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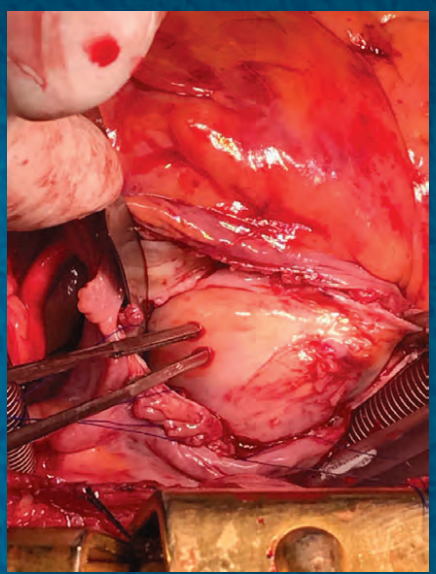
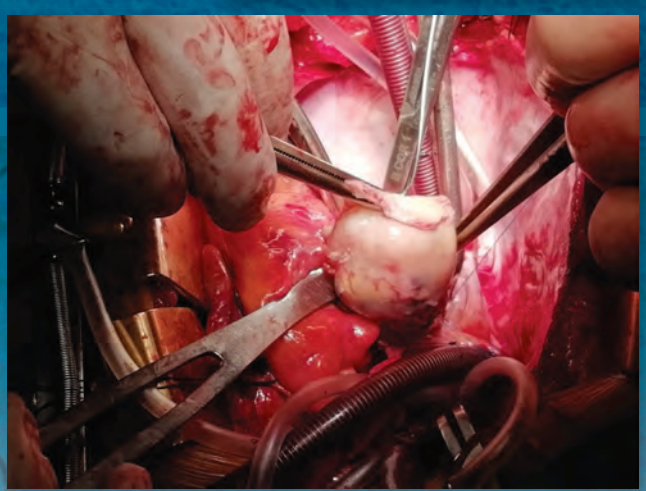
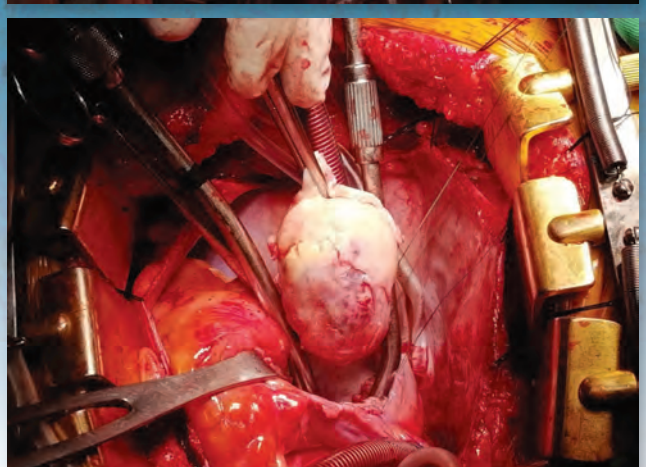






CASE REPORT

Cardiac failure due to left atrial angiosarcoma

PAGE 5

Plus, reports from the annual meeting of The Connective Tissue Oncology Society.

Sarcoma SFA Foundation of America
finding the cure in our time

START WITH A BREAKTHROUGH

FOR YOUR PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA DETERMINED TO START STRONG

INDICATION

LARTRUVO—a fully human monoclonal antibody—is indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.

This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

LARTRUVO, in combination with doxorubicin, was granted Breakthrough Therapy designation by the FDA.

IMPORTANT SAFETY INFORMATION FOR LARTRUVO

Warnings and Precautions

Infusion-Related Reactions

- Infusion-related reactions (IRR) occurred in 70 (14%) of 485 patients who received at least one dose of LARTRUVO across clinical trials. For 68 of these 70 patients (97%), the first occurrence of IRR was in the first or second cycle. Grade ≥3 IRR occurred in 11 (2.3%) of 485 patients, with one (0.2%) fatality. Symptoms of IRR included flushing, shortness of breath, bronchospasm, or fever/chills, and in severe cases symptoms manifested as severe hypotension, anaphylactic shock, or cardiac arrest. Infusion-related reactions required permanent discontinuation in 2.3% of patients and interruption of infusion in 10% of patients. All 59 patients with Grade 1 or 2 IRR resumed LARTRUVO; 12 (20%) of these patients had a Grade 1 or 2 IRR with rechallenge. The incidence of IRR in the overall safety database (N=485) was similar (18% versus 12%) between those who did (56%) and those who did not (44%) receive premedication. Monitor patients during and following LARTRUVO infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Immediately and permanently discontinue LARTRUVO for Grade 3 or 4 IRR.

Embryo-Fetal Toxicity

- Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm when administered to a pregnant woman. Animal knockout models link disruption of platelet-derived growth factor receptor alpha (PDGFR-α) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-α antibody to pregnant mice during organogenesis caused malformations and skeletal variations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose.

Most Common Adverse Reactions/Lab Abnormalities

- The most commonly reported adverse reactions (all grades; grade 3-4) occurring in ≥20% of patients receiving LARTRUVO plus doxorubicin versus doxorubicin alone were nausea (73% vs 52%; 2% vs 3%), fatigue (69% vs 69%; 9% vs 3%), musculoskeletal pain (64% vs 25%; 8% vs 2%), mucositis (53% vs 35%; 3% vs 5%), alopecia (52% vs 40%; 0% vs 0%), vomiting (45% vs 19%; 0% vs 0%), diarrhea (34% vs 23%; 3% vs 0%) decreased appetite (31% vs 20%; 2% vs 0%), abdominal pain (23% vs 14%; 3% vs 0%), neuropathy (22% vs 11%; 0% vs 0%), and headache (20% vs 9%; 0% vs 0%).
- The most common laboratory abnormalities (all grades; grade 3-4) occurring in ≥20% of patients receiving LARTRUVO plus doxorubicin versus doxorubicin alone were lymphopenia (77% vs 73%; 44% vs 37%), neutropenia (65% vs 63%; 48% vs 38%) and thrombocytopenia (63% vs 44%; 6% vs 11%), hyperglycemia (52% vs 28%; 2% vs 3%), elevated aPTT (33% vs 13%; 5% vs 0%), hypokalemia (21% vs 15%; 8% vs 3%), and hypophosphatemia (21% vs 7%; 5% vs 3%).

Use in Specific Populations

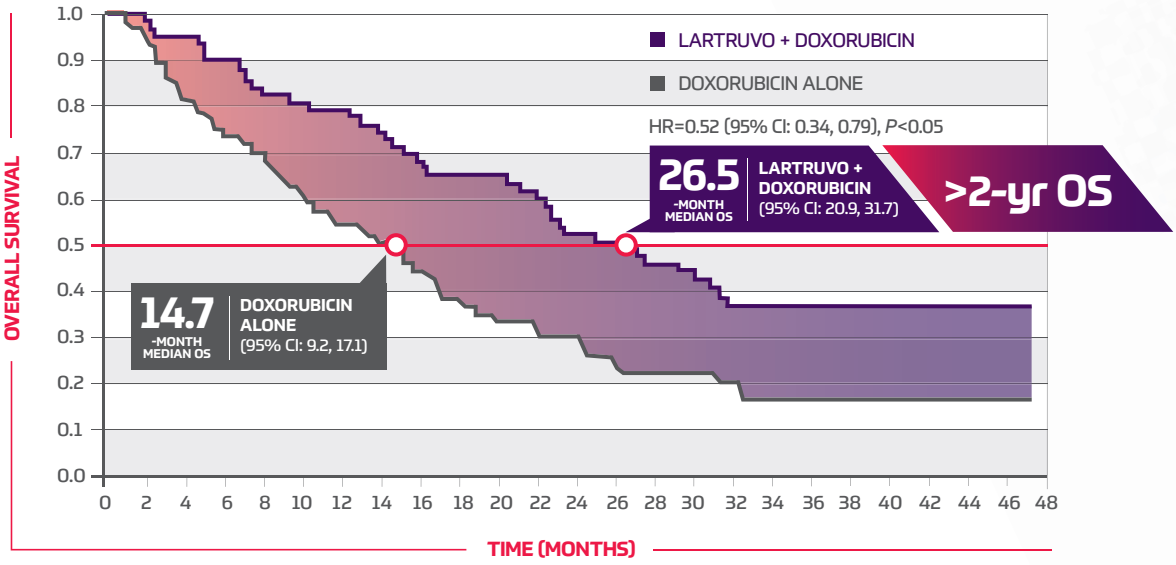
- Lactation: Because of the potential risk for serious adverse reactions in breastfeeding infants, advise women not to breastfeed during treatment with LARTRUVO and for at least 3 months following the last dose.

Please see Brief Summary of Prescribing Information on adjacent pages.

OR HCP ISI 19OCT2016

LARTRUVO + DOXORUBICIN: THE 1ST AND ONLY FRONT-LINE ADVANCEMENT FOR STS IN MORE THAN 4 DECADES[1]

LARTRUVO + DOXORUBICIN SIGNIFICANTLY EXTENDED OVERALL SURVIVAL (OS) VS DOXORUBICIN ALONE



NUMBER AT RISK

LARTRUVO + Doxorubicin	66	62	60	57	52	51	50	47	43	41	41	39	33	32	29	26	16	16	15	8	3	3	1	1	0
Doxorubicin Alone	67	61	51	46	43	37	34	32	28	23	21	19	19	15	13	13	10	7	6	6	5	3	2	1	0

There were 39 (59%) deaths among patients taking LARTRUVO + doxorubicin compared to 52 (78%) deaths among patients taking doxorubicin alone.

CI=confidence interval; HR=hazard ratio.

OBJECTIVE RESPONSE RATE (ORR)*

18.2% LARTRUVO + DOXORUBICIN (95% CI: 9.8, 29.6)

- VS -

7.5% DOXORUBICIN ALONE (95% CI: 2.5, 16.6)

PROGRESSION-FREE SURVIVAL (PFS)†

8.2 -MONTH MEDIAN PFS LARTRUVO + DOXORUBICIN (95% CI: 5.5, 9.8)

- VS -

4.4 -MONTH MEDIAN PFS DOXORUBICIN ALONE (95% CI: 3.1, 7.4)

HR=0.74 (95% CI: 0.46, 1.19)

*ORR=complete response (CR) + partial response (PR). LARTRUVO + doxorubicin: CR=4.5%, PR=13.6%; doxorubicin alone: CR=1.5%, PR=6%. Based on independent review assessed according to RECIST criteria v1.1.

ORR does not include stable disease.

†LARTRUVO + doxorubicin led to 37 (56%) total events compared to 34 (51%) events with doxorubicin alone.

PFS based on independent review.

HEAD-TO-HEAD, PHASE 2 TRIAL ACROSS MULTIPLE STS HISTOLOGICAL SUBTYPES

Study 1 was an open-label, Phase 2, randomized (1:1), active-controlled study (N=133) of LARTRUVO + doxorubicin (n=66) vs doxorubicin alone (n=67) in patients with soft tissue sarcoma not amenable to curative treatment with surgery or radiotherapy, a histologic type of sarcoma for which an anthracycline-containing regimen was appropriate but had not been administered, and an ECOG PS of 0-2. LARTRUVO was administered at 15 mg/kg as an IV infusion on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity. All patients received doxorubicin 75 mg/m^2 as an IV infusion on Day 1 of each 21-day cycle for a maximum of eight cycles and were permitted to receive dexrazoxane prior to doxorubicin in Cycles 5 to 8. The efficacy outcome measures were overall survival (OS), progression-free survival (PFS), and objective response rate (ORR). This study excluded patients with an ECOG performance status >2, left ventricular ejection fraction <50%; or unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction within 6 months. Patients had a tumor specimen available for assessment of PDGFR-α expression by an investigational use assay. The histological subtypes included were leiomyosarcoma, liposarcoma, undifferentiated pleomorphic sarcoma, angiosarcoma, undifferentiated sarcoma not otherwise specified, synovial sarcoma, and additional histologies.

ECOG PS=Eastern Cooperative Oncology Group performance status; IV=intravenous.

VISIT LARTRUVO.COM/HCP TO LEARN MORE

Reference: 1. Ravi V, Patel S, Benjamin RS. Chemotherapy for soft-tissue sarcomas. *Oncology* (Williston Park). 2015;29:43-50.

Lartruvo®
(OLARATUMAB)
Injection 10 mg/mL

Lilly

LARTRUVO™ (olaratumab) injection

BRIEF SUMMARY: For complete safety, please consult the full Prescribing Information.

