy TL, Adjei AA, Reid ME, Yendamuri S. 2010. Analysis of second primary lung cancers in the SEER database. *J Surg Res* **162:** 1–6. doi:10.1016/j.jss.2009.12.030

Brambilla E, Travis WD, Colby TV, Corrin B, Shimosato Y. 2001. The new World Health Organization classification of lung tumours. *Eur Respir J* **18:** 1059–1068. doi:10.1183/09031936.01.00275301

Coyte A, Morrison DS, McLoone P. 2014. Second primary cancer risk—the impact of applying different definitions of multiple primaries: results from a retrospective population-based cancer registry study. *BMC Cancer* **14:** 272. doi:10.1186/1471-2407-14-272

Deng W, Wang Y, Liu X, Liu J, Wang L, Yang Z, Yang M, An Y, Tang C, Sanford NN, et al. 2020. Assessment of trends in second primary cancers in patients with metastatic melanoma from 2005 to 2016. *JAMA Netw Open* **3:** e2028627. doi:10.1001/jamanetworkopen.2020.28627

Domblides C, Leroy K, Monnet I, Mazières J, Barlesi F, Gounant V, Baldacci S, Mennecier B, Toffart AC, Audigier-Valette C, et al. 2020. Efficacy of immune checkpoint inhibitors in lung sarcomatoid carcinoma. *J Thorac Oncol* **15:** 860–866. doi:10.1016/j.jtho.2020.01.014

Ebia MI, Capone S, Ricker C, Thomas JS, Tulpule V, Kang I, D'Souza A, Freyer DR, Miller K, In GK. 2021. A case series of multiple primary malignancies among patients with advanced melanoma. *Cureus* **13:** e15480. doi:10.7759/cureus.15480

Fallet V, Saffroy R, Girard N, Mazières J, Lantuejoul S, Vieira T, Rouquette I, Thivolet-Bejui F, Ung M, Poulot V, et al. 2015. High-throughput somatic mutation profiling in pulmonary sarcomatoid carcinomas using the LungCarta™ Panel: exploring therapeutic targets. *Ann Oncol* **26:** 1748–1753. doi:10.1093/annonc/mdv232

Ferguson MK. 1993. Synchronous primary lung cancers. *Chest* **103:** 398S–400S. doi:10.1378/chest.103.4_Supplement.398S

Friedman CF, Hainsworth JD, Kurzrock R, Spigel DR, Burris HA, Sweeney CJ, Meric-Bernstam F, Wang Y, Levy J, Grindheim J, et al. 2022. Atezolizumab treatment of tumors with high tumor mutational burden from mypathway, a multicenter, open-label, phase IIa multiple basket study. *Cancer Discov* **12:** 654–669. doi:10.1158/2159-8290.CD-21-0450

Giroux Leprieur E, Antoine M, Vieira T, Duruisseaux M, Poulot V, Rabbe N, Belmont L, Gounant V, Lavolé A, Milleron B, et al. 2013. Clinical and molecular features in patients with advanced non-small-cell lung carcinoma refractory to first-line platinum-based chemotherapy. *Lung Cancer* **79:** 167–172. doi:10.1016/j.lungcan.2012.10.010

Gomez DR, Blumenschein GR, Lee JJ, Hernandez M, Ye R, Camidge DR, Doebele RC, Skoulidis F, Gaspar LE, Gibbons DL, et al. 2016. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* **17:** 1672–1682. doi:10.1016/S1470-2045(16)30532-0

Huang SY, Shen SJ, Li XY. 2013. Pulmonary sarcomatoid carcinoma: a clinicopathologic study and prognostic analysis of 51 cases. *World J Surg Oncol* **11:** 252. doi:10.1186/1477-7819-11-252

Huey RW, Makawita S, Xiao L, Matamoros A, Estrella JS, Overman MJ, Varadhachary GR, Raghav K. 2019. Sarcomatoid carcinoma presenting as cancers of unknown primary: a clinicopathological portrait. *BMC Cancer* **19:** 965. doi:10.1186/s12885-019-6155-6

