

# the **SARCOMA** **JOURNAL**

*Official Journal  
of the Sarcoma  
Foundation  
of America™*

CASE REPORT

## **Tumor lysis syndrome in an adolescent with recurrence of abdominal rhabdomyosarcoma**

**PAGE 24**

**Clinical trial snapshots**

**PAGE 5**

CASE REPORT

**Anti-PD-1 therapy  
with nivolumab in the  
treatment of metastatic  
malignant PEComa**

**PAGE 7**

CASE REPORT

**Cardiac pleomorphic  
sarcoma after placement  
of a Dacron graft**

**PAGE 9**

ORIGINAL RESEARCH

**Onodera's Prognostic  
Nutritional Index in soft  
tissue sarcoma patients  
as a predictor of wound  
complications**

**PAGE 19**



# THE TABLES ARE TURNING

## 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  $\geq 3$  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- $\alpha$ ) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR- $\alpha$  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  $\geq 20\%$  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  $\geq 20\%$  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%).



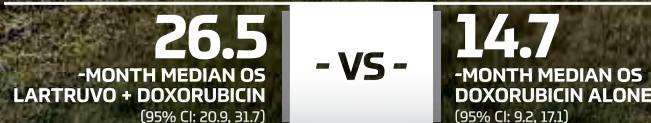
## LARTRUVO + DOXORUBICIN FOR SOFT TISSUE SARCOMA (STS): THE FIRST AND ONLY FRONT-LINE THERAPY WITH OVERALL SURVIVAL BENEFIT VS DOXORUBICIN ALONE

### INDICATION

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.

### OVERALL SURVIVAL (OS)



(HR=0.52 [95% CI: 0.34, 0.79],  $P<0.05$ )

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

### Study Design

Study 1 was an open-label, randomized (1:1), active-controlled study (N=133) of LARTRUVO + doxorubicin (n=66) vs doxorubicin alone (n=67) in patients with STS 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 Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2. The efficacy outcome measures were OS, PFS, and ORR.

This study excluded patients with an ECOG PS >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- $\alpha$  (platelet-derived growth factor receptor- $\alpha$ ) expression.

### IMPORTANT SAFETY INFORMATION FOR LARTRUVO (cont'd)

#### 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 for LARTRUVO on adjacent pages of this advertisement.

OR HCP ISI 19OCT2016

### PROGRESSION-FREE SURVIVAL (PFS)

— 8.2-month (95% CI: 5.5, 9.8) median PFS with LARTRUVO + doxorubicin

— 4.4-month (95% CI: 3.1, 7.4) median PFS with doxorubicin alone

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

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

### OBJECTIVE RESPONSE RATE (ORR)

— 18.2% ORR (95% CI: 9.8, 29.6) with LARTRUVO + doxorubicin

— 7.5% ORR (95% CI: 2.5, 16.6) with doxorubicin alone

ORR=complete response (CR) + partial response (PR).

LARTRUVO + doxorubicin: CR=4.5%, PR=13.6%; doxorubicin alone: CR=1.5%, PR=6%.

ORR was assessed according to RECIST criteria v1.1.



**Lartruvo**<sup>TM</sup>  
(OLARATUMAB)  
Injection 10 mg/mL

C9485 for administration and billing is available; visit [LARTRUVO.com/hcp](http://LARTRUVO.com/hcp) to learn more

PP-OR-US-0263 06/2017 © Lilly USA, LLC 2017. All rights reserved. LARTRUVO<sup>TM</sup> is a trademark owned or licensed by Eli Lilly and Company, its subsidiaries, or affiliates.

## 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  $\geq 3$  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- $\alpha$ ) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR- $\alpha$  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  $\geq 6$  months and 6% were exposed for  $\geq 12$  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<sup>2</sup> 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

LARTRUVO™ (olaratumab) injection

OR HCP BS 21OCT2016

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  $\geq 6$  months and 10 (16%) patients receiving LARTRUVO for  $\geq 12$  months. The median cumulative doxorubicin dose was 488 mg/m<sup>2</sup> in the LARTRUVO plus doxorubicin arm and 300 mg/m<sup>2</sup> 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  $\geq 10\%$  (All Grades) of Patients in the LARTRUVO plus Doxorubicin Arm and at a Higher Incidence than in the Doxorubicin Arm (Between Arm Difference of  $\geq 5\%$  for All Grades or  $\geq 2\%$  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 (%)
<b>Gastrointestinal Disorders</b>				
Nausea	73	2	52	3
Mucositis	53	3	35	5
Vomiting	45	0	19	0
Diarrhea	34	3	23	0
Abdominal Pain <sup>a</sup>	23	3	14	0
<b>General Disorders and Administrative Site Conditions</b>				
Fatigue <sup>b</sup>	69	9	69	3
Infusion-Related Reactions	13	3	3	0
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Musculoskeletal Pain <sup>c</sup>	64	8	25	2
<b>Skin and Subcutaneous Tissue Disorders</b>				
Alopecia	52	0	40	0
<b>Metabolic and Nutritional Disorders</b>				
Decreased Appetite	31	2	20	0
<b>Nervous System Disorders</b>				
Neuropathy	22	0	11	0
Headache	20	0	9	0
<b>Psychiatric Disorder</b>				
Anxiety	11	0	3	0
<b>Eye Disorder</b>				
Dry Eyes	11	0	3	0

<sup>a</sup> Abdominal pain includes: abdominal pain, lower abdominal pain, and upper abdominal pain.

<sup>b</sup> Fatigue includes: asthenia and fatigue.

<sup>c</sup> 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.

LARTRUVO™ (olaratumab) injection

OR HCP BS 21OCT2016

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

**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  $\geq 5\%$  for All Grades or  $\geq 2\%$  for Grades 3 and 4) (Trial 1)**

Laboratory Abnormality	LARTRUVO plus Doxorubicin <sup>a</sup>		Doxorubicin <sup>a</sup>	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Chemistry</b>				
Hyperglycemia	52	2	28	3
Increased aPTT <sup>b</sup>	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
<b>Hematology</b>				
Lymphopenia	77	44	73	37
Neutropenia	65	48	63	38
Thrombocytopenia	63	6	44	11

<sup>a</sup> 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).

<sup>b</sup> 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- $\alpha$ ) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR- $\alpha$  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- $\alpha$  signaling on reproduction and embryo-fetal development. In PDGFR- $\alpha$  knockout mice, disruption of PDGFR- $\alpha$  signaling resulted in embryo-fetal lethality and teratogenicity, including cleft face and spina bifida. Intravenous administration of an anti-murine PDGFR- $\alpha$  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](http://www.LARTRUVO.com/hcp).



**Eli Lilly and Company, Indianapolis, IN 46285, USA**

Copyright © 2016, Eli Lilly and Company. All rights reserved.

OR HCP BS 21OCT2016

LARTRUVO™ (olaratumab) injection

OR HCP BS 21OCT2016

LARTRUVO™ (olaratumab) injection

OR HCP BS 21OCT2016

Editor-in-Chief **WILLIAM D. TAP, MD**  
 Managing Editor **MARY JO DALES**  
 Managing Director **FRANK IORIO**  
 Tel: 973-206-8990  
 Creative Director **MARY ELLEN NIATAS**  
 Art Director **KAREN BLACKWOOD**  
 Director, Journal Manufacturing Services **MICHAEL WENDT**  
 Account Manager, Classified Advertising **TIM LAPELLA**  
 Tel: (484) 921-5001 Fax: (484) 921-5005



Chairman **STEPHEN STONEBURN**  
 President/CEO **ALAN J. IMHOFF**  
 President, Digital & CFO **DOUGLAS E. GROSE**  
 Chief Digital Officer **LEE SCHWEIZER**  
 Vice President, Digital Publishing **AMY PFEIFFER**  
 President, Custom Solutions **JOANN WAHL**  
 Director, Custom Programs **PATRICK FINNEGAN**  
 Vice President, Custom Solutions **WENDY RAUPERS**  
 SVP, Finance **STEVEN J. RESNICK**  
 Vice President, Operations **JIM CHICCA**  
 Vice President, Human Resources & Facility  
 Operations **CAROLYN CACCARELLI**  
 Vice President, Marketing & Customer Advocacy  
**JIM MCDONOUGH**  
 Vice President, Sales **MIKE GUIRE**  
 Vice President, Society Partners **MARK BRANCA**  
 Circulation Director **JARED SONNERS**  
 Corporate Director, Research & Communications  
**LORI RASKIN**  
 Editor-in-Chief **MARY JO DALES**  
 In affiliation with Global Academy for Medical Education, LLC.  
 Vice President, Medical Education & Conferences  
**SYLVIA H. REITMAN**  
 Vice President, Events **DAVID SMALL**  
 Subscription Service Tel: (800) 480-4851

**COPYRIGHT**

© Frontline Medical Communications. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form, or by any means, electronic, mechanical, photocopying, recording, or otherwise, without written permission of the publisher.