INDICATIONS AND USAGE

LARTRUVO is indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery. This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

Infusion-related reactions (IRR) occurred in 70 (14%) of 485 patients who received at least one dose of LARTRUVO across clinical trials. For 68 of these 70 patients (97%), the first occurrence of IRR was in the first or second cycle. Grade ≥3 IRR occurred in 11 (2.3%) of 485 patients, with one (0.2%) fatality. Symptoms of IRR included flushing, shortness of breath, bronchospasm, or fever/chills, and in severe cases symptoms manifested as severe hypotension, anaphylactic shock, or cardiac arrest. Infusion-related reactions required permanent discontinuation in 2.3% of patients and interruption of infusion in 10% of patients. All 59 patients with Grade 1 or 2 IRR resumed LARTRUVO; 12 (20%) of these patients had a Grade 1 or 2 IRR with rechallenge. The incidence of IRR in the overall safety database (N = 485) was similar (18% versus 12%) between those who did (56%) and those who did not (44%) receive premedication. Monitor patients during and following LARTRUVO infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Immediately and permanently discontinue LARTRUVO for Grade 3 or 4 IRR.

Embryo-Fetal Toxicity

Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm when administered to a pregnant woman. Animal knockout models link disruption of platelet-derived growth factor receptor alpha (PDGFR-α) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-α antibody to pregnant mice during organogenesis caused malformations and skeletal variations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data in the Warnings and Precautions section reflect exposure to LARTRUVO in 485 patients from three randomized, open-label, active-controlled clinical trials, which enrolled 256 patients with various tumors who received LARTRUVO in combination with chemotherapy (191 patients) or LARTRUVO as a single agent (65 patients); four open-label single-arm trials which enrolled 96 patients with various tumors who received LARTRUVO as a single agent at doses of 10 to 20 mg/kg; and two trials, including Trial 1, which enrolled 133 patients with soft tissue sarcoma who received LARTRUVO at doses of 15 to 20 mg/kg in combination with doxorubicin (103 patients) or LARTRUVO as a single agent (30 patients). Among the 485 patients, 25% were exposed to LARTRUVO for ≥6 months and 6% were exposed for ≥12 months. The data described below reflect exposure to LARTRUVO in 64 patients with metastatic soft tissue sarcoma enrolled in Trial 1, a multicenter, randomized (1:1), open-label, active-controlled trial comparing LARTRUVO plus doxorubicin with doxorubicin as a single agent. LARTRUVO was administered at 15 mg/kg as an intravenous infusion on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity [see Clinical Studies (14)]. All patients received doxorubicin 75 mg/m^2 as an intravenous infusion on Day 1 of each 21-day cycle for a maximum of eight cycles and received dexrazoxane, prior to doxorubicin in cycles 5 to 8. In Trial 1, no patients had received a prior anthracycline-containing regimen. The trial excluded patients with an ECOG performance status >2; left ventricular ejection fraction <50%; or unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction within 6 months. Baseline demographics and disease characteristics were: median age 58 years (range 22 to 86); 45% male; 87% White, 8% Black, 3% Asian, 2% Other; 57% ECOG PS 0, 39% ECOG PS 1, and 5% ECOG PS 2. The median duration of exposure to LARTRUVO was 6 months (range: 21 days to 29.4 months) with 36 (56%) patients receiving LARTRUVO for ≥6 months and 10 (16%) patients receiving LARTRUVO for ≥12 months. The median cumulative doxorubicin dose was 488 mg/m^2 in the LARTRUVO plus doxorubicin arm and 300 mg/m^2 in the doxorubicin arm. In Trial 1, adverse reactions resulting in permanent discontinuation of LARTRUVO occurred in 8% (5/64) of patients. The most common adverse reaction leading to LARTRUVO discontinuation was infusion-related reaction (3%). Dose reductions of LARTRUVO for adverse reactions occurred in 25% (16/64) of patients; the most common adverse reaction leading to dose reduction was Grade 3 or 4 neutropenia (20%). Dose delays of LARTRUVO for adverse reactions occurred in 52% (33/64) of patients; the most common adverse reactions resulting in dose delays were neutropenia (33%), thrombocytopenia (8%), and anemia (5%). Table 1 summarizes adverse reactions that occurred in at least 10% of patients receiving LARTRUVO in the randomized portion of the study. The most common adverse reactions reported in at least 20% of patients receiving LARTRUVO plus doxorubicin were nausea, fatigue, musculoskeletal pain, mucositis, alopecia, vomiting, diarrhea, decreased appetite, abdominal pain, neuropathy, and headache.

Table 1: Adverse Reactions Occurring in ≥10% (All Grades) of Patients in the LARTRUVO plus Doxorubicin Arm and at a Higher Incidence than in the Doxorubicin Arm (Between Arm Difference of ≥5% for All Grades or ≥2% for Grades 3 and 4) (Trial 1)

Adverse Reactions	LARTRUVO plus Doxorubicin N=64		Doxorubicin N=65	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Gastrointestinal Disorders				
Nausea	73	2	52	3
Mucositis	53	3	35	5
Vomiting	45	0	19	0
Diarrhea	34	3	23	0
Abdominal Pain[a]	23	3	14	0
General Disorders and Administrative Site Conditions				
Fatigue[b]	69	9	69	3
Infusion-Related Reactions	13	3	3	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain[c]	64	8	25	2
Skin and Subcutaneous Tissue Disorders				
Alopecia	52	0	40	0
Metabolic and Nutritional Disorders				
Decreased Appetite	31	2	20	0
Nervous System Disorders				
Neuropathy	22	0	11	0
Headache	20	0	9	0
Psychiatric Disorder				
Anxiety	11	0	3	0
Eye Disorder				
Dry Eyes	11	0	3	0

[a] Abdominal pain includes: abdominal pain, lower abdominal pain, and upper abdominal pain.

[b] Fatigue includes: asthenia and fatigue.

[c] Musculoskeletal pain includes: arthralgia, back pain, bone pain, flank pain, groin pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, muscle spasms, neck pain, and pain in extremity.

In Trial 1, the most common laboratory abnormalities (≥20%) were lymphopenia, neutropenia, thrombocytopenia, hyperglycemia, elevated aPTT, hypokalemia, and hypophosphatemia as shown in Table 2.

LARTRUVO™ (olaratumab) injection OR HCP BS 21OCT2016

Table 2: Laboratory Abnormalities Worsening from Baseline in >10% (All Grades) of Patients in the LARTRUVO plus Doxorubicin Arm and Occurring at a Higher Incidence than in the Doxorubicin Arm (Between Arm Difference ≥5% for All Grades or ≥2% for Grades 3 and 4) (Trial 1)

Laboratory Abnormality	LARTRUVO plus Doxorubicin[a]		Doxorubicin[a]	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Hyperglycemia	52	2	28	3
Increased aPTT[b]	33	5	13	0
Hypokalemia	21	8	15	3
Hypophosphatemia	21	5	7	3
Increased Alkaline Phosphatase	16	0	7	0
Hypomagnesemia	16	0	8	0
Hematology				
Lymphopenia	77	44	73	37
Neutropenia	65	48	63	38
Thrombocytopenia	63	6	44	11

[a] The incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement: LARTRUVO plus doxorubicin arm (range 60 to 63 patients) and doxorubicin arm (range 39 to 62 patients).

[b] aPTT = activated partial thromboplastin time

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In clinical trials, 13/370 (3.5%) of evaluable LARTRUVO-treated patients tested positive for treatment-emergent anti-olaratumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in all patients who tested positive for treatment-emergent anti-olaratumab antibodies. The effects of anti-olaratumab antibodies on efficacy, safety, and exposure could not be assessed due to the limited number of patients with treatment-emergent anti-olaratumab antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to LARTRUVO with the incidences of antibodies to other products may be misleading.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm. There are no available data on LARTRUVO use in pregnant women. No animal studies using olaratumab have been conducted to evaluate its effect on female reproduction and embryo-fetal development. Animal knockout models link disruption of platelet-derived growth factor receptor alpha (PDGFR-α) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-α antibody to pregnant mice during organogenesis at exposures less than the exposure at the maximum recommended human dose caused malformations and skeletal variations *[see Data]*. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

No animal studies have been conducted using olaratumab to evaluate the effect of blocking PDGFR-α signaling on reproduction and embryo-fetal development. In PDGFR-α knockout mice, disruption of PDGFR-α signaling resulted in embryo-fetal lethality and teratogenicity, including cleft face and spina bifida. Intravenous administration of an anti-murine PDGFR-α antibody once every 3 days to pregnant mice during organogenesis at 50 and 150 mg/kg resulted in increased malformations (abnormal eyelid development) and skeletal variations (additional ossification sites in the frontal/parietal skull). Increased post-implantation loss occurred at a dose of 5 mg/kg. The effects on fetal development in mice administered this antibody occurred at exposures less than the AUC exposure at the maximum recommended human dose of 15 mg/kg LARTRUVO.

Lactation

Risk Summary

There are no data on the presence of olaratumab in human milk, or its effects on the breastfed infant or on milk production. Because of the potential risk for serious adverse reactions in breastfeeding infants from olaratumab, advise women not to breastfeed during treatment with LARTRUVO and for 3 months following the last dose.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action, LARTRUVO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose.

Infertility

Males

Based on animal models, LARTRUVO may impair male fertility.

Pediatric Use

The safety and effectiveness of LARTRUVO in pediatric patients have not been established.

Geriatric Use

Clinical studies of LARTRUVO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

PATIENT COUNSELING INFORMATION

Infusion-Related Reactions

Advise patients to report signs and symptoms of infusion reactions.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential of the potential risk to the fetus, to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose, and to inform their healthcare provider of a known or suspected pregnancy.

Lactation

Advise patients not to breastfeed during treatment with LARTRUVO and for 3 months after the last dose.

Additional information can be found at www.LARTRUVO.com/hcp.

Lilly

Eli Lilly and Company, Indianapolis, IN 46285, USA

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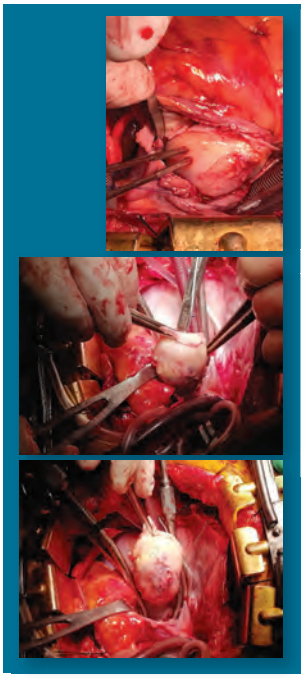

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Cardiac failure due to left atrial angiosarcoma

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Primary heart sarcomas are rare and represent 20% of all primary cardiac tumors. Symptoms depend on which chambers and cardiac structures are involved. Angiosarcoma is one of the most common and the most aggressive types of primary heart sarcomas. Typically, these tumors are found in the right atrium; however, cardiac angiosarcomas may involve any part of the heart. Most of these tumors are diagnosed in advanced stages and the patient prognosis is poor. Most tumors are diagnosed using echocardiography. Computed tomography (CT) and magnetic resonance imaging (MRI) provide useful information on tumor size and location for planning surgery, which is the only treatment shown to increase survival. We present the case of a 69-year-old woman who presented to the emergency department with hypotension, dyspnea and progressive shortness of breath. After adequate resuscitation, a cardiac mass was identified and surgery was successfully performed. Pathology confirmed a grade 2 primary heart angiosarcoma. Following surgery, the patient was admitted to the intensive care unit and later died secondary to multiorgan system failure.

Introduction

Primary heart angiosarcoma is an aggressive and usually fatal cardiac neoplasm[1]. Angiosarcomas can originate at any location in the heart[2, 3], but these tumors typically reside in the right atrium and frequently cause nonspecific symptoms such as dyspnea, cough, heart failure, and arrhythmias.[2] Surgery followed by chemotherapy is the typical approach to these tumors.[4]

We present the case of a 69-year-old woman who presented to the emergency department with hypotension and severe dyspnea.

Case report:

The patient was a 69-year-old woman with a medical history of diabetes. A week before seeking care in the emergency department, she experienced a general feeling of unwellness, dyspnea, and mild respiratory distress. She reported these symptoms had become more and more severe in the last 24 hours and were accompanied by acute chest pain and progressive shortness of breath.

On clinical examination, the patient was hypotensive, had tachypnea and tachycardia, and was hypoxic. Cardiac auscultation detected a systolic murmur in the apex, and auscultation of the lungs revealed crackles and rales, especially at the bases of the lungs. The remainder of her clinical examination was unremarkable. She had sinus tachycardia on an electrocardiogram. A chest x-ray showed a left atrial enlargement along with some patchy opacities in the middle and lower zones of the lungs, along with Kerley B lines suggestive of pulmonary edema.

With these findings, and after adequate resuscitation, a contrast-enhanced computed tomography (CT) scan detected a filling defect in the left atrium suggestive of a large intracardiac mass with a thick and hyperenhanced interatrial septum. Bilateral pleural effusions also were evident, (FIGURE 1A) hence an echocardiogram was requested and it confirmed the presence of a 30 x 29 x 40 mm lobulated highly mobile mass in the left atrium. The mass had a heterogeneous echogenicity along with some hypoechogenic areas. The tumor was attached to the surface of the anterior leaflet of the mitral valve and had a broad base that extended toward the interatrial septum. In the diastolic phase, the lesion insinuated toward the ventricle without exceeding the limits of the leaflets, causing severe valve dysfunction, (FIGURE 2A). Diminished left ventricular ejection fraction was noted as well.