Ishida T, Tateishi M, Kaneko S, Yano T, Mitsudomi T, Sugimachi K, Hara N, Ohta M. 1990. Carcinosarcoma and spindle cell carcinoma of the lung. Clinicopathologic and immunohistochemical studies. *J Thorac Cardiovasc Surg* **100:** 844–852. doi:10.1016/S0022-5223(19)36826-6

Jiao XD, Qin BD, You P, Cai J, Zang YS. 2018. The prognostic value of TP53 and its correlation with EGFR mutation in advanced non–small cell lung cancer, an analysis based on cBioPortal data base. *Lung Cancer* **123:** 70–75. doi:10.1016/j.lungcan.2018.07.003

Kim S, Kim M-Y, Koh J, Go H, Lee DS, Jeon YK, Chung DH. 2015a. Programmed death-1 ligand 1 and 2 are highly expressed in pleomorphic carcinomas of the lung: comparison of sarcomatous and carcinomatous areas. *Eur J Cancer* **51:** 2698–2707. doi:10.1016/j.ejca.2015.08.013

Kim SW, Kong KA, Kim DY, Ryu YJ, Lee JH, Chang JH. 2015b. Multiple primary cancers involving lung cancer at a single tertiary hospital: clinical features and prognosis. *Thorac Cancer* **6:** 159–165. doi:10.1111/1759-7714.12158

Kowanetz M, Zou W, Shames DS, Cummings C, Rizvi N, Spira AI, Frampton GM, Leveque V, Flynn S, Mocci S, et al. 2016. 77P: tumor mutation load assessed by FoundationOne (FM1) is associated with improved efficacy of atezolizumab (atezo) in patients with advanced NSCLC. *Ann Oncol* **27:** vi23. doi:10.1093/annonc/mdw363.25

Larkin J, Chiarion-Sileni V, Gonzalez R, Grob J-J, Rutkowski P, Lao CD, Cowey CL, Schadendorf D, Wagstaff J, Dummer R, et al. 2019. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* **381:** 1535–1546. doi:10.1056/NEJMoa1910836

Lee JS, Moon W, Park SJ, Park MI, Kim KJ, Jang LL, Park MJ, Chun BK. 2010. Triple synchronous primary cancers of rectum, thyroid, and uterine cervix detected during the workup for hematochezia. *Intern Med* **49:** 1745–1747. doi:10.2169/internalmedicine.49.3549

Li X, Wang D, Zhao Q, Ren D, Ren F, Chen G, Liu H, Chen J. 2017. Clinical significance and next-generation sequencing of Chinese pulmonary sarcomatoid carcinoma. *Sci Rep* **7:** 3947. doi:10.1038/s41598-017-04296-2

Li X, Wu D, Liu H, Chen J. 2020. Pulmonary sarcomatoid carcinoma: progress, treatment and expectations. *Ther Adv Med Oncol* **12:** 1758835920950207. doi:10.1177/1758835920950207

Lin Y, Yang H, Cai Q, Wang D, Rao H, Lin S, Long H, Fu J, Zhang L, Lin P, et al. 2016. Characteristics and prognostic analysis of 69 patients with pulmonary sarcomatoid carcinoma. *Am J Clin Oncol* **39:** 215–222. doi:10.1097/COC.0000000000000101

Mandelker D, Ceyhan-Birsoy O. 2020. Evolving significance of tumor-normal sequencing in cancer care. *Trends Cancer* **6:** 31–39. doi:10.1016/j.trecan.2019.11.006

Maneenil K, Xue Z, Liu M, Boland J, Wu F, Stoddard SM, Molina J, Yang P. 2018. Sarcomatoid carcinoma of the lung: the Mayo Clinic experience in 127 patients. *Clin Lung Cancer* **19:** e323–e333. doi:10.1016/j.cllc.2017.12.008

Manzotti G, Torricelli F, Benedetta D, Lococo F, Sancisi V, Rossi G, Piana S, Ciarrocchi A. 2019. An epithelial-to-mesenchymal transcriptional switch triggers evolution of pulmonary sarcomatoid carcinoma (PSC) and identifies dasatinib as new therapeutic option. *Clin Cancer Res* **25:** 2348–2360. doi:10.1158/1078-0432.CCR-18-2364

Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, Chung HC, Kindler HL, Lopez-Martin JA, Miller WH, et al. 2020. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol* **21:** 1353–1365. doi:10.1016/S1470-2045(20)30445-9

Mehrad M, Roy S, LaFramboise WA, Petrosko P, Miller C, Incharoen P, Dacic S. 2018. *KRAS* mutation is predictive of outcome in patients with pulmonary sarcomatoid carcinoma. *Histopathology* **73:** 207–214. doi:10.1111/his.13505

Noh SK, Yoon JY, Ryoo UN, Choi CH, Sung CO, Kim TJ, Bae DS, Kim BG. 2008. A case report of quadruple cancer in a single patient including the breast, rectum, ovary, and endometrium. *J Gynecol Oncol* **19:** 265–269. doi:10.3802/jgo.2008.19.4.265

Ouziane I, Boutayeb S, Mrabti H, Lalya I, Rimani M, Errihani H. 2014. Sarcomatoid carcinoma of the lung: a model of resistance of chemotherapy. *N Am J Med Sci* **6:** 342–345. doi:10.4103/1947-2714.136920

Pecuchet N, Vieira T, Rabbe N, Antoine M, Blons H, Cadranel J, Laurent-Puig P, Wislez M. 2017. Molecular classification of pulmonary sarcomatoid carcinomas suggests new therapeutic opportunities. *Ann Oncol* **28:** 1597–1604. doi:10.1093/annonc/mdx162

Pelosi G, Fraggetta F, Nappi O, Pastorino U, Maisonneuve P, Pasini F, Iannucci A, Solli P, Musavinasab HS, De Manzoni G, et al. 2003. Pleomorphic carcinomas of the lung show a selective distribution of gene products involved in cell differentiation, cell cycle control, tumor growth, and tumor cell motility: a clinicopathologic and immunohistochemical study of 31 cases. *Am J Surg Pathol* **27:** 1203–1215. doi:10.1097/00000478-200309000-00003

Pelosi G, Sonzogni A, De Pas T, Galetta D, Veronesi G, Spaggiari L, Manzotti M, Fumagalli C, Bresaola E, Nappi O, et al. 2010. Review article: pulmonary sarcomatoid carcinomas: a practical overview. *Int J Surg Pathol* **18:** 103–120. doi:10.1177/1066896908330049

Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csöszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, et al. 2016. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* **375:** 1823–1833. doi:10.1056/NEJMoa1606774

Rosso S, De Angelis R, Ciccolallo L, Carrani E, Soerjomataram I, Grande E, Zigon G, Brenner H, Group EW. 2009. Multiple tumours in survival estimates. *Eur J Cancer* **45:** 1080–1094. doi:10.1016/j.ejca.2008.11.030

Sánchez de Cos Escuín J, Rodríguez López DP, Utrabo Delgado I, Gallego Domínguez R, Sojo González MA, Hernández Valle M. 2016. Disease recurrence and second tumors in long-term survivors of lung cancer. *Arch Bronconeumol* **52:** 183–188. doi:10.1016/j.arbres.2015.07.013

Schrock AB, Li SD, Frampton GM, Suh J, Braun E, Mehra R, Buck SC, Bufill JA, Peled N, Karim NA, et al. 2017. Pulmonary sarcomatoid carcinomas commonly harbor either potentially targetable genomic alterations or high tumor mutational burden as observed by comprehensive genomic profiling. *J Thorac Oncol* **12:** 932–942. doi:10.1016/j.jtho.2017.03.005

Socinski MA, Nishio M, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Rodríguez-Abreu D, Moro-Sibilot D, Thomas CA, et al. 2021. IMpower150 final overall survival analyses for atezolizumab plus bevacizumab and chemotherapy in first-line metastatic nonsquamous NSCLC. *J Thorac Oncol* **16:** 1909–1924. doi:10.1016/j.jtho.2021.07.009

Terra SBSP, Jang JS, Bi L, Kipp BR, Jen J, Yi ES, Boland JM. 2016. Molecular characterization of pulmonary sarcomatoid carcinoma: analysis of 33 cases. *Mod Pathol* **29:** 824–831. doi:10.1038/modpathol.2016.89