**PERMISSIONS POLICY**

Authorization to photocopy articles in this publication for internal or personal use, or for the internal or personal use of specific clients, is granted by Frontline Medical Communications to libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that a fee of \$3.00 per article is paid directly to: CCC, 222 Rosewood Dr., Danvers, MA 01923. Telephone: (508) 750-8400. Fax: (508) 750-4744, or at www.copyright.com. CCC is a not-for-profit organization that provides copyright licensing on behalf of FMC. This consent does not apply to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

**Reprint requests:** For article reprints, eprints, or licensing in the United States and Canada, please contact Wright's Media toll free at 877-652-5295.

For all others outside the USA & Canada contact Ray Thibodeau at Content Ed Net. Tel: 267-895-1758.

**EDITORIAL AND ADVERTISING POLICY**

Statements and opinions expressed in articles and communications herein are those of the author(s) and not necessarily those of the editor, publisher, or any organizations endorsing this journal. Neither the editor, publisher, nor organizations endorsing this journal guarantee, warrant, or endorse any product or service advertised in this journal, nor do they guarantee any claim made by the manufacturer of such product or service. Except as noted, authors have reported no competing interests.

**CHANGE OF ADDRESS**

Please send address changes to The Sarcoma Journal, Subscription Service, 7 Century Drive, Suite 302, Parsippany, NJ 07054. Attn: Frank Iorio. Call 973-206-8990 or email fiorio@frontlinemedcom.com. Enclose address label, provide complete new address, and allow 8 weeks for processing.



COVER: © Marc Phares/Science Source

**5**

Clinical trial snapshots

**7**

**CASE REPORTS**

Anti-PD-1 therapy with nivolumab in the treatment of metastatic malignant PEComa

Parva K. Bhatt, MD; Ross A. Abrams, MD; Steven Gitelis, MD; Marta Batus MD

**9**

Cardiac pleomorphic sarcoma after placement of a Dacron graft

Monaliben Patel, MD; Walid Saad, MD; Peter Georges, MD; George Kaddissi, MD; Thomas Holdbrook, MD; Priya Singh, MD

**24**

Tumor lysis syndrome in an adolescent with recurrence of abdominal rhabdomyosarcoma

Sabrina Solorzano, DO; Matteo Trucco, MD; John M. Goldberg, MD; Fernando F. Corrales-Medina, MD

**19**

**ORIGINAL RESEARCH**

Onodera's Prognostic Nutritional Index in soft tissue sarcoma patients as a predictor of wound complications

Tae Won B Kim, MD; Samuel Hardy, MD; Danijel J Pericic, MS; John Gaughan, MS, PhD, MBA; and Mark Angelo, MD



The Sarcoma Journal, Official Journal of the Sarcoma Foundation of America™ (ISSN 2573-1521) is published monthly by Frontline Medical Communications, 7 Century Drive, Suite 302, Parsippany, NJ 07054. The contents of this publication may not be reproduced in whole or part without the written consent of the owner. 2018 subscription rates (includes full-text access to sarcomajournal.com): United States: \$177 individuals (print & online), \$309 institutions (print only), \$89 students; elsewhere (excluding Japan): \$235 individual (print & online), \$403 institutions (print only), \$89 students. (All students/residents: Send proof of status.) Single copy orders must be prepaid: United States: \$30; elsewhere: \$34. Please contact Customer Service (800-480-4851) for pricing information. Periodicals postage paid at Parsippany, NJ and additional mailing offices. The GST number for Canadian subscribers is 124002536. Orders and claims: The Sarcoma Journal, Subscription Service, 7 Century Drive, Suite 302, Parsippany, NJ 07054. Attn: Frank Iorio. Claims for missing issues will be serviced within 3 months of cover date in the United States; 6 months elsewhere. Only 1 request honored for each missing issue. POSTMASTER: Please send address changes to The Sarcoma Journal, Subscription Service, 7 Century Drive, Suite 302, Parsippany, NJ 07054. Attn: Frank Iorio. Call 973-206-8990 or email fiorio@mdedge.com.

# Clinical trial snapshots

*Updates of ongoing clinical trials*

## Randomized Phase 3 Trial Evaluating the Addition of the IGF-1R Monoclonal Antibody Ganitumab (AMG 479, NSC# 750008) to Multiagent Chemotherapy for Patients With Newly Diagnosed Metastatic Ewing Sarcoma

**NCT02306161**

**Sponsor:** National Cancer Institute (NCI)  
**Principal Investigator:** Steven DuBois, Children's Oncology Group and Dana-Farber Cancer Institute, Boston.

**Study locations:** Over 300 U.S. cancer centers

**Study summary:** This randomized phase 3 trial examines whether the monoclonal antibody ganitumab plus combination chemotherapy (vincristine sulfate, doxorubicin hydrochloride, cyclophosphamide, ifosfamide, and etoposide) improves event-free survival for patients with newly-diagnosed, metastatic Ewing sarcoma. Secondary outcomes include overall survival rate and comparative evaluations of toxicity.

Patients are randomized to induction and consolidation therapy with vincristine sulfate, doxorubicin hydrochloride and cyclophosphamide [VDC] and ifosfamide and etoposide [IE]) or to the same regimen plus ganitumab. Between weeks 13-18 of the trial, patients undergo surgery and/or radiation therapy for local control. Patients with lung metastases undergo definitive stereotactic body radiation therapy or external beam radiation therapy over 5 days.

**Study inclusion summary:** Patients up to 50 years old are eligible to participate in this trial if they have newly-diagnosed Ewing sarcoma or peripheral primitive neuroectodermal tumor (PNET) arising from bone or soft tissue and with met-

astatic disease involving lung, bone, bone marrow, or other metastatic site. Submission of pre-treatment serum, tumor tissue and whole blood is required. Patients should only have had a biopsy of the primary tumor without an attempt at complete or partial resection; patients will still be eligible if excision was attempted or accomplished as long as adequate anatomic imaging (MRI for most primary tumor sites) was obtained prior to surgery. Creatinine clearance or radioisotope glomerular filtration rate (GFR) must be at least 70 mL/min/1.73 m<sup>2</sup> or greater. Total bilirubin must be less than 1.5 times the upper limit of normal, alanine aminotransferase must be less than 3 times the upper limit of normal, blood sugar must be normal, and heart ejection fraction must exceed 50%.

**Induction therapy:** Patients receive vincristine sulfate intravenously (IV) over 1 minute on day 1; doxorubicin hydrochloride IV over 1-15 minutes on days 1 and 2; and cyclophosphamide IV over 30-60 minutes on day 1 of weeks 1, 5, and 9; and ifosfamide IV over 1 hour on days 1 to 5 and etoposide IV over 1-2 hours on days 1 to 5 of weeks 3, 7, and 11. Patients in the control group receive induction therapy and placebo and patients in the treatment group receive induction therapy and ganitumab IV over 30-60 minutes or 60-120 minutes on day 1 of weeks 1, 3, 5, 7, 9, and 11.

**Consolidation therapy:** Patients receive vincristine sulfate IV over 1 minute on day 1 of weeks 1, 7, 9, and 13; doxorubicin hydrochloride IV over 1-15 minutes on days 1 and 2 of weeks 1 and 7; cyclophosphamide IV over 30-60 minutes on day 1 of weeks 1, 7, 9, and 13; ifosfamide IV over 1 hour on days 1 to 5 of weeks 3, 5, 11, and 15; and etoposide IV over 1-2 hours on days 1 to 5 of weeks 3, 5,

➤ THIS RANDOMIZED PHASE 3 TRIAL EXAMINES WHETHER THE MONOCLONAL ANTIBODY GANITUMAB PLUS COMBINATION CHEMOTHERAPY (VINCRIStINE SULFATE, DOXORUBICIN HYDROCHLORIDE, CYCLOPHOSPHAMIDE, IFOSFAMIDE, AND ETOPOSIDE) IMPROVES EVENT-FREE SURVIVAL FOR PATIENTS WITH NEWLY-DIAGNOSED, METASTATIC EWING SARCOMA.

➤ THIS RANDOMIZED PHASE 3 TRIAL COMPARES STANDARD COMBINATION CHEMOTHERAPY WITH AND WITHOUT TEMSIROLIMUS FOR PATIENTS WITH RHABDOMYOSARCOMA THAT HAS AN INTERMEDIATE CHANCE OF RECURRENCE AFTER TREATMENT.