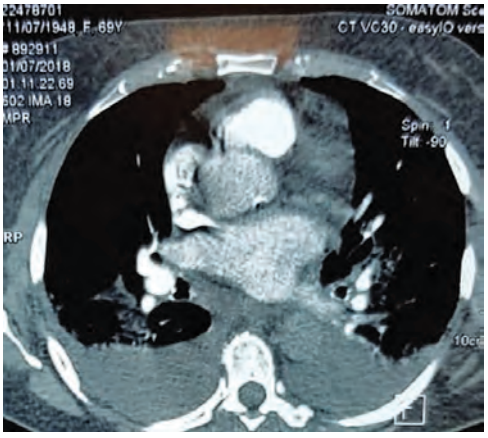

FIGURE 1A Contrast-enhanced chest CT, a filling defect in the left atrium, with a thick and hyperenhanced interatrial septum and bilateral pleural effusions are seen.

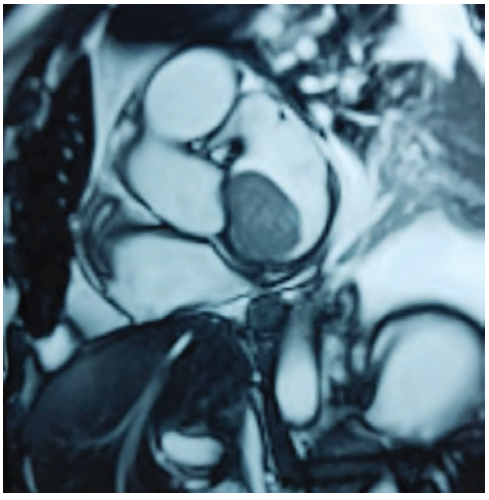

FIGURE 3A Cardiac MRI, a well-circumscribed hyperemic mass, on the anterior leaflet of the mitral valve is seen.

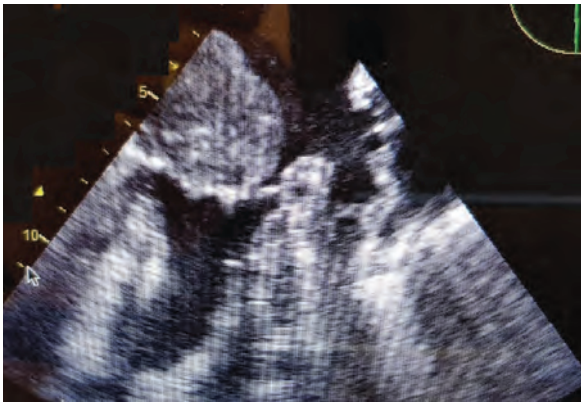

FIGURE 2A Echocardiography revealing the cardiac mass within the left atrium.

After a cardiothoracic consultation, cardiac magnetic resonance imaging (MRI) was performed. The findings showed the presence of a 58 x 45 x 6 mm well-circumscribed hyperemic mass on the anterior leaflet of the mitral valve and a second 10 x 10 x 6 mm smaller mass firmly adhered to the posterior leaflet of the mitral valve. As contrast passed through the coronary arteries, the contrast filled the mass confirming its vascular nature (FIGURE 3A).

The patient, who was hypotensive and hypoxic, was admitted to the hospital for surgical treatment.

Following sternotomy and cardiopulmonary bypass, a right atriotomy was performed using a trans-septal approach. The large left atrial mass was firmly adhered to the endocardium at the level of the anterior leaflet of the mitral valve and the interatrial septum was identified. The mass had a grey and whitish appearance with some bluish necrotic patches, (FIGURES 1B, 2B, 3B). A second 14x10x6 mm mass and a small 1x1x5 mm mass firmly adhered to the posterior leaflet of the mitral valve. Based on these findings, the cardiac masses were completely resected and bovine pericardium was used to repair the septal defect. The remainder of the procedure continued without any complications. Pathology reported a tumor that consisted of spindle-shaped tumor cells, with significant pleomorphism and numerous irregular vascular channels. Cells were strongly positive for CD34 and weakly positive for FLI-1. A grade 2 primary heart angiosarcoma was the final diagnosis. (FIGURES 1C, 2C)

The patient had a complicated postoperative course in the intensive care unit (ICU) and needed inotropic support and vasoactive agents. A postop echocardiogram indicated appropriate left ventricle systolic function, nonetheless, the patient persisted in a hypotensive status that caused refractory shock and ultimately provoked severe organ dysfunction that led to the patient's death.

Discussion

Primary heart sarcomas are extremely rare malignant neoplasms derived from mesenchymal cells,[1] with an incidence ranging from 0.001% to 0.28% at autopsy.[2] Primary heart sarcomas represent 10%-20% of all

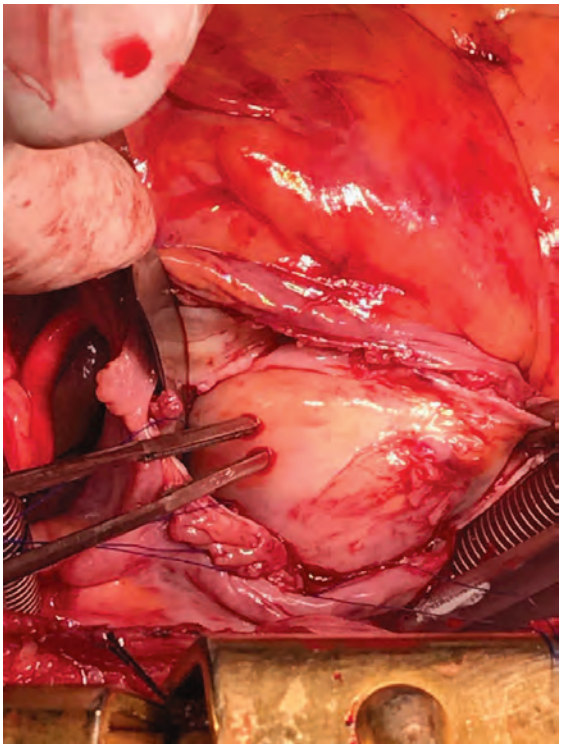

FIGURE 1B Left atrium mass firmly adhered to the endocardium at the level of the anterior leaflet of the mitral valve and the interatrial septum

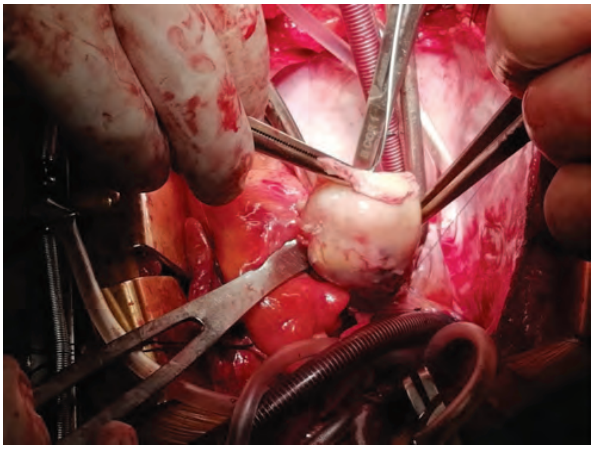

FIGURE 2B Resection of the left atrium mass after cardiopulmonary bypass.

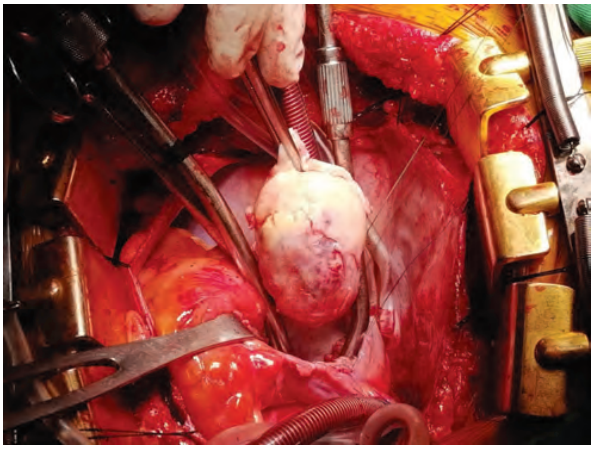

FIGURE 3B Complete resection of the left atrium mass

primary heart tumors[3] and are thought to arise from a pluripotent mesenchymal cell with k-ras and p53 mutations, however, the molecular histogenesis pathways are still poorly understood.[1] Primary heart sarcomas are classified according to their cell pattern, undifferentiated sarcomas and angiosarcomas are the two most common types, accounting for up to 66% of all primary heart sarcomas.[1,3] Primary heart sarcomas may originate from any part of the heart, without any gender or age predominance.[1] They can also arise from surrounding cardiac structures and are capable of mimicking almost any cardiovascular disorder.[2]

Cardiac angiosarcomas (CA) account for one-third of all primary heart sarcomas[4] and usually develop as gray-brown masses with hemorrhagic patches in the right atrium of male patients. The tumors are filled with vascular channels and their cells are positive for CD34 and factor VIII.[5] Left-sided cardiac angiosarcoma can cause heart failure early in the disease process, but the tumors tend to be more circumscribed, less infiltrative, and associated with better overall survival.[6,7] Most patients are asymptomatic early in their disease,[2] making the diagnosis even more difficult and worsening its already poor prognosis.[1] The preference of cardiac angiosarcomas for the right heart often leads to a presentation with right-sided congestive heart failure.[2] At later stages, symptoms depend on the structures compromised and range from mild dyspnea on exertion to cardiogenic shock.[8] Cardiac angiosarcomas tend to have a notable intracavitary element, and in some cases may intermittently compromise a cardiac valve, thereby simulating a stenosis or regurgitation.[2,7]

Our patient presented with acute cardiac failure, pulmonary edema, and severe valve dysfunction because of a mass in the left atrium. The tumor had a vascular supply and showed positivity for CD34.

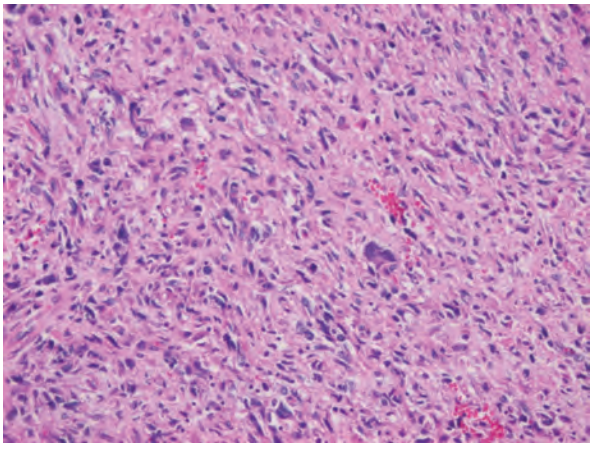

FIGURE 1C Hematoxylin-eosin staining, lesion constituted by spindle-shaped tumor cells, with important pleomorphism (400x magnification).

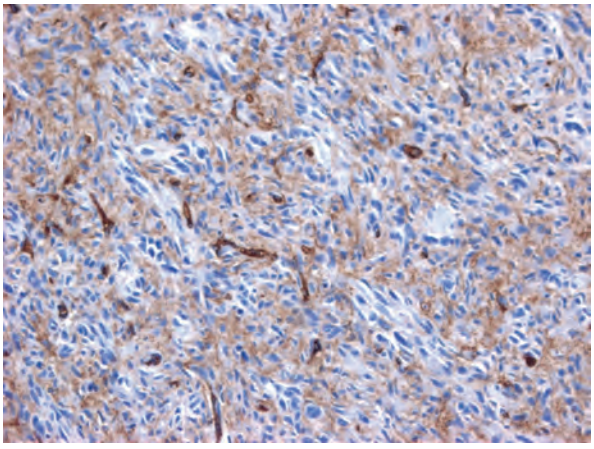

FIGURE 2C Immunohistochemical stain for CD-34 in endothelial cells (400x amplification).

Most patients with cardiac angiosarcoma have metastases, typically to the lung, at diagnosis.[1] Several decades ago, cardiac angiosarcoma was mainly diagnosed postmortem.[1] Now, it can be suspected when cardiomegaly or pleural effusions are seen on chest x-rays.[8] Echocardiography is the most useful diagnostic tool;[2] however, CT and MRI can provide useful information on tumor size, invasion, and localization.[2,9] This imaging combination generally provides an excellent anatomic description for preoperative planning.[1,9]

In our patient, progressive dyspnea was the main symptom, and after a prompt evaluation, an intracardiac mass was identified as the cause of severe cardiac dysfunction. Because of this finding and the clinical condition of the patient, surgery was planned.