Travis LB, Demark Wahnefried W, Allan JM, Wood ME, Ng AK. 2013. Aetiology, genetics and prevention of secondary neoplasms in adult cancer survivors. *Nat Rev Clin Oncol* **10:** 289–301. doi:10.1038/nrclinonc.2013.41

Ung M, Rouquette I, Filleron T, Taillandy K, Brouchet L, Bennouna J, Delord JP, Milia J, Mazières J. 2016. Characteristics and clinical outcomes of sarcomatoid carcinoma of the lung. *Clin Lung Cancer* **17:** 391–397. doi:10.1016/j.cllc.2016.03.001

Velcheti V, Rimm DL, Schalper KA. 2013. Sarcomatoid lung carcinomas show high levels of programmed death ligand-1 (PD-L1). *J Thorac Oncol* **8:** 803–805. doi:10.1097/JTO.0b013e318292be18

Vieira T, Girard N, Ung M, Monnet I, Cazes A, Bonnette P, Duruisseaux M, Mazières J, Antoine M, Cadranel J, et al. 2013. Efficacy of first-line chemotherapy in patients with advanced lung sarcomatoid carcinoma. *J Thorac Oncol* **8:** 1574–1577. doi:10.1097/01.JTO.0000437008.00554.90

Vieira T, Antoine M, Hamard C, Fallet V, Duruisseaux M, Rabbe N, Rodenas A, Cadranel J, Wislez M. 2016. Sarcomatoid lung carcinomas show high levels of programmed death ligand-1 (PD-L1) and strong immune-cell infiltration by TCD3 cells and macrophages. *Lung Cancer* **98:** 51–58. doi:10.1016/j.lungcan.2016.05.013

Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T, Omlin A. 2017. Multiple primary tumours: challenges and approaches, a review. *ESMO Open* **2:** e000172. doi:10.1136/esmoopen-2017-000172

Weir HK, Johnson CJ, Thompson TD. 2013. The effect of multiple primary rules on population-based cancer survival. *Cancer Causes Control* **24:** 1231–1242. doi:10.1007/s10552-013-0203-3

Whitworth J, Smith PS, Martin JE, West H, Luchetti A, Rodger F, Clark G, Carss K, Stephens J, Stirrups K, et al. 2018. Comprehensive cancer-predisposition gene testing in an adult multiple primary tumor series shows a broad range of deleterious variants and atypical tumor phenotypes. *Am J Hum Genet* **103:** 3–18. doi:10.1016/j.ajhg.2018.04.013

Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, Lao CD, Wagstaff J, Schadendorf D, Ferrucci PF, et al. 2017. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* **377:** 1345–1356. doi:10.1056/NEJMoa1709684

Yang Z, Xu J, Li L, Li R, Wang Y, Tian Y, Guo W, Wang Z, Tan F, Ying J, et al. 2020. Integrated molecular characterization reveals potential therapeutic strategies for pulmonary sarcomatoid carcinoma. *Nat Commun* **11:** 4878. doi:10.1038/s41467-020-18702-3

Yendamuri S, Caty L, Pine M, Adem S, Bogner P, Miller A, Demmy TL, Groman A, Reid M. 2012. Outcomes of sarcomatoid carcinoma of the lung: a surveillance, epidemiology, and end results database analysis. *Surgery* **152:** 397–402. doi:10.1016/j.surg.2012.05.007

Yu H, Boyle TA, Zhou C, Rimm DL, Hirsch FR. 2016. PD-L1 expression in lung cancer. *J Thorac Oncol* **11:** 964–975. doi:10.1016/j.jtho.2016.04.014

Zhang C, Yin K, Liu SY, Yan LX, Su J, Wu YL, Zhang XC, Zhong WZ, Yang XN. 2021. Multiomics analysis reveals a distinct response mechanism in multiple primary lung adenocarcinoma after neoadjuvant immunotherapy. *J Immunother Cancer* **9:** e002312. doi:10.1136/jitc-2020-002312

Zhou F, Huang Y, Cai W, Li J, Su C, Ren S, Wu C, Zhou C. 2021. The genomic and immunologic profiles of pure pulmonary sarcomatoid carcinoma in Chinese patients. *Lung Cancer* **153:** 66–72. doi:10.1016/j.lungcan.2021.01.006