11, and 15. In addition to this standard consolidation therapy, pPatients in the active treatment group receive ganitumab IV over 30-60 minutes or 60-120 minutes on day 1 of weeks 7, 9, 11, 13, and 15.

**Maintenance therapy:** Patients receive ganitumab IV over 30-60 minutes or 60-120 minutes on day 1 in weeks 1, 4, 7, 10, 13, 16, 19, and 22.

**Follow up:** After completion of study treatment, patients are followed for 10 years.

### Combination Chemotherapy With or Without Temsirolimus in Treating Patients With Intermediate Risk Rhabdomyosarcoma

**NCT02567435**

**Sponsor:** National Cancer Institute (NCI)  
**Principal Investigator:** Abha Gupta, Children's Oncology Group, The Hospital for Sick Children and Princess Margaret Cancer Centre.

**Study locations:** 293 cancer centers in the U.S. and Canada

**Study summary:** This randomized phase 3 trial compares standard combination chemotherapy with and without temsirolimus for patients with rhabdomyosarcoma that has an intermediate chance of recurrence after treatment. It is not yet known whether combination chemotherapy or combination chemotherapy plus temsirolimus is more effective in treating patients with intermediate-risk rhabdomyosarcoma.

**Study inclusion summary:** Patients up to age 40 with newly diagnosed RMS of any subtype, except adult-type pleomorphic, based upon institutional histopathologic classification, are eligible to enroll on the study. Lansky performance status score must be at least 50 for patients age 16 years and under; Karnofsky

performance status score must be 50 or greater for patients over age 16. Peripheral absolute neutrophil count must be at least 750/uL and platelet count at least 75,000/uL. Creatinine clearance or radioisotope glomerular filtration rate must be at least 70 mL/min/1.73 m<sup>2</sup>. Total bilirubin must be no more than 1.5 times the upper limit of normal for patient age.

**Treatment regimen:** Patients are randomized to one of three study arms. One group receives vincristine sulfate IV over 1 minute on day 1 of weeks 1-13, 16, 17, 19, 20, 22-26, 28, 31-34, 37, 38, and 40, dactinomycin IV over 1-5 minutes on day 1 of weeks 1, 7, 13, 22, 28, 34, and 40, cyclophosphamide IV over 60 minutes on day 1 of weeks 1, 7, 13, 22, 28, 34, and 40, irinotecan hydrochloride IV over 90 minutes on days 1-5 of weeks 4, 10, 16, 19, 25, 31, and 37. The second group receives the same regimen plus temsirolimus IV over 30-60 minutes on day 1 of weeks 1-12 and 21-42. The third group receives vincristine sulfate IV over 1 minute on day 1 of weeks 1-10 and 13-22, dactinomycin IV over 1-5 minutes on day 1 of weeks 1, 4, 7, 10, 13, 16, 19, and 22, cyclophosphamide IV over 60 minutes on day 1 of weeks 1, 4, 7, and 10. Patients in all three groups also undergo radiation therapy beginning at week 13 for 6 weeks. Treatment continues in all three groups in the absence of disease progression or unacceptable toxicity.

**Outcome Measures:** The primary outcome measure is event-free survival (EFS) measured from study enrollment to the first occurrence of progression, relapse, second malignant neoplasm, or death as a first event. The secondary outcome measure is overall survival measured from study enrollment to death from any cause, assessed up to 10 years. **TSJ**

# Anti-PD-1 therapy with nivolumab in the treatment of metastatic malignant PEComa

**P**erivascular epithelioid cell neoplasms (PEComas) are an uncommon class of tumors consisting on histology of perivascular epithelioid cells occurring in both localized and metastatic forms at various body sites. The approach to treatment of these tumors generally involves a combination of surgical resection, chemotherapy, and/or radiation therapy.<sup>1</sup>

## CASE PRESENTATION AND SUMMARY

A 46-year-old man presented to our institution with a non-tender, slowly enlarging, 8.3 cm mass in his right popliteal fossa. Upon biopsy, the pathologic findings were consistent with an epithelioid malignancy with melanocytic differentiation most consistent with a PEComa. Discussion of the pathologic diagnosis of our patient has been reported by the pathology group at our institution in a separate case report.<sup>2</sup>

Our patient was initially offered and refused amputation. He was started on therapy with the mechanistic Target of Rapamycin (mTOR) inhibitor everolimus, but was unable to tolerate the side effects after the first week of treatment. He then elected to monitor his symptoms clinically.

Approximately one year after his initial diagnosis, he presented to our facility with sepsis and bleeding from a now fungating tumor on his right knee. At this time, emergent above-knee amputation was performed. Re-staging images now showed the presence of multiple pulmonary nodules in his right lung as well as a lytic rib lesion, a concerning finding for metastatic disease. Video-Assisted Thorascopic Surgery (VATS) and

right lower lobe wedge resection were performed and findings confirmed metastatic PEComa.

Given the patient's intolerance to everolimus, he was started on the growth factor inhibitor, pazopanib. His disease did not progress on pazopanib, and improvement was noted in the dominant pulmonary nodule. Subsequently, however, he developed significant skin irritation and discontinued pazopanib. Repeat imaging approximately 2 months after stopping pazopanib showed significant disease progression.

We elected to start the patient on a non-standard approach to therapy with nivolumab infusions once every 2 weeks and concurrent radiation therapy to the rib lesion. At 2 and 5 months after initiating this treatment approach, CT imaging showed improvement in disease. At 12 months, significant disease response was noted (**FIGURE 1**).

The patient is now at 12 months of nivolumab therapy with progression free survival and no new identifiable metastatic lesions. He has been tolerating the medication with minimal side effects and has had an overall improvement in his pain and functional status. He continues to work full time.

## DISCUSSION

Our patient's response presents a unique opportunity to talk about the role of immunotherapy as a treatment modality in patients with PEComa. The efficacy of check-point blockade in soft tissue sarcoma is still unclear predominantly because it is difficult to assess the degree of expression of immunogenic cell surface markers such as programmed cell

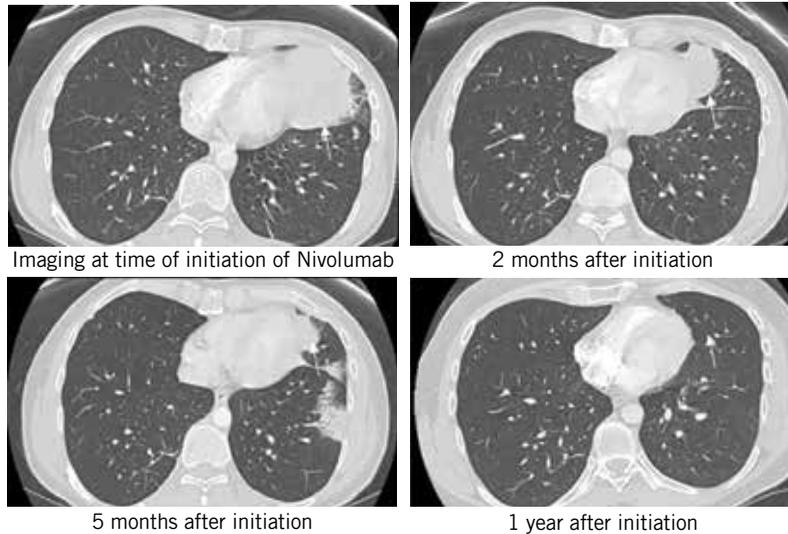
**Parva K. Bhatt, MD; Ross A. Abrams, MD; Steven Gitelis, MD; Marta Batus MD**  
Rush University Medical Center; Chicago, IL.

## DISCLOSURES

The authors have no relevant financial disclosures or conflicts of interest.

DOI: 10.12788/sarcj.0002

➤ TO OUR KNOWLEDGE, THERE HAS NOT YET BEEN ANOTHER REPORTED CASE OF PEComa THAT HAS BEEN TREATED WITH IMMUNOTHERAPY AND ACHIEVED A SUSTAINED RESPONSE.