Complete resection of the tumor is the treatment of choice and is the only therapy currently seen to influence survival.[8] But because of the highly aggressive behavior and a high incidence of systemic metastases with cardiac angiosarcomas, a complete surgical resection is often hampered.[1] Cardiac angiosarcoma carries a grim prognosis as these tumors are universally fatal with a mean survival time of several months after initial presentation even after successful surgery[2] Chemotherapy is recommended after surgery, even when clear surgical margins are obtained because of the high probability of missed microscopic disease.[1,2]

High clinical suspicion together with an appropriate history, a thorough physical examination, and precise complementary tests are vital for timely diagnosis and proper treatment.

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Primary renal synovial sarcoma – a diagnostic dilemma

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Soft-tissue sarcomas are rare mesenchymal tumors that comprise 1% of all malignancies. Synovial sarcoma accounts for 5%-10% of adult soft-tissue sarcomas and usually occurs in close association with joint capsules, tendon sheaths, and bursa in the extremities of young and middle-aged adults.[1] Synovial sarcomas have been reported in other unusual sites, including the head and neck, thoracic and abdominal wall, retroperitoneum, bone, pleura, and visceral organs such as the lung, prostate, or kidney.[2] Primary renal synovial sarcoma is an extremely rare tumor accounting for <2% of all malignant renal tumors.[3] To the best of our knowledge, fewer than 50 cases of primary renal synovial sarcoma have been described in the English literature.[4] It presents as a diagnostic dilemma because of the dearth of specific clinical and imaging findings and is often confused with benign and malignant tumors. The differential diagnosis includes angiomyolipoma, renal cell carcinoma with sarcomatoid differentiation, metastatic sarcoma, hemangiopericytoma, malignant solitary fibrous tumor, Wilms tumor, and malignant peripheral nerve sheath tumor. Hence, a combination of histomorphologic, immunohistochemical, cytogenetic, and molecular studies that show a unique chromosomal translocation t(X;18)(p11;q11) is imperative in the diagnosis of primary renal synovial sarcoma.[4] In the present report, we present the case of a 38-year-old man who was diagnosed with primary renal synovial sarcoma.

Case presentation and summary

A 38-year-old man with a medical history of gastroesophageal reflux disease and Barrett's esophagus presented to our hospital for the first time with persistent and progressive right-sided flank and abdominal pain that was aggravated after a minor trauma to the back. There was no associated hematuria or dysuria.

Of note is that he had experienced intermittent flank pain for 2 years before this transfer. He had initially been diagnosed at his local hospital close to his home by ultrasound with an angiomyolipoma of 2 × 3 cm arising from the upper pole of his right kidney, which remained stable on repeat sonograms. About 22 months after his initial presentation at his local hospital, the flank pain increased, and a computed-tomographic (CT) scan revealed a perinephric hematoma that was thought to originate from a ruptured angiomyolipoma. He subsequently underwent embolization, but his symptoms recurred soon after. He presented again to his local hospital where CT imaging revealed a significant increase in the size of the retroperitoneal mass, and findings were suggestive of a hematoma. Subsequent angiogram did not reveal active extravasation, so a biopsy was performed.

Before confirmatory pathologic evaluation could be completed, the patient presented to his local hospital again in excruciating pain. A CT scan of his abdomen and pelvis demonstrated a massive subacute on chronic hematoma in the right retroperitoneum measuring 22 × 19 × 18 cm, with calcifications originating from an

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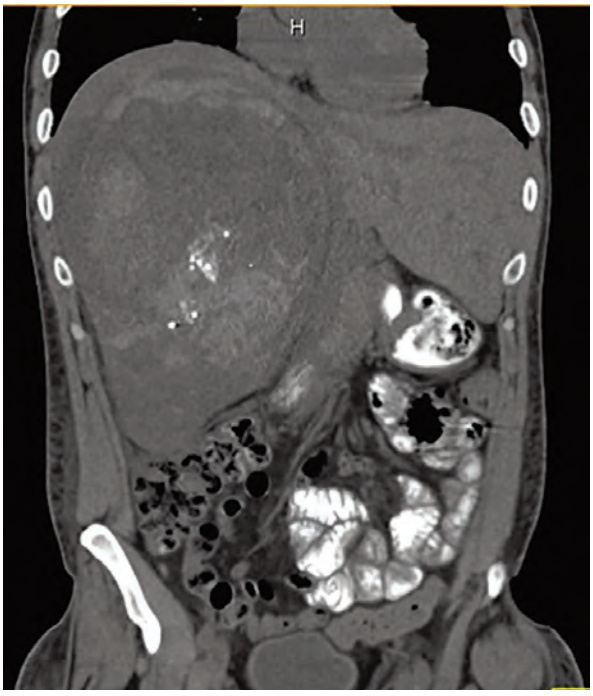


FIGURE 1 Coronal section of a computed-tomographic scan of the abdomen and pelvis, showing large right retroperitoneal hematoma with indwelling punctate calcifications, raising concern for underlying retroperitoneal or renal neoplasia and mass. Right kidney is displaced anteroinferiorly.

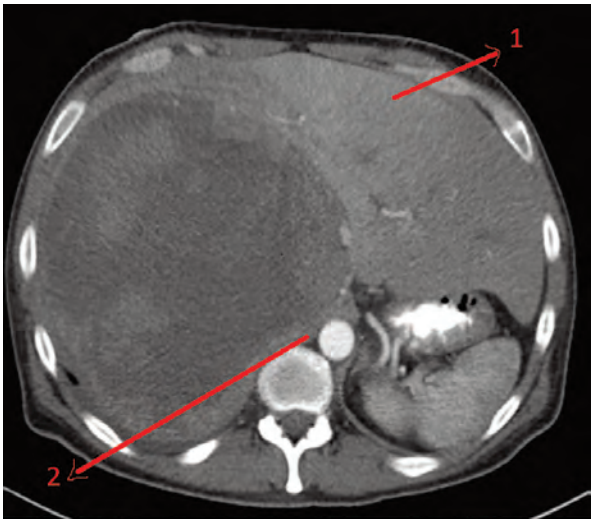


FIGURE 2 Cross-section of the abdomen and pelvis with contrast, showing the liver displaced to the left (1) and the inferior vena cava displaced anteriorly and to the left (2).

upper pole right renal neoplasm. The right kidney was displaced anteroinferiorly, and the inferior vena cava was displaced anteriorly and to the left. The preliminary pathology returned with findings suggestive of sarcoma (FIGURES 1 and 2).

The patient was then transferred to our institution, where he was evaluated by medical and surgical oncology. A CT scan of the chest and magnetic resonance imaging (MRI) of the brain did not reveal metastatic disease. He underwent exploratory laparotomy that involved the resection of a 22-cm retroperitoneal mass, right nephrectomy, right adrenalectomy, partial right hepatectomy, and a full-thickness resection of the right posteroinferior diaphragm followed by mesh repair because of involvement by the tumor.

In its entirety, the specimen was a mass of 26 × 24 × 14 cm. It was sectioned to show extensively necrotic and hemorrhagic variegated white to tan-red parenchyma (FIGURE 3). Histology revealed a poorly differentiated malignant neoplasm composed of round cells with scant amphophilic cytoplasm arranged in solid, variably sized nests separated by prominent thin-walled branching vascular channels (4). The mitotic rate was high. It was determined to be a histologically ungraded sarcoma according to the French Federation of Comprehensive Cancer Centers system of grading soft tissue sarcomas; the margins were indeterminate. Immunohistochemistry was positive for EMA, *TLE1*, and negative for AE1/AE3, S100, *STAT6*, and *Nkx2.2*. Molecular pathology fluorescent in situ hybridization (FISH) analysis demonstrated positivity for *SS18* gene rearrangement (*SS18-SSX1* fusion).

After recovering from surgery, the patient received adjuvant chemotherapy with doxorubicin and ifosfamide. It has been almost 16 months since we first saw this patient. He was started on doxorubicin 20 mg/m^2 on days 1-4, ifosfamide 2,500 mg on days 1-4, and mesna 800 mg on days 1-4, for a total of six cycles. He did well for the first 5 months, after which he developed disease recurrence in the postoperative nephrectomy bed (a biopsy showed it to be recurrent synovial sarcoma) as well as pulmonary nodules, for which he was started on trabectedin 1.5 mg/m^2 every 3 weeks. Two months later, a CT scan showed an increase in the size of his retroperitoneal mass, and the treatment was changed to pazopanib 400 mg daily orally, on which he remained at the time of publication.

Discussion

Synovial sarcoma is the fourth most common type of soft-tissue sarcoma, accounting for 2.5%-10.5% of all

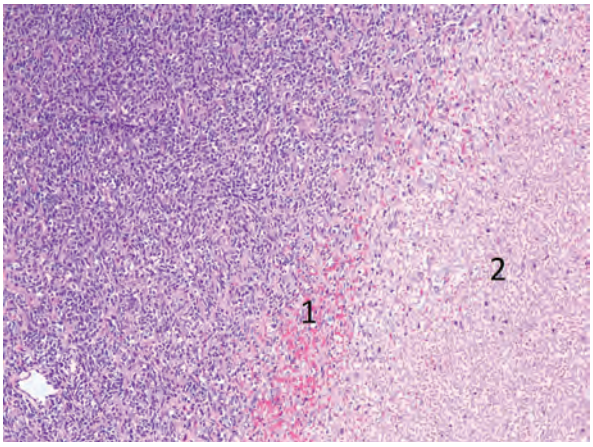


FIGURE 3 Histology of the tumor showing hemorrhage (1) and gross necrosis (2) (H&E, 10×).

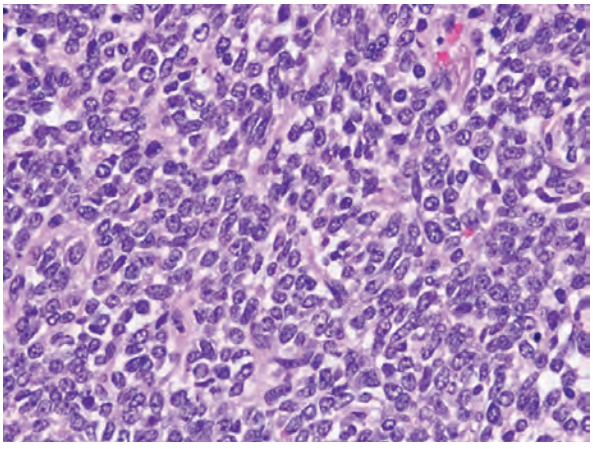


FIGURE 4 Tumor comprising round cells with scant amphiphilic cytoplasm arranged in solid nests separated by prominent thin-walled branching vascular channels (H&E, 40×).

primary soft tissue malignancies worldwide. It occurs most frequently in adolescents and young adults, with most patients presenting between the ages of 15 and 40 years. Median age of presentation is 36 years. Despite the nomenclature, synovial sarcoma does not arise in intra-articular locations but typically occurs in proximity to joints in the extremities. Synovial sarcomas are less commonly described in other sites, including the head and neck, mediastinum, intraperitoneum, retroperitoneum, lung, pleura, and kidney.[4,5] Renal synovial sarcoma was first described in a published article by Argani and colleagues in 2000.[5]

Adult renal mesenchymal tumors are classified into benign and malignant tumors on the basis of the histologic features and clinicobiologic behavior.[6,7] The benign esenchymal renal tumors include angiomyolipoma, leiomyoma, hemangioma, lymphangioma, juxtaglomerular cell tumor, renomedullary interstitial cell tumor (medullary fibroma), lipoma, solitary fibrous tumor, and schwannoma. Malignant renal tumors of mesenchymal origin include leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, solitary fibrous tumor, and synovial sarcoma.

Most of these tumor types cause the same nonspecific symptoms in patients – abdominal pain, flank pain, abdominal fullness, a palpable mass, and hematuria – although they can be clinically silent. The average duration of symptoms in synovial sarcoma is 2 to 4 years.[8] The long duration of symptoms and initial slow growth of synovial sarcomas may give a false impression of a benign process.

A preoperative radiologic diagnosis of primary renal synovial sarcoma may be suspected by analyzing the tumor's growth patterns on CT scans.[9] Renal synovial sarcomas often appear as large, well-defined soft-tissue masses that can extend into the renal pelvis or into the perinephric region.[9] A CT scan may identify soft-tissue calcifications, especially subtle ones in areas where the tumor anatomy is complex. A CT scan may also reveal areas of hemorrhage, necrosis, or cyst formation within the tumor, and can easily confirm bone involvement. Intravenous contrast may help in differentiating the mass from adjacent muscle and neurovascular complex.[9,10] On MRI, renal synovial sarcomas are often described as nonspecific heterogeneous masses, although they may also exhibit heterogeneous enhancement of hemorrhagic areas, calcifications, and air-fluid levels (known as "triple sign") as well as septae. The triple sign may be identified as areas of low, intermediate, and high signal intensity, correlating with areas of hemorrhage, calcification, and air-fluid level.[9,10] Signal intensity is about equal to that of skeletal muscle on T1-weighted MRI and higher than that of subcutaneous fat on T2-weighted MRI.

In the present case, the tumor was initially misdiagnosed as an angiomyolipoma, the most common benign tumor of the kidney. Angiomyolipomas are usually solid triphasic tumors arising from the renal cortex and are composed of three major elements: dysmorphic blood vessels, smooth muscle components, and adipose tissue. When angiomyolipomas are large

enough, they are readily recognized by the identification of macroscopic fat within the tumor, either by CT scan or MRI.[11] When they are small, they may be difficult to distinguish from a small cyst on CT because of volume averaging.

On pathology, synovial sarcoma has dual epithelial and mesenchymal differentiation. They are frequently multilobulated, and areas of necrosis, hemorrhage, and cyst formation are also common. There are three main histologic subtypes of synovial sarcoma: biphasic (20%-30%), monophasic (50%-60%), and poorly differentiated (15%-25%). Poorly differentiated synovial sarcomas are generally epithelioid in morphology, have high mitotic activity (usually 10-20 mitoses/10 high-power field; range is <5 for well-differentiated, low-grade tumors), and can be confused with round cell tumors such as Ewing sarcoma. Poorly differentiated synovial sarcomas are high-grade tumors.

Immunohistochemical studies can confirm the pathological diagnosis. Synovial sarcomas usually stain positive for Bcl2, CD99/Mic2, CD56, Vim, and focally for EMA but negatively for desmin, actin, WT1, S-100, CD34, and CD31.[5] Currently, the gold standard for diagnosis and hallmark for synovial sarcomas are the t (X;18) translocation and *SYT-SSX* gene fusion products (*SYT-SSX1* in 67% and *SYT-SSX2* in 33% of cases). These can be detected either by FISH or reverse-transcription polymerase chain reaction. This genetic alteration is identified in more than 90% of synovial sarcomas and is highly specific.

The role of *SYT-SSX* gene fusion in the pathogenesis of synovial sarcoma is an active area of investigation. The fusion of SYT with SSX translates into a fusion protein that binds to the transcription activator SMARCA4 that is involved in chromatin remodeling, thus displacing both the wildtype SYT and the tumor suppressor gene *SMARCB1*. The modified protein complex then binds at several superenhancer loci, unlocking suppressed genes such as *Sox2*, which is known to be necessary for synovial sarcoma proliferation. Alterations in *SMARCB1* are involved in several cancer types, implicating this event as a driver of these malignancies.[12] This results in a global alteration in chromatin remodeling that needs to be better understood to design targeted therapies.

The clinical course of synovial sarcoma, regardless of the tissue of origin, is typically poor. Multiple clinical and pathologic factors, including tumor size, location, patient age, and presence of poorly differentiated areas, are thought to have prognostic significance. A tumor size of more than 5 cm at presentation has the greatest impact on prognosis, with studies showing 5-year survival rates of 64% for patients with tumors smaller than 5 cm and 26% for patients with masses greater than 5 cm.[13,14] High-grade synovial sarcoma is favored in tumors that have cystic components, hemorrhage, and fluid levels and the triple sign.

Patients with tumors in the extremities have a more favorable prognosis than do those with lesions in the head and neck area or axially, a feature that likely reflects better surgical control available for extremity lesions. Patient age of less than 15-20 years is also associated with a better long-term prognosis.[15,16] Varela-Duran and Enzinger[17] reported that the presence of extensive calcifications suggests improved long-term survival, with 5-year survival rates of 82% and decreased rates of local recurrence (32%) and metastatic disease (29%). The poorly differentiated subtype is associated with a worsened prognosis, with a 5-year survival rate of 20% through 30%.[18,19] Other pathologic factors associated with worsened prognosis include presence of rhabdoid cells, extensive tumor necrosis, high nuclear grade, *p53* mutations, and high mitotic rate (>10 mitoses/10 high-power field). More recently, the gene fusion type *SYT-SSX2* (more common in monophasic lesions) has been associated with an improved prognosis, compared with that for *SYT-SSX1*, and an 89% metastasis-free survival.[20]

Although there are no guidelines for the treatment of primary renal synovial sarcoma because of the limited number of cases reported, surgery is considered the first choice. Adjuvant chemotherapy with an anthracycline (doxorubicin or epirubicin) combined with ifosfamide has been the most frequently used regimen in published cases, especially in those in which patients have poor prognostic factors as mentioned above.

Overall, the 5-year survival rate ranges from 36% to 76%.[14] The clinical course of synovial sarcoma is characterized by a high rate of local recurrence (30%-50%) and metastatic disease (41%). Most metastases occur within the first 2-5 years after treatment cessation. Metastases are present in 16%-25% of patients at their initial presentation, with the most frequent metastatic site being the lung, followed by the lymph nodes (4%-18%) and bone (8%-11%).

Continued on page 19

Offer your patients with advanced liposarcoma a treatment that provides a **SIGNIFICANT OVERALL SURVIVAL BENEFIT**[1]

HALAVEN® improved median overall survival vs dacarbazine (15.6 months vs 8.4 months)[1]

Indication

Liposarcoma

HALAVEN (eribulin mesylate) Injection is indicated for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen.

Selected Safety Information

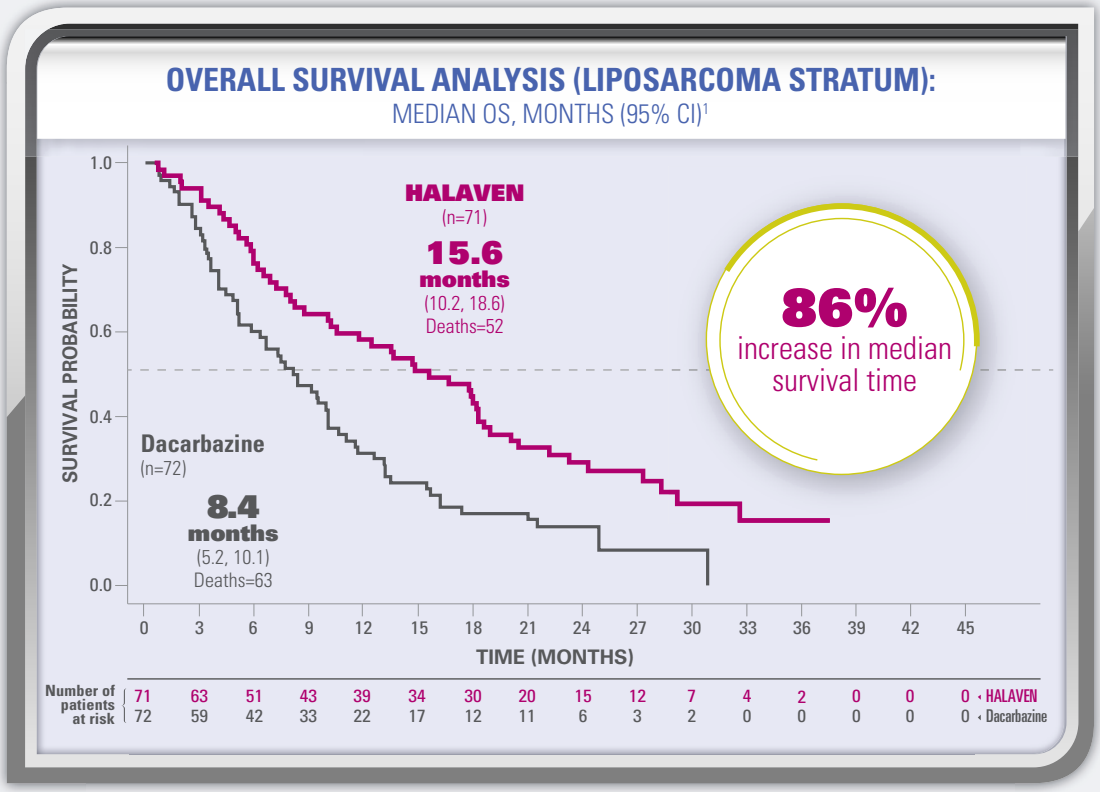
Warnings and Precautions

Neutropenia: Severe neutropenia (ANC <500/mm^3) lasting >1 week occurred in 12% of patients with liposarcoma or leiomyosarcoma. Febrile neutropenia occurred in 0.9% of patients and fatal neutropenic sepsis occurred in 0.9% of patients. Monitor complete blood cell counts prior to each dose, and increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting >7 days.

Please see all Selected Safety Information throughout and adjacent brief summary of HALAVEN full Prescribing Information.

Halaven®
(eribulin mesylate) Injection | 0.5 mg per mL

The first and only single agent to show a significant survival advantage in a Phase III study of patients with advanced liposarcoma[2]



The efficacy and safety of HALAVEN were evaluated in an open-label, randomized (1:1), multicenter, active-controlled trial. Eligible patients were required to have unresectable, locally advanced, or metastatic liposarcoma or leiomyosarcoma, at least 2 prior systemic chemotherapies (one of which must have included an anthracycline), and disease progression within 6 months of the most recent chemotherapy regimen. Patients were randomized to HALAVEN 1.4 mg/m^2 administered intravenously on Days 1 and 8 of a 21-day cycle or to dacarbazine at a dose of 850 mg/m^2, 1,000 mg/m^2, or 1,200 mg/m^2 administered intravenously every 21 days (dacarbazine dose was selected by the investigator prior to randomization). Treatment continued until disease progression or unacceptable toxicity. Randomization was stratified by histology (liposarcoma or leiomyosarcoma), number of prior therapies (2 vs >2), and geographic region. The most common (>40%) prior systemic chemotherapies were doxorubicin (90%), ifosfamide (62%), gemcitabine (59%), trabectedin (50%), and docetaxel (48%).[1]

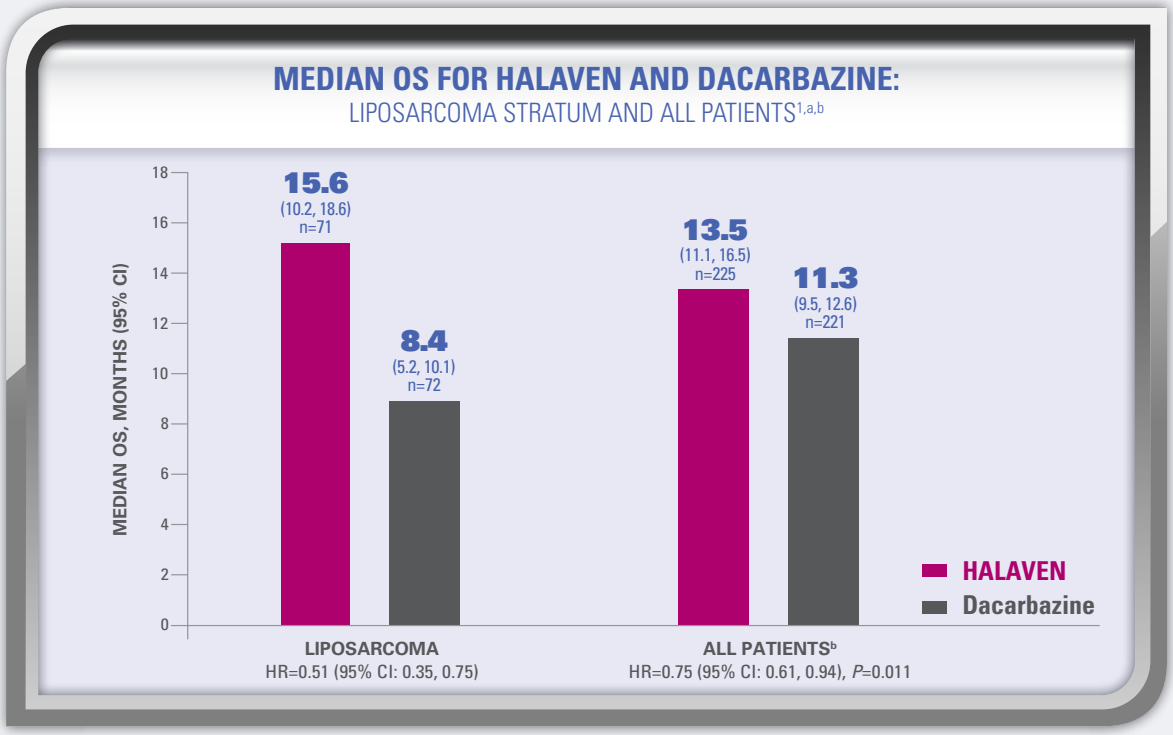
OS=overall survival; CI=confidence interval.

HALAVEN was studied in patients with dedifferentiated, myxoid/round cell, and pleomorphic liposarcoma subtypes[1]

Selected Safety Information

Peripheral Neuropathy: Grade 3 peripheral neuropathy occurred in 3.1% of patients with liposarcoma and leiomyosarcoma receiving HALAVEN and neuropathy lasting more than 60 days occurred in 58% (38/65) of patients who had neuropathy at the last treatment visit. Patients should be monitored for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy until resolution to Grade 2 or less.