**FIGURE 1.** Computerized Tomographic (CT) Imaging of dominant lingular lobe pericardial lesion. Interval decrease in size at 2, 5, and 1 year after initiation of Nivolumab.

death protein 1 (PD-1).<sup>1,3</sup> Nivolumab has been tried in small cohorts for treatment of soft tissue sarcomas that express PD-1 and results showed some clinical benefit in about half of patients.<sup>4</sup> Further, the expression of PD-1 has been assessed in soft tissue sarcomas and has been reported to suggest a negative prognostic role.<sup>5</sup>

To our knowledge, there has not yet been another reported case of PEComa that has been treated with immunotherapy and achieved a sustained response. Further clinical studies need to be done to assess response to agents such as nivolumab in the treatment of PEComa to bolster our observation that nivolumab is a viable treatment option that may lead to lasting remission. Our patient's case also brings to light the need for further inquiry into assessing the immune tumor microenvironments, particularly looking at the expression of cell surface proteins such as PD-1, as it ultimately affects treatment options. **TSJ**

CORRESPONDENCE

Parva K. Bhatt, MD; Parva\_K\_Bhatt@rush.edu

REFERENCES

1. Burgess, Melissa, et al. "Immunotherapy in Sarcoma: Future Horizons." *Current Oncology Reports*, vol. 17, no. 11, 2015, doi:10.1007/s11912-015-0476-7.
2. Alnajar, Hussein, et al. "Metastatic Malignant PEComa of the Leg with Identification of ATRX Mutation by next-Generation Sequencing." *Virchows Archiv* (2017). <https://doi:10.1007/s004280172208-x>.
3. Ghosn, Marwan, et al. "Immunotherapies in Sarcoma: Updates and Future Perspectives." *World Journal of Clinical Oncology*, vol. 8, no. 2, 2017, p. 145., doi:10.5306/wjco.v8.i2.145.
4. Paoluzzi, L., et al. "Response to Anti-PD1 Therapy with Nivolumab in Metastatic Sarcomas." *Clinical Sarcoma Research*, vol. 6, no. 1, 2016, doi:10.1186/s13569-016-0064-0.
5. Kim, Chan, et al. "Prognostic Implications of PD-L1 Expression in Patients with Soft Tissue Sarcoma." *BMC Cancer*, BioMed Central 8 July 2016.

# Cardiac pleomorphic sarcoma after placement of a Dacron graft

**P**rimarily cardiac tumors, either benign or malignant, are very rare. The combined incidence is 0.002% on pooled autopsy series.<sup>1</sup> The benign tumors account for 63% of primary cardiac tumors and include myxoma, the most common, and followed by papillary fibroelastoma, fibroma, and hemangioma. The remaining 37% are malignant tumors, essentially predominated by sarcomas.<sup>1</sup>

Although myxoma is the most common tumor arising in the left atrium, we present a case that shows that sarcoma can also arise from the same chamber. In fact, sarcomas could mimic cardiac myxoma.<sup>2</sup> The cardiac sarcomas can have similar clinical presentation and more importantly can share similar histopathological features. Sarcomas may have myxoid features.<sup>2</sup> Cases diagnosed as cardiac myxomas should be diligently worked up to rule out the presence of sarcomas with myxoid features. In addition, foreign bodies have been found to induce sarcomas in experimental animals.<sup>3,4</sup> In particular, 2 case reports have described sarcomas arising in association with Dacron vascular prostheses in humans.<sup>5,6</sup> We present here the case of a patient who was diagnosed with cardiac pleomorphic sarcoma 8 years after the placement of a Dacron graft.

## CASE PRESENTATION AND SUMMARY

A 56-year-old woman with history of left atrial myxoma status after resection in 2005 and placement of a Dacron graft, morbid obesity, hypertension, and asthma presented to the emergency department with progressively worsening shortness of breath and blurry vision over period of 2 months. Acute coronary

syndrome was ruled out by electrocardiogram and serial biomarkers. A computed-tomography angiogram was pursued because of her history of left atrial myxoma, and the results suggested the presence of a left atrial tumor. She underwent a transesophageal echocardiogram, which confirmed the presence of a large left atrial mass that likely was attached to the interatrial septum prolapsing across the mitral valve and was suggestive for recurrent left atrial myxoma (**FIGURE 1**). The results of a cardiac catheterization showed normal coronaries.

The patient subsequently underwent an excision of the left atrial tumor with profound internal and external myocardial cooling using antegrade blood cardioplegia under mildly hypothermic cardiopulmonary bypass. Frozen sections showed high-grade malignancy in favor of sarcoma. The hematoxylin and eosin stained permanent sections showed sheets of malignant pleomorphic spindle cells focally arranged in a storiform pattern. There were areas of necrosis and abundant mitotic activity. By immunohistochemical (IHC) stains, the tumor cells were diffusely positive for vimentin, and negative for pan-cytokeratin antibody (AE1/AE3), S-100 protein, Melan-A antibody, HMB45, CD34, CD31, myogenin, and MYOD1. IHC stains for CK-OSCAR, desmin, and smooth muscle actin were focally positive, and a ki-67 stain showed a proliferation index of about 80%. The histologic and IHC findings were consistent with a final diagnosis of high-grade undifferentiated pleomorphic sarcoma (**FIGURE 2**).

A positron emission tomography scan performed November 2013 did not show any other activity. The patient was scheduled for chemotherapy with adriamycin

**Monaliben Patel, MD,<sup>a†</sup> Walid Saad, MD,<sup>b</sup> Peter Georges, MD,<sup>a</sup> George Kaddissi, MD,<sup>b</sup> Thomas Holdbrook, MD,<sup>c</sup> and Priya Singh, MD<sup>a</sup>**

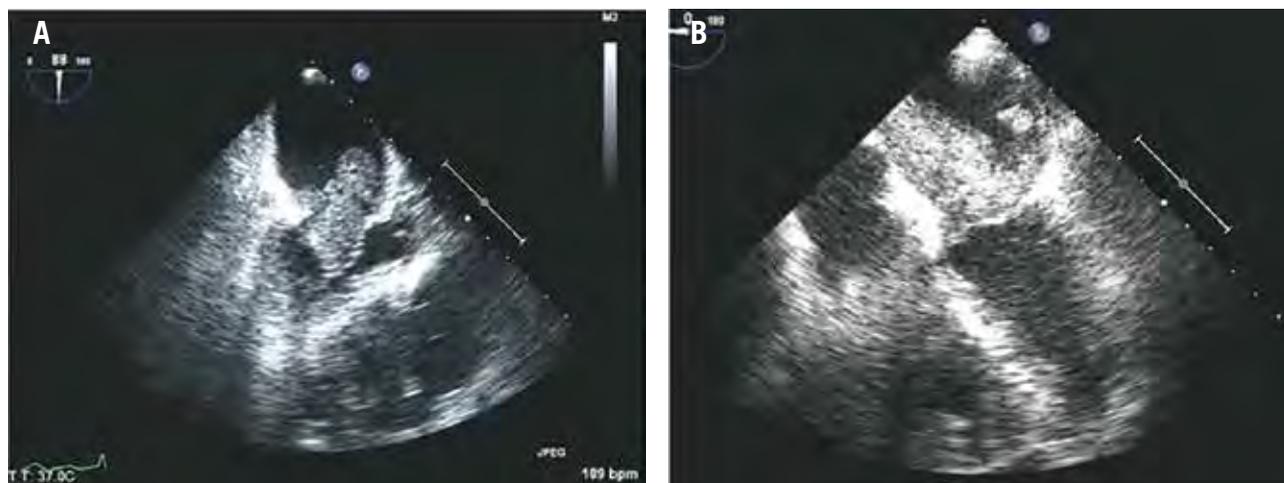
Departments of <sup>a</sup>Hematology and Oncology, <sup>b</sup>Cardiology, and <sup>c</sup>Pathology, Cooper University Hospital, Camden, New Jersey

<sup>†</sup>Dr Patel is now at University of Massachusetts Memorial Medical Center, Worcester, Massachusetts.

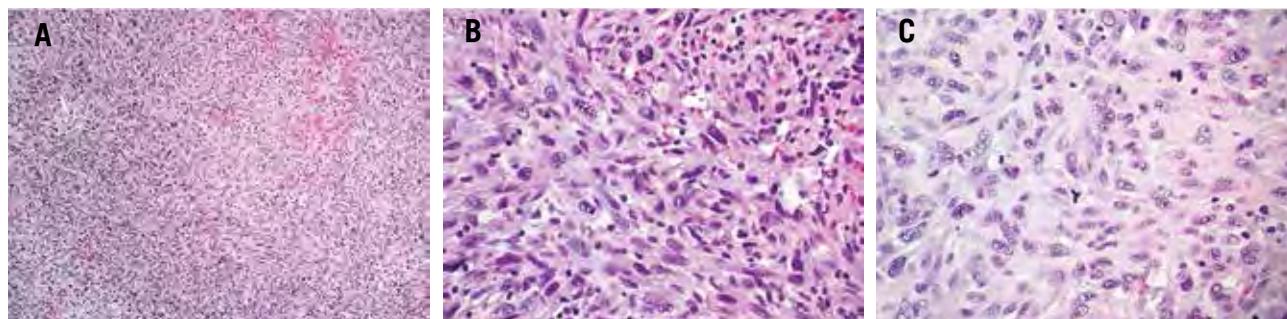
## DISCLOSURES

*The authors report no disclosures or conflicts of interest.*

This article was originally published in the Journal of Community and Supportive Oncology JCSO 2018;16(1):e40–e42. ©2018 Frontline Medical Communications. doi: 10.12788/jcs0.0202. It is reproduced here with permission from the copyright owner. Further reproduction prohibited without permission.



**FIGURE 1.** A transthoracic echocardiogram confirmed the presence of a large atrial mass: A, 2 chamber view, and B, 4 chamber view.



**FIGURE 2.** Undifferentiated pleomorphic sarcoma showing: A, Pleomorphic spindle cells arranged in a storiform pattern (H&E, x100); B, markedly pleomorphic spindle cells at high magnification (H&E, x400); C, an atypical mitotic figure in the center (H&E, x400).

and ifosfamide with a plan for total of 6 cycles. Before her admission for the chemotherapy, the patient was admitted to the hospital for atrial fibrillation with rapid ventricular response and had multiple complications requiring prolonged hospitalization and rehabilitation. Repeat imaging 2 months later showed diffuse metastatic disease. However, her performance status had declined and she was not eligible for chemotherapy. She was placed under hospice care.

### DISCUSSION

This case demonstrates development of a cardiac pleomorphic sarcoma, a rare tumor, after placement of a Dacron graft. Given that foreign bodies have been found to induce sarcomas in experimental animals,<sup>3,4</sup> and a few case reports have described sarcomas arising in association

with Dacron vascular prostheses,<sup>5-10</sup> it seems that an exuberant host response around the foreign body might represent an important intermediate step in the development of the sarcoma.

There is no clearly defined pathogenesis that explains the link between a Dacron graft and sarcomas. In 1950s, Oppenheimer and colleagues described the formation of malignant tumors by various types of plastics, including Dacron, that were embedded in rats.<sup>3,4</sup> Most of the tumors were some form of sarcomas. It was inferred that physical properties of the plastics may have some role in tumor development. Plastics in sheet form or film that remained in situ for more than 6 months induced significant number of tumors compared with other forms such as sponges, films with holes, or powders.<sup>3,4</sup> The 3-dimensional poly-

meric structure of the Dacron graft seems to play a role in induction of sarcoma as well. A pore diameter of less than 0.4 mm may increase tumorigenicity.<sup>11</sup> The removal of the material before the 6-month mark does not lead to malignant tumors, which further supports the link between Dacron graft and formation of tumor. A pocket is formed around the foreign material after a certain period, as has been shown in histologic studies as the site of tumor origin.<sup>9,10</sup>

At the molecular level, the MDM-2/p53 pathway has been cited as possible mechanism for pathogenesis of intimal sarcoma.<sup>12,13</sup> It has been suggested that endothelial dysplasia occurs as a precursor lesion in these sarcomas.<sup>14</sup> The Dacron graft may cause a dysplastic effect on the endothelium leading to this precursor lesion and in certain cases transforming into sarcoma. Further definitive studies are required.

The primary treatment for cardiac sarcoma is surgical removal, although it is not always feasible. Findings in a Mayo clinic study showed that the median survival was 17 months for patients who underwent complete surgical excision, compared with 6 months for those who complete resection was not possible.<sup>15</sup> In addition, a 10% survival rate at 1 year has been reported in primary cardiac sarcomas that are treated without any type of surgery.<sup>16</sup>

There is no clear-cut evidence supporting or refuting adjuvant chemotherapy for cardiac sarcoma. Some have inferred a potential benefit of adjuvant chemotherapy although definitive conclusions cannot be drawn. The median survival was 16.5 months in a case series of patients who received adjuvant chemotherapy, compared with 9 months and 11 months in 2 other case series.<sup>17,18,19</sup> Multiple chemotherapy regimens have been used in the past for treatment. A retrospective study by Llombart-Cussac colleagues, analyzed 15 patients who had received doxorubicin-containing chemotherapy, in most cases combined with ifosfamide or dacarbazine.<sup>20</sup> Resection was complete in 6 patients and incomplete in 9. The patients were given

chemotherapy within 6 weeks of surgery. Five patients developed metastatic disease during therapy. The median interval to first relapse was 10 months and overall median survival was 12 months in these patients.<sup>20</sup> Other regimens that have been used for treatment are mitomycin, doxorubicin, and cisplatin (MAP); doxorubicin, cyclophosphamide, and vincristine (DCV); ifosfamide and etoposide (IE); ifostamide, doxorubicin, and decarbazine; doxorubicin and paclitaxel, and paclitaxel alone.<sup>4</sup> Of those, a patient with on the IE survived the longest, 32 months. Radiation showed some benefit in progression-free survival in a French retrospective study.<sup>21</sup> Radiation therapies have been tried in other cases, as well in addition to chemotherapy. However, there is not enough data to support or refute it at this time.<sup>15,17,20</sup> Several sporadic cases reported show benefit of cardiac transplantation.<sup>21,22</sup>

## CONCLUSION

In consideration of the placement of the Dacron graft 8 years before the tumor occurrence, the anatomic proximity of the tumor to the Dacron graft, and the association between sarcoma with Dacron in medical literature, it seems logical to infer that this unusual malignancy in our patient is associated with the Dacron prosthesis. **TSJ**

## CORRESPONDENCE

Monaliben Patel, MD; Monaliben.Patel@umassmemorial.org.

## REFERENCES

1. Patil HR, Singh D, Hajdu M. Cardiac sarcoma presenting as heart failure and diagnosed as recurrent myxoma by echocardiogram. *Eur J Echocardiogr.* 2010;11(4):E12.
2. Awamleh P, Alberca MT, Gamallo C, Enrech S, Sarraj A. Left atrium myxosarcoma: an exceptional cardiac malignant primary tumor. *Clin Cardiol.* 2007;30(6):306-308.
3. Oppenheimer BS, Oppenheimer ET, Stout AP, Danishefsky I. Malignant tumors resulting from embedding plastics in rodents. *Science.* 1953;118:305-306.
4. Oppenheimer BS, Oppenheimer ET, Stout AP, Willhite M, Danishefski, I. The latent period in carcinogenesis by plastics in rats and its relation to the presarcomatous stage. *Cancer.* 1958;11(1):204-213.

**> THE DACRON GRAFT MAY CAUSE A DYSPLASTIC EFFECT ON THE ENDOTHELIUM LEADING TO THIS PRECURSOR LESION AND IN CERTAIN CASES TRANSFORMING INTO SARCOMA. FURTHER DEFINITIVE STUDIES ARE REQUIRED.**