Treatment effects of HALAVEN® were demonstrated in patients with advanced liposarcoma based on the preplanned, exploratory subgroup analysis of OS and PFS[1]



PFS=progression-free survival; HR=hazard ratio.

[a]Efficacy data from 1 study site enrolling 6 patients were excluded.

[b]All patients=liposarcoma and leiomyosarcoma.

- There was no evidence of efficacy of HALAVEN in patients with advanced or metastatic leiomyosarcoma in this trial[1]

Secondary endpoint: PFS[1]

- Median PFS in the liposarcoma stratum was 2.9 months (95% CI: 2.6, 4.8) for patients receiving HALAVEN vs 1.7 months (95% CI: 1.4, 2.6) for patients receiving dacarbazine, HR=0.52 (95% CI: 0.35, 0.78)
- Median PFS in all patients was 2.6 months (95% CI: 2.0, 2.8) for patients receiving HALAVEN vs 2.6 months (95% CI: 1.7, 2.7) for patients receiving dacarbazine, HR=0.86 (95% CI: 0.69, 1.06)

Selected Safety Information

Embryo-Fetal Toxicity: HALAVEN can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with HALAVEN and for at least 2 weeks following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with HALAVEN and for 3.5 months following the final dose.

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Learn more about the efficacy of HALAVEN at
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Selected Safety Information

QT Prolongation: Monitor for prolonged QT intervals in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating HALAVEN and monitor these electrolytes periodically during therapy. Avoid in patients with congenital long QT syndrome.

Adverse Reactions

In patients with liposarcoma and leiomyosarcoma receiving HALAVEN, the most common adverse reactions (≥25%) reported in patients receiving HALAVEN were fatigue (62%), nausea (41%), alopecia (35%), constipation (32%), peripheral neuropathy (29%), abdominal pain (29%), and pyrexia (28%). The most common (≥5%) Grade 3-4 laboratory abnormalities reported in patients receiving HALAVEN were neutropenia (32%), hypokalemia (5.4%), and hypocalcemia (5%). Neutropenia (4.9%) and pyrexia (4.5%) were the most common serious adverse reactions. The most common adverse reactions resulting in discontinuation were fatigue and thrombocytopenia (0.9% each).

Use in Specific Populations

Lactation: Because of the potential for serious adverse reactions in breastfed infants from eribulin mesylate, advise women not to breastfeed during treatment with HALAVEN and for 2 weeks after the final dose.

Hepatic and Renal Impairment: A reduction in starting dose is recommended for patients with mild or moderate hepatic impairment and/or moderate or severe renal impairment.

References: 1. HALAVEN [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2016. **2.** Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet.* 2016;387(10028):1629-1637.

Please see all Selected Safety Information throughout and adjacent brief summary of HALAVEN full Prescribing Information.

Halaven® (eribulin mesylate) Injection | 0.5 mg per mL

HALAVEN® (eribulin mesylate) Injection, for intravenous use

BRIEF SUMMARY – See package insert for full prescribing information.

DOSAGE AND ADMINISTRATION

Recommended Dose: The recommended dose of HALAVEN is 1.4 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

The recommended dose of HALAVEN in patients with mild hepatic impairment (Child-Pugh A) is 1.1 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

The recommended dose of HALAVEN in patients with moderate hepatic impairment (Child-Pugh B) is 0.7 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

The recommended dose of HALAVEN in patients with moderate or severe renal impairment (creatinine clearance (CLcr) 15-49 mL/min) is 1.1 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

Dose Modification: Assess for peripheral neuropathy and obtain complete blood cell counts prior to each dose.

Recommended dose delays

- Do not administer HALAVEN on Day 1 or Day 8 for any of the following:
  - ANC < 1,000/mm^3
  - Platelets < 75,000/mm^3
  - Grade 3 or 4 non-hematological toxicities.
- The Day 8 dose may be delayed for a maximum of 1 week.
  - If toxicities do not resolve or improve to ≤ Grade 2 severity by Day 15, omit the dose.
  - If toxicities resolve or improve to ≤ Grade 2 severity by Day 15, administer HALAVEN at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

Recommended dose reductions

- If a dose has been delayed for toxicity and toxicities have recovered to Grade 2 severity or less, resume HALAVEN at a reduced dose as set out in Table 1.
- Do not re-escalate HALAVEN dose after it has been reduced.

Table 1: Recommended Dose Reductions

Event Description	Recommended HALAVEN Dose
Permanently reduce the 1.4 mg/m^2 HALAVEN dose for any of the following:	1.1 mg/m^2
ANC <500/mm^3 for >7 days	
ANC <1,000 /mm^3 with fever or infection	
Platelets <25,000/mm^3	
Platelets <50,000/mm^3 requiring transfusion	
Non-hematologic Grade 3 or 4 toxicities	
Omission or delay of Day 8 HALAVEN dose in previous cycle for toxicity	
Occurrence of any event requiring permanent dose reduction while receiving 1.1 mg/m^2	0.7 mg/m^2
Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m^2	Discontinue HALAVEN

ANC = absolute neutrophil count.
Toxicities graded in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

WARNINGS AND PRECAUTIONS

Neutropenia: In Study 1, severe neutropenia (ANC < 500/mm^3) lasting more than one week occurred in 12% (62/503) of patients with metastatic breast cancer, leading to discontinuation in <1% of patients. Febrile neutropenia (fever ≥38.5°C with Grade 3 or 4 neutropenia) occurred in 5% (23/503) of patients; two patients (0.4%) died from complications of febrile neutropenia.

In Study 1, patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × ULN (upper limit of normal) experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal aminotransferase levels. Patients with bilirubin > 1.5 × ULN also had a higher incidence of Grade 4 neutropenia and febrile neutropenia.

In Study 2, severe neutropenia (ANC < 500/mm^3) lasting more than one week occurred in 12% (26/222) of patients with liposarcoma or leiomyosarcoma. Febrile neutropenia occurred in 0.9% of patients treated with HALAVEN and fatal neutropenic sepsis in 0.9%.

Monitor complete blood counts prior to each dose; increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration of HALAVEN and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days. Clinical studies of HALAVEN did not include patients with baseline neutrophil counts below 1,500/mm^3.

Peripheral Neuropathy: In Study 1, Grade 3 peripheral neuropathy occurred in 8% (40/503) of patients, and Grade 4 in 0.4% (2/503) of patients with metastatic breast cancer (MBC). Peripheral neuropathy was the most common toxicity leading to discontinuation of HALAVEN (5% of patients; 24/503) in Study 1. Neuropathy lasting more than one year occurred in 5% (26/503) of patients. Twenty-two percent (109/503) of patients developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days).

In Study 2, Grade 3 peripheral neuropathy occurred in 3.1% (7/223) of HALAVEN-treated patients. Peripheral neuropathy led to discontinuation of HALAVEN in 0.9% of patients. The median time to first occurrence of peripheral neuropathy of any severity was 5 months (range: 3.5 months to 9 months). Neuropathy lasting more than 60 days occurred in 58% (38/65) of patients. Sixty three percent (41/65) had not recovered within a median follow-up duration of 6.4 months (range: 27 days to 29 months).

Monitor patients closely for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy, until resolution to Grade 2 or less.

Embryo-Fetal Toxicity: Based on findings from an animal reproduction study and its mechanism of action, HALAVEN can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of HALAVEN in pregnant women. In animal reproduction studies, eribulin mesylate caused embryo-fetal toxicity when administered to pregnant rats during organogenesis at doses below the recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with HALAVEN and for at least 2 weeks following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with HALAVEN and for 3.5 months following the final dose.

QT Prolongation: In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating HALAVEN and monitor these electrolytes periodically during therapy. Avoid HALAVEN in patients with congenital long QT syndrome.

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

The following adverse reactions are discussed in detail in other sections of the labeling:

- Neutropenia
- Peripheral neuropathy
- QT prolongation

In clinical trials, HALAVEN has been administered to 1963 patients including 467 patients exposed to HALAVEN for 6 months or longer. The majority of the 1963 patients were women (92%) with a median age of 55 years (range: 17 to 85 years). The racial and ethnic distribution was White (72%), Black (4%), Asian (9%), and other (3%).

Metastatic Breast Cancer: The most common adverse reactions (≥25%) reported in patients receiving HALAVEN were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions reported in patients receiving HALAVEN were febrile neutropenia (4%) and neutropenia (2%). The most common adverse reaction resulting in discontinuation of HALAVEN was peripheral neuropathy (5%).

The adverse reactions described in Table 2 were identified in 750 patients treated in Study 1. In Study 1, patients were randomized (2:1) to receive either HALAVEN (1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle) or single agent treatment chosen by their physician (control group). A total of 503 patients received HALAVEN and 247 patients in the control group received therapy consisting of chemotherapy [total 97% (anthracyclines 10%, capecitabine 18%, gemcitabine 19%, taxanes 15%, vinorelbine 25%, other chemotherapies 10%)] or hormonal therapy (3%). The median duration of exposure was 118 days for patients receiving HALAVEN and 63 days for patients receiving control therapy. Table 2 reports the most common adverse reactions occurring in at least 10% of patients in either group.

Table 2: Adverse Reactions[a] with a Per-Patient Incidence of at Least 10% in Study 1

Adverse Reactions	HALAVEN n=503		Control Group n=247	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Blood and lymphatic system disorders[b]				
Neutropenia	82%	57%	53%	23%
Anemia	58%	2%	55%	4%
Nervous system disorders				
Peripheral neuropathy[c]	35%	8%	16%	2%
Headache	19%	<1%	12%	<1%
General disorders				
Asthenia/Fatigue	54%	10%	40%	11%
Pyrexia	21%	<1%	13%	<1%
Mucosal inflammation	9%	1%	10%	2%
Gastrointestinal disorders				
Nausea	35%	1%	28%	3%
Constipation	25%	1%	21%	1%
Vomiting	18%	1%	18%	1%
Diarrhea	18%	0	18%	0
Musculoskeletal and connective tissue disorders				
Arthralgia/Myalgia	22%	<1%	12%	1%
Back pain	16%	1%	7%	2%
Bone pain	12%	2%	9%	2%
Pain in extremity	11%	1%	10%	1%
Metabolism and nutrition disorders				
Decreased weight	21%	1%	14%	<1%
Anorexia	20%	1%	13%	1%
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	16%	4%	13%	4%
Cough	14%	0	9%	0
Skin and subcutaneous tissue disorders				
Alopecia	45%	NA[d]	10%	NA[d]
Infections				
Urinary Tract Infection	10%	1%	5%	0

[a] adverse reactions were graded per National Cancer Institute Criteria for Adverse Events version 4.0.
[b] based upon laboratory data.
[c] includes peripheral neuropathy, peripheral sensorimotor neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.
[d] not applicable; (grading system does not specify > Grade 2 for alopecia).

Cytopenias: Grade 3 neutropenia occurred in 28% (143/503) of patients who received HALAVEN in Study 1, and 29% (144/503) of patients experienced Grade 4 neutropenia. Febrile neutropenia occurred in 5% (23/503) of patients; two patients (0.4%) died from complications of febrile neutropenia. Dose reduction due to neutropenia was required in 12% (62/503) of patients and discontinuation was required in <1% of patients. The mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (<500/mm^3) was 8 days. Grade 3 or greater thrombocytopenia occurred in 1% (7/503) of patients. G-CSF (granulocyte colony-stimulating factor) or GM-CSF (granulocyte–macrophage colony-stimulating factor) was used in 19% of patients who received HALAVEN.

Peripheral Neuropathy: In Study 1, 17% of enrolled patients had Grade 1 peripheral neuropathy and 3% of patients had Grade 2 peripheral neuropathy at baseline. Dose reduction due to peripheral neuropathy was required by 3% (14/503) of patients who received HALAVEN. Four percent (20/503) of patients experienced peripheral motor neuropathy of any grade and 2% (8/503) of patients developed Grade 3 peripheral motor neuropathy.

Liver Function Test Abnormalities: Among patients with Grade 0 or 1 ALT levels at baseline, 18% of HALAVEN-treated patients experienced Grade 2 or greater ALT elevation. One HALAVEN-treated patient without documented liver metastases had concomitant Grade 2 elevations in bilirubin and ALT; these abnormalities resolved and did not recur with re-exposure to HALAVEN.

Less Common Adverse Reactions: The following additional adverse reactions were reported in ≥5% to <10% of the HALAVEN-treated group:

- **Eye Disorders:** increased lacrimation
- **Gastrointestinal Disorders:** dyspepsia, abdominal pain, stomatitis, dry mouth
- **General Disorders and Administration Site Conditions:** peripheral edema
- **Infections and Infestations:** upper respiratory tract infection
- **Metabolism and Nutrition Disorders:** hypokalemia
- **Musculoskeletal and Connective Tissue Disorders:** muscle spasms, muscular weakness
- **Nervous System Disorders:** dysgeusia, dizziness
- **Psychiatric Disorders:** insomnia, depression
- **Skin and Subcutaneous Tissue Disorders:** rash

Liposarcoma: The safety of HALAVEN was evaluated in Study 2, an open-label, randomized, multicenter, active-controlled trial, in which patients were randomized (1:1) to receive either HALAVEN 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle or dacarbazine at doses of 850 mg/m^2 (20%), 1000 mg/m^2 (64%), or 1200 mg/m^2 (16%) every 3 weeks. A total of 223 patients received HALAVEN and 221 patients received dacarbazine. Patients were required to have received at least two prior systemic chemotherapy regimens. The trial excluded patients with pre-existing ≥ Grade 3 peripheral neuropathy, known central nervous system metastasis, elevated serum bilirubin or significant chronic liver disease, history of myocardial infarction within 6 months, history of New York Heart Association Class II or IV heart failure, or cardiac arrhythmia requiring treatment. The median age of the safety population in Study 2 was 56 years (range: 24 to 83 years); 67% female; 73% White, 3% Black or African American, 8% Asian/Pacific Islander, and 15% unknown; 99% received prior anthracycline-containing regimen; and 99% received ≥ 2 prior regimens. The median duration of exposure was 2.3 months (range: 21 days to 26 months) for patients receiving HALAVEN.

The most common adverse reactions (≥25%) reported in patients receiving HALAVEN were fatigue, nausea, alopecia, constipation, peripheral neuropathy, abdominal pain, and pyrexia. The most common (≥5%) Grade 3-4 laboratory abnormalities reported in patients receiving HALAVEN were neutropenia, hypokalemia, and hypocalcemia. The most common serious adverse reactions reported in patients receiving HALAVEN were neutropenia (4.9%) and pyrexia (4.5%). Permanent discontinuation of HALAVEN for adverse reactions occurred in 8% of patients. The most common adverse reactions resulting in discontinuation of HALAVEN were fatigue and thrombocytopenia (0.9% each). Twenty-six percent of patients required at least one dose reduction. The most frequent adverse reactions that led to dose reduction were neutropenia (18%) and peripheral neuropathy (4.0%).

Table 3 summarizes the incidence of adverse reactions occurring in at least 10% of patients in the HALAVEN-treated arm in Study 2.

Table 3: Adverse Reactions[a] Occurring in ≥10% (all Grades) of Patients Treated on the HALAVEN arm and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% for All Grades or ≥2% for Grades 3 and 4) (Study 2)[b]

Adverse Reaction	HALAVEN n=223		Dacarbazine n=221	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Nervous system disorders				
Peripheral Neuropathy[c]	29%	3.1%	8%	0.5%
Headache	18%	0%	10%	0%
General disorders				
Pyrexia	28%	0.9%	14%	0.5%
Gastrointestinal disorders				
Constipation	32%	0.9%	26%	0.5%
Abdominal pain[d]	29%	1.8%	23%	4.1%
Stomatitis	14%	0.9%	5%	0.5%
Skin and subcutaneous tissue disorders				
Alopecia	35%	NA[e]	2.7%	NA[e]
Infections				
Urinary tract infection	11%	2.2%	5%	0.5%

[a] Adverse reactions were graded per National Cancer Institute Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).
[b] Safety data from one study site enrolling six patients were excluded.
[c] Includes peripheral neuropathy, peripheral sensorimotor neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.
[d] Includes abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort.
[e] Not applicable; (grading system does not specify > Grade 2 for alopecia).

Other clinically important adverse reactions occurring in ≥10% of the HALAVEN-treated patients were:

- **Gastrointestinal Disorders:** nausea (41%); vomiting (19%), diarrhea (17%)
- **General Disorders:** asthenia/fatigue (62%); peripheral edema (12%)
- **Metabolism and Nutrition Disorders:** decreased appetite (19%)
- **Musculoskeletal and Connective Tissue Disorders:** arthralgia/myalgia (16%); back pain (16%)
- **Respiratory Disorders:** cough (18%)

Less Common Adverse Reactions: The following additional clinically important adverse reactions were reported in ≥5% to <10% of the HALAVEN-treated group:

- **Blood and Lymphatic System Disorders:** thrombocytopenia
- **Eye Disorders:** increased lacrimation
- **Gastrointestinal Disorders:** dyspepsia
- **Metabolism and Nutrition Disorders:** hyperglycemia
- **Musculoskeletal and Connective Tissue Disorders:** muscle spasms, musculoskeletal pain
- **Nervous System Disorders:** dizziness, dysgeusia
- **Psychiatric Disorders:** insomnia, anxiety
- **Respiratory, Thoracic, and Mediastinal Disorders:** oropharyngeal pain
- **Vascular Disorders:** hypotension

Table 4: Laboratory Abnormalities Occurring in ≥10% (all Grades) of Patients Treated on the HALAVEN arm and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% for All Grades or ≥2% for Grades 3 and 4)[a] (Study 2)[†]

Laboratory Abnormality	Halaven		Dacarbazine	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Hematology				
Anemia	70%	4.1%	52%	6%
Neutropenia	63%	32%	30%	8.9%
Chemistry				
Increased alanine aminotransferase (ALT)	43%	2.3%	28%	2.3%
Increased aspartate aminotransferase (AST)	36%	0.9%	16%	0.5%
Hypokalemia	30%	5.4%	14%	2.8%
Hypocalcemia	28%	5%	18%	1.4%
Hypophosphatemia	20%	3.2%	11%	1.4%

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study measurement and at least 1 grade increase from baseline.Halaven group (range 221-222) and dacarbazine group (range 214-215)
[†] Laboratory results were graded per NCI CTCAE v4.03.

Postmarketing Experience: The following adverse drug reactions have been identified during post-approval of HALAVEN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **Blood and Lymphatic System Disorders:** lymphopenia
- **Gastrointestinal Disorders:** pancreatitis
- **Hepatobiliary Disorders:** hepatotoxicity
- **Immune System Disorders:** drug hypersensitivity
- **Infections and Infestations:** pneumonia, sepsis/neutropenic sepsis
- **Metabolism and Nutrition Disorders:** hypomagnesemia, dehydration
- **Respiratory, thoracic and mediastinal disorders:** interstitial lung disease
- **Skin and Subcutaneous Tissue Disorders:** pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary: Based on findings from an animal reproduction study and its mechanism of action, HALAVEN can cause fetal harm when administered to a pregnant woman. There are no available data on the use of HALAVEN during pregnancy. In an animal reproduction study, eribulin mesylate caused embryo-fetal toxicity when administered to pregnant rats during organogenesis at doses below the recommended human dose. Advise pregnant women of the potential risk to a fetus.

The estimated background risks of major birth defects and miscarriage for the indicated populations are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: In an embryo-fetal developmental toxicity study, pregnant rats received intravenous infusion of eribulin mesylate during organogenesis (Gestation Days 8, 10, and 12) at doses approximately 0.04, 0.13, 0.43 and 0.64 times the recommended human dose, based on body surface area. Increased abortion and severe fetal external or soft tissue malformations, including the absence of a lower jaw and tongue, or stomach and spleen, were observed at doses 0.64 times the recommended human dose of 1.4 mg/m^2 based on body surface area. Increased embryo-fetal death/resorption, reduced fetal weights, and minor skeletal anomalies consistent with developmental delay were also reported at doses at or above a maternally toxic dose of approximately 0.43 times the recommended human dose.

Females and Males of Reproductive Potential

Contraception

Females: Based on findings from an animal reproduction study and its mechanism of action, HALAVEN can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with HALAVEN and for at least 2 weeks following the final dose.

Males: Based on its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during treatment with HALAVEN and for 3.5 months following the final dose.

Infertility

Males: Based on animal data, HALAVEN may result in damage to male reproductive tissues leading to impaired fertility of unknown duration.

Pediatric Use: The safety and effectiveness of HALAVEN in pediatric patients below the age of 18 years have not been established.

Hepatic Impairment: Administration of HALAVEN at a dose of 1.1 mg/m^2 to patients with mild hepatic impairment and 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m^2 to patients with normal hepatic function. Therefore, a lower starting dose of 1.1 mg/m^2 is recommended for patients with mild hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh B). HALAVEN was not studied in patients with severe hepatic impairment (Child-Pugh C).

Renal Impairment: For patients with moderate or severe renal impairment (CLcr 15-49 mL/min), reduce the starting dose to 1.1 mg/m^2.

OVERDOSAGE

Overdosage of HALAVEN has been reported at approximately 4 times the recommended dose, which resulted in Grade 3 neutropenia lasting seven days and a Grade 3 hypersensitivity reaction lasting one day.

There is no known antidote for HALAVEN overdose.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies have not been conducted with eribulin mesylate. Eribulin mesylate was not mutagenic in *in vitro* bacterial reverse mutation assays (Ames test). Eribulin mesylate was positive in mouse lymphoma mutagenesis assays, and was clastogenic in an *in vivo* rat bone marrow micronucleus assay.

Fertility studies have not been conducted with eribulin mesylate in humans or animals; however, nonclinical findings in repeat-dose dog and rat toxicology studies suggest that male fertility may be compromised by treatment with eribulin mesylate. Rats exhibited testicular toxicity (hypocellularity of seminiferous epithelium with hypospermia/aspermia) following dosing with eribulin mesylate at or above 0.43 times the recommended human dose (based on body surface area) given once weekly for 3 weeks, or at or above 0.21 times the recommended human dose (based on body surface area) given once weekly for 3 out of 5 weeks, repeated for 6 cycles. Testicular toxicity was also observed in dogs given 0.64 times the recommended human dose (based on body surface area) weekly for 3 out of 5 weeks, repeated for 6 cycles.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Neutropenia: Advise patients to contact their health care provider for a fever of 100.5°F or greater or other signs or symptoms of infection such as chills, cough, or burning or pain on urination.

Peripheral Neuropathy: Advise patients to inform their healthcare providers of new or worsening numbness, tingling and pain in their extremities.

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy.
- Advise females of reproductive potential to use effective contraception during treatment with HALAVEN and for at least 2 weeks after the final dose.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with HALAVEN and for 3.5 months following the final dose.

Lactation: Advise women not to breastfeed during treatment with HALAVEN and for 2 weeks after the final dose.

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Conclusion

Primary renal synovial sarcoma is extremely rare, and preoperative diagnosis is difficult in the absence of specific clinical or imaging findings. A high index of suspicion combined with pathologic, immunohistochemical, cytogenetic, and molecular studies is essential for accurate diagnosis and subsequent treatment planning. The differential diagnosis of renal synovial sarcoma can be extensive, and our experience with this patient illustrates the diagnostic dilemma associated with renal synovial sarcoma.

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This issue of *The Sarcoma Journal* features reports from the annual meeting of the Connective Tissue Oncology Society held in Rome, Nov. 14-17, 2018.

This year's annual meeting brought new insights on intimal sarcoma. Four studies in a featured session at the meeting examined both current and novel treatments for this rare and aggressive cancer, and emphasized the need for new therapies.

Anthracycline-based regimens as preferred first-line therapies

Anthracycline-based regimens were the preferred first-line therapies used in 83 adults with intimal sarcomas in a retrospective study of data from the World Sarcoma Network, reported by Anna Maria Frezza, MD, of the, Fondazione IRCCS Istituto Nazionale Tumori, Milan, and her colleagues.

The researchers described the experience with anthracycline-based regimens as well as gemcitabine-based regimens and pazopanib among MDM2-positive patients with intimal sarcomas treated at 16 sarcoma reference centers in Europe, the United States, and Japan. Their findings speak to the need for new active drugs, which they said should target the MDM2 and CDK4 overexpression seen in patients with this rare sarcoma.

Of the 83 patients studied, nearly all (76 patients) initially received an anthracycline-based regimen. Gemcitabine-based regimens were used in 29 patients and pazopanib in 10 patients; 20 of the 39 patients received more than one treatment.

Anthracycline-based regimens were associated with a 12-month progression-free survival rate of 38% in 76 patients with intimal sarcomas. All of the 76 patients received anthracycline regimens as their initial systemic therapy; 27 were treated for localized disease with a curative intent and the remaining 49 had advanced disease. The researchers also noted that anthracycline regimens were safely used in 22 patients with cardiac intimal sarcomas, as none of them died of cardiotoxicity.

Based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 measures, the overall response rate was 37% in 57 evaluable patients: 3 patients had a complete response, 18 had a partial response, 27 had stable disease, and 9 had progressive disease. For those with localized disease, the median time to progression was 14 months, and overall survival time was 51 months. For patients with advanced disease, the median time to progression was 8 months and overall survival was 22 months.

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Outcomes were less favorable when patients were treated with gemcitabine regimens or pazopanib. In most of these cases, however, patients were either on their second (gemcit-

abine) or third (pazopanib) lines of therapy.

In the gemcitabine group, 2 patients were treated for localized disease with curative intent and 27 for advanced disease. Of 28 evaluable patients, best response was partial remission in 3, stable disease in 8, and progressive disease in 17. In the 27 patients with advanced disease, the median progression-free survival time was 3 months and overall survival was 13 months.