5. Almeida NJ, Hoang P, Biddle P, Arouni A, Esterbrooks D. Primary cardiac angiosarcoma: in a patient with a Dacron aortic prosthesis. *Tex Heart Inst J*. 2011;38(1):61-65; discussion 65.
6. Stewart B, Manglik N, Zhao B, et al. Aortic intimal sarcoma: report of two cases with immunohistochemical analysis for pathogenesis. *Cardiovasc Pathol*. 2013;22(5):351-356.
7. Umscheid TW, Rouhani G, Morlang T, et al. Hemangiosarcoma after endovascular aortic aneurysm repair. *J Endovasc Ther*. 2007;14(1):101-105.
8. Ben-Izhak O, Vlodaysky E, Ofer A, Engel A, Nitecky S, Hoffman A. Epithelioid angiosarcoma associated with a Dacron vascular graft. *Am J Surg Pathol*. 1999;23(11):1418-1422.
9. Fyfe BS, Quintana CS, Kaneko M, Griep RB. Aortic sarcoma four years after Dacron graft insertion. *Ann Thorac Surg*. 1994;58(6):1752-1754.
10. O'Connell TX, Fee HJ, Golding A. Sarcoma associated with Dacron prosthetic material: case report and review of the literature. *J Thorac Cardiovasc Surg*. 1976;72(1):94-96.
11. Karp RD, Johnson KH, Buoen LC, et al. Tumorigenesis by millipore filters in mice: histology and ultrastructure of tissue reactions, as related to pore size. *J Natl Cancer Inst*. 1973;51:1275-1285.
12. Bode-Lesniewska B, Zhao J, Speel EJ, et al. Gains of 12q13-14 and overexpression of mdm2 are frequent findings in intimal sarcomas of the pulmonary artery. *Virchows Arch*. 2001;438:57-65.
13. Zeitz C, Rossle M, Haas C, et al. MDM-2 oncoprotein overexpression, p53 gene mutation, and VEGF up-regulation in angiosarcomas. *Am J Surg Pathol*. 1998;153:1425-1433.
14. Haber LM, Truong L. Immunohistochemical demonstration of the endothelial nature of aortic intimal sarcoma. *Am J Surg Pathol*. 1988 Oct;12(10):798-802. PubMed PMID: 3138923.
15. Simpson L, Kumar SK, Okuno SH, et al. Malignant primary cardiac tumors: review of a single institution experience. *Cancer*. 2008;112(11):2440-2446.
16. Leja MJ, Shah DJ, Reardon MJ. Primary cardiac tumors. *Tex Heart Inst J*. 2011;38(3):261-262.
17. Donsbeck AV, Ranchere D, Coindre JM, Le Gall F, Cordier JF, Loire R. Primary cardiac sarcomas: an immunohistochemical and grading study with long-term follow-up of 24 cases. *Histopathology*. 1999;34(4):295-304.
18. Putnam JB, Sweeney MS, Colon R, Lanza LA, Frazier OH, Cooley DC. Primary cardiac sarcomas. *Ann Thorac Surg*. 1990; 51; 906-910.
19. Murphy WR, Sweeney MS, Putnam JB et al. Surgical treatment of cardiac tumors: a 25-year experience. *Ann Thorac Surg*. 1990;49:612-618.
20. Llombart-Cussac A, Pivot X, Contesso G, et al. Adjuvant chemotherapy for primary cardiac sarcomas: the IGR experience. *Br J Cancer*. 1998;78(12):1624-1628.
21. Isambert N, Ray-Coquard I, Italiano A, et al. Primary cardiac sarcomas: a retrospective study of the French Sarcoma Group. *Eur J Cancer*. 2014;50(1):128-136.
22. Agaimy A, Rösch J, Weyand M, Strecker T. Primary and metastatic cardiac sarcomas: a 12-year experience at a German heart center. *Int J Clin Exp Pathol*. 2012;5(9):928-938.

Offer your patients with advanced liposarcoma a treatment that provides a

# **SIGNIFICANT OVERALL SURVIVAL BENEFIT<sup>1</sup>**

**HALAVEN<sup>®</sup> improved median overall survival vs dacarbazine (15.6 months vs 8.4 months)<sup>1</sup>**

## **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**

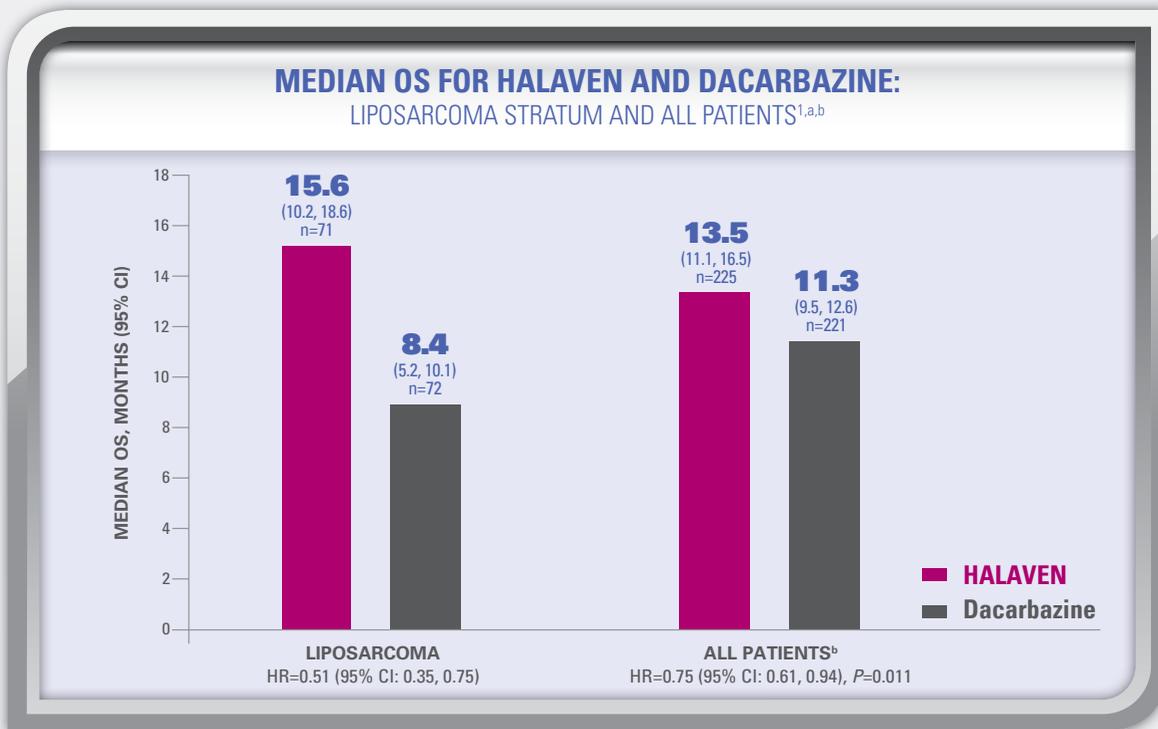
**Neutropenia:** Severe neutropenia (ANC <500/mm<sup>3</sup>) lasting >1 week occurred in 12% of patients with liposarcoma or leiomyosarcoma. Febrile neutropenia occurred in 0.9% of patients and fatal neutropenic sepsis occurred in 0.9% of patients. Monitor complete blood cell counts prior to each dose, 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<sup>®</sup>**  
(eribulin mesylate) Injection | 0.5 mg per mL



# Treatment effects of HALAVEN® were demonstrated in patients with advanced liposarcoma based on the preplanned, exploratory subgroup analysis of OS and PFS<sup>1</sup>



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

<sup>a</sup>Efficacy data from 1 study site enrolling 6 patients were excluded.

<sup>b</sup>All patients=liposarcoma and leiomyosarcoma.

- There was no evidence of efficacy of HALAVEN in patients with advanced or metastatic leiomyosarcoma in this trial<sup>1</sup>

## Secondary endpoint: PFS<sup>1</sup>

- 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.

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

 **Halaven**<sup>®</sup>  
(eribulin mesylate) Injection | 0.5 mg per mL

# Learn about the HALAVEN \$0 Co-Pay Program and the Eisai Assistance Program

by visiting [www.eisaireimbursement.com/hcp/halaven](http://www.eisaireimbursement.com/hcp/halaven)  
or calling **1.866.61.EISAI** (1.866.613.4724)  
Monday-Friday, 8 AM to 8 PM, ET

Learn more about the efficacy of HALAVEN at  
[www.halaven.com/hcp/advanced-liposarcoma](http://www.halaven.com/hcp/advanced-liposarcoma)

## 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 ( $\geq 25\%$ ) 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 ( $\geq 5\%$ ) 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® is a registered trademark used by Eisai Inc. under license from Eisai R&D Management Co., Ltd.  
© 2018 Eisai Inc. All rights reserved. Printed in USA/March 2018 HALA-US2052



## HALAVEN® (eribulin mesylate) Injection, for intravenous use

### BRIEF SUMMARY – See package insert for full prescribing information.

#### DOSE AND ADMINISTRATION

**Recommended Dose:** The recommended dose of HALAVEN is 1.4 mg/m<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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 (Cl<sub>cr</sub>) 15-49 mL/min) is 1.1 mg/m<sup>2</sup> 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<sup>3</sup>
  - Platelets < 75,000/mm<sup>3</sup>
  - Grade 3 or 4 non-hematologic 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
<b>Permanently reduce the 1.4 mg/m<sup>2</sup> HALAVEN dose for any of the following:</b>	1.1 mg/m <sup>2</sup>
ANC < 500/mm <sup>3</sup> for > 7 days	
ANC < 1,000/mm <sup>3</sup> with fever or infection	
Platelets < 25,000/mm <sup>3</sup>	
Platelets < 50,000/mm <sup>3</sup> requiring transfusion	
Non-hematologic Grade 3 or 4 toxicities	
Omission or delay of Day 8 HALAVEN dose in previous cycle for toxicity	0.7 mg/m <sup>2</sup>
<b>Occurrence</b> of any event requiring permanent dose reduction while receiving 1.1 mg/m <sup>2</sup>	
<b>Occurrence</b> of any event requiring permanent dose reduction while receiving 0.7 mg/m <sup>2</sup>	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<sup>3</sup>) 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<sup>3</sup>) 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<sup>3</sup>.

**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<sup>2</sup> 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\* 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
<b>Blood and lymphatic system disorders<sup>a</sup></b>				
Neutropenia	82%	57%	53%	23%
Anemia	58%	2%	55%	4%
<b>Nervous system disorders</b>				
Peripheral neuropathy <sup>f</sup>	35%	8%	16%	2%
Headache	19%	<1%	12%	<1%
<b>General disorders</b>				
Asthenia/Fatigue	54%	10%	40%	11%
Pyrexia	21%	<1%	13%	<1%
Mucosal inflammation	9%	1%	10%	2%
<b>Gastrointestinal disorders</b>				
Nausea	35%	1%	28%	3%
Constipation	25%	1%	21%	1%
Vomiting	18%	1%	18%	1%
Diarrhea	18%	0	18%	0
<b>Musculoskeletal and connective tissue disorders</b>				
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%
<b>Metabolism and nutrition disorders</b>				
Decreased weight	21%	1%	14%	<1%
Anorexia	20%	1%	13%	1%
<b>Respiratory, thoracic, and mediastinal disorders</b>				
Dyspnea	16%	4%	13%	4%
Cough	14%	0	9%	0
<b>Skin and subcutaneous tissue disorders</b>				
Alopecia	45%	NA <sup>d</sup>	10%	NA <sup>d</sup>
<b>Infections</b>				
Urinary Tract Infection	10%	1%	5%	0

<sup>a</sup> adverse reactions were graded per National Cancer Institute Criteria for Adverse Events version 4.0.

<sup>b</sup> based upon laboratory data.

<sup>c</sup> includes peripheral neuropathy, peripheral sensorimotor neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.

<sup>d</sup> 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<sup>3</sup>) 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<sup>2</sup> on Days 1 and 8 of a 21-day cycle or dacarbazine at doses of 850 mg/m<sup>2</sup> (20%), 1000 mg/m<sup>2</sup> (64%), or 1200 mg/m<sup>2</sup> (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\* 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)<sup>†</sup>**

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

\* Adverse reactions were graded per National Cancer Institute Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).

<sup>†</sup> Safety data from one study site enrolling six patients were excluded.

<sup>‡</sup> Includes peripheral neuropathy, peripheral sensorimotor neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.

<sup>§</sup> Includes abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort.

<sup>e</sup> 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)<sup>†</sup> (Study 2)<sup>‡</sup>**

Laboratory Abnormality	Halaven		Dacarbazine	
	All Grades	Grades 3-4	All Grades	Grades 3-4
<b>Hematology</b>				
Anemia	70%	4.1%	52%	6%
Neutropenia	63%	32%	30%	8.9%
<b>Chemistry</b>				
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%

<sup>†</sup> 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)

<sup>‡</sup> 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<sup>2</sup> 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<sup>2</sup> to patients with mild hepatic impairment and 0.7 mg/m<sup>2</sup> to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m<sup>2</sup> to patients with normal hepatic function. Therefore, a lower starting dose of 1.1 mg/m<sup>2</sup> is recommended for patients with mild hepatic impairment (Child-Pugh A) and of 0.7 mg/m<sup>2</sup> 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<sup>2</sup>.

### 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.

HALAVEN® is a registered trademark used by Eisai Inc. under license from Eisai R&D Management Co., Ltd.

© 2016 Eisai Inc. All rights reserved.

Printed in USA / December 2016



# Onodera's Prognostic Nutritional Index in soft tissue sarcoma patients as a predictor of wound complications

**Background** The ability to predict a wound complication after radiation therapy and surgery for soft tissue sarcomas remains difficult. Preoperative nutritional status, as determined by Onodera's Prognostic Nutritional Index (OPNI), has been a predictor of complications in patients undergoing gastrointestinal surgery. However, the role OPNI has in predicting wound complications for soft tissue sarcoma remains unknown.

**Objective** To evaluate the role OPNI has in predicting wound complication in patients treated with radiation and surgery for soft tissue sarcomas.

**Methods** OPNI was calculated based on the published formula  $OPNI = (10 \times \text{albumin level [g/dL]}) + (0.005 \times \text{total lymphocyte count})$ . The albumin level and total lymphocyte counts closest to the index operation were chosen. Major and minor wound complications were identified. A receiver operating curve was calculated to identify a cut-off point value for OPNI and for age based on the best combination of sensitivity and specificity.

**Results** 44 patients were included in the study. Patients with an OPNI of <45.4 had a 7.5-times increased risk of a wound complication ( $P = .005$ ; 95% confidence interval [CI], 1.8-31.0). An OPNI of <45.4 had a sensitivity of 62% and specificity of 82% of predicting a wound complication. Being older than 73 years was associated with a 6.8-times increased risk of wound complications ( $P = .01$ ; 95% CI, 1.6-28.7).

**Limitations** Small sample size for patients with a rare condition

**Conclusion** An OPNI of <45.4 and being older than 73 years are strong predictors of which patients will have a wound complication after radiation therapy for soft tissue sarcomas. Preoperative nutritional status could be an important modifiable factor to help decrease wound complications.

Tae Won B Kim, MD,<sup>a</sup> Samuel Hardy, MD,<sup>b</sup> Danijel J Pericic, MS,<sup>c</sup> John Gaughan, MS, PhD, MBA,<sup>d</sup> and Mark Angelo, MD<sup>e</sup>  
<sup>a</sup>Department of Orthopaedic Surgery and <sup>b</sup>Palliative Care Program, Cooper University Hospital; <sup>c</sup>Cooper Medical School of Rowan University; and <sup>d</sup>Cooper Research Institute and <sup>e</sup>Palliative Care Program, Cooper University Hospital, all in Camden, New Jersey

## DISCLOSURES

The authors report no disclosures or conflicts of interest.

This article was originally published in the Journal of Community and Supportive Oncology JCSO 2017;15(4):e204-e207. ©2017 Frontline Medical Communications. doi: <https://doi.org/10.12788/jcso.0353>. It is reproduced here with permission from the copyright owner. Further reproduction prohibited without permission.

Wound complications after pre- or post-operative radiation for soft tissue sarcomas are well established.<sup>1</sup> The ability to predict who will have a wound complication remains difficult. Some studies have looked at risk factors such as smoking, and the preoperative nutritional status of patients has been identified as a risk factor for wound complication in patients with elective orthopedic surgical procedures.<sup>2</sup> One validated method of measuring preoperative nutritional status in patients with gastrointestinal malignant tumors has been with Onode-

ra's Prognostic Nutritional Index (OPNI). It uses the patient's preoperative albumin (g/dL) and absolute lymphocyte values (per mm<sup>3</sup>). The prognostic value of the OPNI has been demonstrated in patients with colorectal, esophageal, and gastric cancers, and has been shown to be prognostic for postoperative wound healing and overall prognosis.<sup>3-5</sup> In this study, we investigate the significance of preoperative nutritional status, measured by OPNI, as a predictor of wound complications in patients treated with pre- or postoperative radiation for soft tissue sarcoma.

› IN OUR STUDY, WE APPLIED OPNI TO ORTHOPEDIC ONCOLOGY AND SHOWED THAT THE PATIENT'S AGE AND PREOPERATIVE NUTRITIONAL STATUS WERE SIGNIFICANT PREDICTORS OF DEVELOPING A WOUND COMPLICATION.

## METHODS

After receiving Institutional Review Board approval for the study, we conducted a retrospective review of consecutive patients treated during July 2012-April 2016 for a soft tissue sarcoma by the orthopedic oncology division at Cooper University Hospital in Camden, New Jersey. Inclusion criteria were patients with biopsy-proven soft tissue sarcoma, who were older than 18 years, had received pre- or postoperative radiation, and who had a recorded preoperative albumin and total lymphocyte count. A minimum follow-up of 3 months was required to assess for postoperative wound complications. Exclusion criteria included patients who had a bone sarcoma, had not received radiation therapy, or had a missing preoperative albumin or total lymphocyte count.

All of the surgeries were performed by 2 fellowship-trained orthopedic oncologists. Patients received either pre- or postoperative radiation therapy by multiple radiation oncologists.

The OPNI was calculated based on the published formula  $OPNI = (10 \times \text{albumin level [g/dL]}) + (0.005 \times \text{total lymphocyte count [per mm}^3\text{)})$ . The albumin level and total lymphocyte counts closest to the index operation were chosen.