All 10 patients in the pazopanib group had advanced disease and had undergone a median of two prior lines of therapy. One patient had a partial remission, three had stable disease, and six had progressive disease. The median progression-free survival was 4 months and median overall survival was 12 months.

Rarest of the rare: Primary malignant sarcoma of the heart

Luke Smith of the School of Clinical Medicine, University of Cambridge, England, detailed the experience of 28 patients diagnosed with sarcomas of the heart or great vessels at the university's Royal Papworth Hospital and Addenbrooke's Hospital during 2000-2018.

Based on this retrospective review, surgery offers the best chance for long-term survival for these patients, who would otherwise experience progressive heart failure and die. Adjuvant chemotherapy and radiation therapy might be able to extend their survival and improve symptomatic relief, he said, but these outcomes have not been prospectively studied.

Typically, the patients in this series, 20 with pulmonary artery sarcoma and 8 with cardiac sarcoma, presented with symptoms mimicking heart failure, pulmonary hypertension, or thromboembolic disease. Nearly all, 24 patients, reported breathlessness. Eight patients had chest pain or tightness, six had cough, six had peripheral edema, six had constitutional symptoms, three had hemoptysis, and one had a TIA. Only one patient had a seriously impaired left ventricular ejection fraction of less than 30%. LVEF was normal at 55% or more in 16 patients, and moderately impaired at 30% or more in 10 patients.

Median overall survival was 17 months. The 19 patients who underwent surgical resection of their primary tumor survived much longer than the 10 patients who did not – median overall survival of 20 months vs. 9 months – but this finding may simply reflect more advanced disease in patients with inoperable disease. There were 3 perioperative deaths among the 19 patients who underwent surgery: 14 with pulmonary artery sarcomas had pulmonary endarterectomy and 4 with cardiac sarcomas underwent resection or maximal debulking of their tumors.

Based on the retrospective study, adjuvant chemotherapy and radiation were safe and may lead to better outcomes for these patients. Active chemotherapy regimens in the palliative setting included paclitaxel (angiosarcoma) and anthracycline ± ifosfamide.

Nine patients received postsurgical chemotherapy, and after completion five also had radiotherapy. The three cardiac sarcoma patients who had surgical resection with curative intent were treated with adjuvant ifosfamide-based chemotherapy (with close monitoring of fluid balance), and showed no evidence of disease on last follow-ups. One patient received postoperative paclitaxel following maximal debulking of a cardiac angiosarcoma.

Postsurgical anthracycline with and without ifosfamide were used in patients with pulmonary artery sarcomas with no clinical cardiotoxicity. Although the median overall survival for patients who received postoperative chemo- and radiotherapy was 28 months and the median overall survival with surgery alone was 9 months, the difference was not statistically significant.

In the palliative setting, partial responses were observed with paclitaxel and anthracycline (including liposomal doxorubicin) in patients with cardiac angiosarcoma. For pulmonary artery intimal sarcomas, partial responses were achieved with anthracycline with and without ifosfamide.

Radiotherapy provided good local control.

The longest-surviving pulmonary artery sarcoma patient, at 103 months, had pulmonary artery endarterectomy, followed by adjuvant epirubicin and radiotherapy. She developed lung metastases 7 years later and was treated with radiofrequency ablation. The longest-surviving cardiac sarcoma patient, at 24 months, remains disease free. He had surgery to resect a high-grade undifferentiated sarcoma with involved margins, followed by adjuvant ifosfamide and radiotherapy to the right atrium.

Therapeutically exploitable genetic aberrations in intimal sarcomas

Imatinib and olaratumab might prove to be therapeutic approaches for some patients with intimal sarcomas, based on a retrospective evaluation of genetic aberrations in 11 patients with intimal sarcomas, Jason Roszik, PhD, MBA, reported at the meeting.

Dr. Roszik and his colleagues at the University of Texas MD Anderson Cancer Center, Houston, analyzed information on 11 patients with intimal sarcomas in the American Association for Cancer Research project, Genomics Evidence Neoplasia Information Exchange. Sampling was taken from the primary tumor in eight patients and from the metastatic site in the other three.

MDM2 amplifications were seen in 8 of 10 patients with available copy number alterations. Amplifications in the CDK pathway were present in five, PDGFRA gain was seen in four, and CDKN2A copy number loss was present in three. Mutations that could be targeted with drugs included ALK, ATM/ATR, PTCH1 and PDGFRB, he said.

Unique genomic rearrangement events included PDE4DIP-NOTCH2 and MRPS30-ARID2 fusions. Co-occurring alterations included a NOTCH2 copy number gain in the PDE4DIP-NOTCH2 fusion tumor, and PDGFRB mutations in both fusion-positive cases.

The researchers also drew on the published findings of whole-exome sequencing and array-comparative genomic hybridization from an autopsy case of cardiac intimal sarcoma (Virchows Arch. 2017 Sep;471(3):423-8). That study identified concurrent PDGFRA amplification and PDGFRB mutation.

The researchers additionally examined clinical trial enrollments and could find no patient with intimal sarcoma among 406 sarcoma enrolled patients. Intimal sarcomas were not eligible for any clinical trial given the location of the tumors in major blood vessels.

"The somatic mutations and DNA copy number alterations in the PDGFR pathway relevant to the pathogenesis and potential targeted therapy of cardiac intimal sarcoma may be targeted by imatinib or olaratumab. Inclusion of such rare tumors in targeted therapy basket trials with a waiver for inclusion criteria is warranted," Dr. Roszik and his colleagues concluded in the abstract of their presentation.

The promise of combination therapy

The "largest experience using multimodality therapy with proton based local therapy" for sarcomas involving the pericardium, myocardium, valves, pulmonary veins, or pulmonary arteries was reported by Yen-Lin E. Chen, MD, and her colleagues at Massachusetts General Hospital, Boston.

They examined an institutional sarcoma data repository of 13,950 patients and found 37 patients with sarcomas arising from the pericardium, myocardium, valves, pulmonary veins, or pulmonary arteries. These included nine with unclassified

pleomorphic sarcoma/malignant fibrous histiocytoma, eight with angiosarcoma, four with spindle cell sarcoma, four with sarcoma not otherwise specified, three with leiomyosarcoma, two with osteosarcoma, two with Ewing sarcoma, and one each with chondrosarcoma, malignant peripheral nerve sheath tumor, rhabdomyosarcoma, synovial sarcoma, and intimal sarcoma.

Two-thirds of the patients had induction chemotherapy with or without maintenance therapy. Adriamycin, ifosfamide, and taxol therapies were most common. Two-thirds received proton based radiotherapy. Of the 23 patients who underwent resection, 11 were R2 (macroscopic positive margins), 3 were R1 (microscopic positive margins), and 9 were R0 (clear margins).

The 1-year overall survival rate was 64%, which fell to 37% at 3 years and to 28% at 5 years. Median survival was 28 months, twice that typically seen in the literature, Dr. Chen said.

For patients receiving proton-based radiotherapy to a median dose of 64.8 GyRBE (range 63-72 GyRBE, 3 with additional intraoperative electrons), local failure-free survivals were 80%, 64%, and 52% at 1, 3, and 5 years, respectively. For patients who did not receive radiotherapy, local failure-free survival rates were 13%, 10%, 10%, respectively.

Overall, the 1-, 3-, and 5-year metastatic-free survival rates were 25%, 14%, and 14%.

Survival rate was significantly better for patients with tumors smaller than 5 cm (P = .036), those over 40 years old (P = .028), those able to have surgery (P = .011), and those with non–angiosarcoma histologies (P = .002).

Soft-Tissue Sarcoma Chemotherapy

Predicting response to chemotherapy

The prognostic nomogram called Sarculator was used effectively to define a high-risk subgroup of patients likely to benefit from adjuvant chemotherapy, Sandro Pasquali, MD, of the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, and his colleagues reported at the meeting.

Perioperative chemotherapy was shown to afford no survival advantage over observation in the European Organization for Research and Treatment of Cancer (EORTC)–62931 study of adjuvant doxorubicin plus ifosfamide (Lancet Oncol 2012;13:1045-54). However, subsequent analyses of that data attributed this finding to variations in treatment schedules and the inclusion of low-risk tumors, which may have diluted the effect of chemotherapy, the researchers said in their abstract.

Further, a recent interim report of the ISG-1001 trial showed a survival benefit for patients who received neoadjuvant epirubicin plus ifosfamide therapy for localized high-risk soft-tissue sarcoma of the extremities or trunk wall (Lancet Oncol 2017;18:812-822).

The researchers performed a retrospective analysis of individual data for 290 patients with extremity and trunk wall soft-tissue sarcomas in the EORTC-STBSG 62931 study. The Sarculator was used to calculate 10-year predicted probability of overall survival (pr-OS) for each patient.

Patients were grouped in two categories of predicted overall survival: high predicted survival (more than 60%) and low predicted overall survival (60% or less). Overall survival and disease-free survival were calculated at 8 years, the study's median follow-up.

The 8-year probability of overall survival and disease-free survival was 58% (95% confidence interval, 52%-63%) and 51% (95% CI, 46%-57%), respectively. In the 290 patients with extremity and trunk wall soft-tissue sarcomas, adjuvant chemotherapy was not associated with an overall survival benefit (hazard ratio, 0.91; 95% CI, 0.63-1.31). The Sarcolator Nomogram detected 80 patients who were at greater risk of death compared to the 210 patients with higher predicted overall survival. The risk of death was significantly lower with adjuvant chemotherapy in the group with low predicted survival based

on the Sarculator nomogram (HR, 0.50; 95% CI, 0.30-0.90). Consistently, the risk of recurrence was significantly lower when adjuvant chemotherapy was used in the group with predicted overall survival of less than 60% (HR, 0.49; 95% CI, 0.28-0.85) while this difference was not observed in patients with high predicted overall survival (HR, 0.95; 95% CI, 0.62-1.44).

Doxorubicin plus dacarbazine deserve evaluation in prospective trials in leiomyosarcoma

Doxorubicin plus dacarbazine appeared to best the outcomes seen with doxorubicin plus ifosfamide and with doxorubicin alone in terms of overall response rate and progression-free survival as first-line treatment in patients with advanced leiomyosarcomas, based on a retrospective analysis presented by Lorenzo D'Ambrosio, MD, of the Unitversity of Turin, Italy, and his associates.

As patients in the trial were not randomized to therapy, the researchers used a logistic regression model that accounted for histology, site of primary, age, sex, performance status, tumor extent, and tumor grade. Patients were then matched across the different groups by their propensity scores.

The 303 patients, 216 of them women, were enrolled from 18 European Organization for Research and Treatment of Cancer–Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) sites. Doxorubicin plus dacarbazine was given to 117 patients (39%), doxorubicin plus ifosfamide was given to 71 (23%), and doxorubicin alone was given to 115 (38%). There were no significant differences among the regimens in terms of dose reductions of more than 10%, delays of greater than 72 hours, or granulocyte-colony stimulating factor use.

In the whole population, unadjusted median progression-free survival was 9.4 months (95% confidence interval, 6.1-9.7 months) for those given doxorubicin plus dacarbazine, 6.8 months (4.5-9.5 months) for those given doxorubicin plus ifosfamide), and 5.4 months (3.8-6.8 months) for those given doxorubicin alone. The respective overall response rates for the three regimens were 36.8%, 21.5%, and 25.9%.

When using propensity scores to adjust for lack of randomization, progression free survival was significantly longer with doxorubicin plus dacarbazine (median 9.2 months: 95% CI, 5.2-9.7 months) than with doxorubicin (median 4.8 months: 95% CI, 2.3-6.0 months; hazard ratio, 0.72 [0.52-0.99]). The difference was not significant when compared with doxorubicin plus ifosfamide (8.2 months [5.2-10.1]; HR 1.01; [0.68-1.50]). Progression-free survival did not differ significantly between doxorubicin plus ifosfamide, and doxorubicin (HR 0.71 [0.48-1.06]).

In the same matched population, overall response rates were 30.9%, 19.5%, and 25.6% for doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, and doxorubicin, respectively.

Overall survival comparisons were weakened by a shorter median follow-up in the doxorubicin plus dacarbazine groups (32 months), compared with the doxorubicin plus ifosfamide group (50 months) and the doxorubicin group (46 months). With this limit, patients in the doxorubicin plus dacarbazine arm had longer overall survival (median 36.8 months [27.9-47.2]) when compared with both doxorubicin plus ifosfamide (21.9 months [16.7-33.4]; HR, 0.65 [0.40-1.06]); and doxorubicin arms (30.3 months [21.0-36.3]; HR, 0.66 [0.43-0.99]).

Subsequent treatments were well balanced across arms. None of the selected factors for multivariate analysis (age, sex, Eastern Cooperative Oncology Group [ECOG] performance status, histotype, site of primary tumor, tumor grade, and tumor extent) significantly affected the progression-free survival and overall survival associated with the treatments.

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