Demographic information including gender, age at diagnosis, height, and weight were recorded. Data related to the patients' pathologic diagnosis, stage at presentation, radiation therapy, and surgical resection were collected. A minor wound complication was defined as a wound problem that did not require operative intervention. Major wound complication was defined as a complication requiring operative intervention with or without flap reconstruction. Wound complications occurring within the 3-month postoperative period were considered.

Univariate and multiple variable analysis was performed. A *P* value  $<.05$  was considered significant. A receiver operating curve as well as recursive partitioning was performed for OPNI and age to determine the best cut-off point to use in the analysis. The Sobel test was used to evaluate mediation. All statistical anal-

ysis was performed using SAS v9.4 and JMP10. (SAS Institute, Cary, NC).

## RESULTS

In all, 44 patients (28 men, 16 women) were included in the study. Their mean age was 61.2 years (range, 19-94). The average size of the tumors was 8.5 cm in greatest dimension (range, 1.2-27.4 cm), and all of the patients had nonmetastatic disease at the time of surgical resection; 37 patients had R0 resections, and 7 patients had a positive margin from an outside hospital, but obtained R0 resections on a subsequent resection (TABLE 1 AND TABLE 2). In all, 30 patients received preoperative radiation, 14 patients received postoperative radiation, 32 patients received external beam radiation, 8 received Cyberknife treatment, and information for 4 patients was not unavailable. Mean preoperative external beam radiation and Cyberknife dose was 4,931 Gy and 3,750 Gy, respectively. Mean postoperative external beam and Cyberknife radiation dose was 6,077 Gy and 4,000 Gy, respectively. When evaluating radiation dose delivered between those who had wound complications and those who did not, there was no significant difference (TABLE 3).

Of the total, 13 patients had a wound complication (30%). Ten patients had preoperative radiation, and 3 had postoperative radiation. Ten patients had major wound complications requiring a combined 27 surgeries. Three patients had minor wound complications, which resolved with conservative management. One patient had a major wound complication in the group that had an initial R1 resection.

The OPNI was calculated based on the aforementioned formula. When the univariate analysis was performed, only age and OPNI were statistically significant. Patients older than 72.6 years had a 6.8 times higher risk of a wound complication ( $P = .01$ ; 95% confidence interval [CI], 1.6-28.7). When the OPNI value of 45.4 was used as the threshold, a patient with a preoperative OPNI value of  $<45.4$  had a 7.5 times increased risk of developing a wound complication ( $P = .005$ ; 95% CI, 1.8-31.0).

When the receiver operating curve and recursive partitioning was performed, an OPNI value of 45.4 showed a sensitivity of 62% and specificity of 82% in predicting wound complications (FIGURE 1).

When a multiple variable analysis was performed, OPNI and age were not statistically significant ( $P = .06$  and  $P = .11$ , respectively). A test for mediation was performed, and the OPNI seemed to mediate the effect age has on wound complications, accounting for 36% of the total effect (Sobel test statistic, 1.79;  $P = .07$ ).

## DISCUSSION

Wound complications after pre- and postoperative radiation for soft tissue sarcomas are well known. The best study to date to demonstrate that relationship was a randomized controlled trial performed in Canada, which showed that preoperative radiation resulted in 37% wound complications, compared with 17% for postoperative radiation.<sup>6</sup> In that study, of the wound complications in both radiation types, more than 50%-60% required a secondary surgical procedure, designating it as a major wound complication. Other variables that have been shown to contribute to wound complications include being older than 40 years and/or having large tumors, diabetes, peripheral vascular disease, and being a smoker.<sup>7-10</sup>

In our study, we applied OPNI to orthopedic oncology and showed that the patient's age and preoperative nutritional status were significant predictors of developing a wound complication. An OPNI of <45.4 increased the chance of a wound complication by 7.5 times. Being older than 73 years increased the risk of a wound complication by 6.8 times. Most of these wound complications were major and required surgical intervention.

In general surgical oncology, the evaluation of nutritional status has had a significant impact on the care of patients, especially for those patients undergoing gastrointestinal surgery. The OPNI was initially designed to assess the nutritional and immunological statuses of patients undergoing gastrointestinal surgery.<sup>11</sup> Preoperative OPNI has been shown to be

**TABLE 1** Anatomic locations of soft tissue sarcomas (N = 44)

Location	No. of patients
Proximal thigh	14
Upper extremity	13
Distal thigh/knee	6
Axial	6
Leg	5

**TABLE 2** Pathologic diagnoses of soft tissue sarcomas (N = 44)

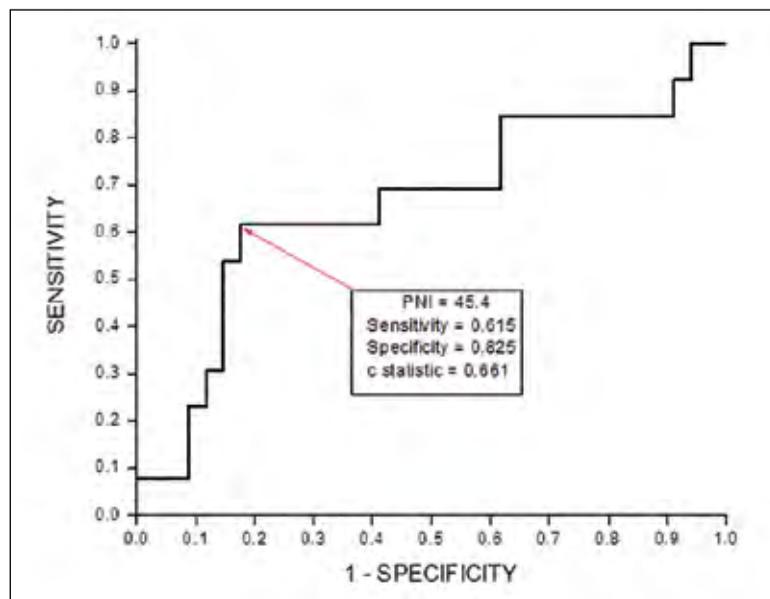
Diagnosis	No. of patients
Undifferentiated pleomorphic sarcoma	11
Myxofibrosarcoma	8
Synovial sarcoma	4
Leiomyosarcoma	4
Myxoid liposarcoma	2
Angiosarcoma	2
Liposarcoma	2
High-grade soft tissue sarcoma	2
Spindle cell sarcoma	2
Solitary fibrous tumor	1
Mesenchymal chondrosarcoma	1
Low-grade soft tissue sarcoma	1
Dedifferentiated liposarcoma	1
Neurofibrosarcoma	1
Extraskeletal osteosarcoma	1
Pleomorphic rhabdomyosarcoma	1

**TABLE 3** Average radiation doses among patients with and without wound complications (N = 44)

Type of radiation	Wound complication, dosage in Gy (n)		P-value
	Without	With	
EBRT and IMRT	5,480 (24)	4,989 (9)	$P = .16$
Cyberknife	3,812 (8)	3,750 (4)	$P = .85$

EBRT, external beam radiation therapy; IMRT, intensity-modulated radiation therapy

a good predictor of postoperative complications and survival in patients with colorectal cancer, malignant mesothelioma,



**FIGURE 1.** The receiver operating curve for Onodera's Prognostic Nutritional Index in patients treated with radiation and surgery for soft tissue sarcoma. An OPNI threshold value of 45.4 had the highest sensitivity and specificity in predicting a wound complication.

hepatocellular carcinoma and in patients who undergo total gastrectomy.<sup>12-15</sup> Chen and colleagues evaluated the significance of OPNI in patients with colorectal cancer. They found an optimal cut-off value of 45. An OPNI value <45 has a sensitivity and specificity of 85% and 69%, respectively, in predicting 5-year overall survival.<sup>16</sup> Hong and colleagues noted that an OPNI cut-off value of 52.6 as a predictor of overall survival.<sup>17</sup>

Poor preoperative nutritional status has been shown to have a negative impact on wound healing. In patients who underwent emergency laparotomy, a low OPNI had significantly higher rates of wound dehiscence and infection.<sup>18</sup> This happens because protein deficiency leads to decreased wound tensile strength, decreased T-cell function, decreased phagocytic activity, which ultimately diminish the patient's ability to heal and defend against wound infections.<sup>19-21</sup>

In soft tissue sarcoma patients, poor preoperative nutritional status is further compromised by radiation therapy to the wound. Gu and colleagues showed that radiation to wounds in mice showed ear-

ly inhibition of the inflammatory phase, injury and inhibition of fibroblasts, and collagen formation, and then prolonged re-epithelialization.<sup>22</sup> This "double hit" with radiation onto host tissue that is already nutritionally compromised could be an important cause of why wound complications occur at such high rates in our soft tissue sarcoma patients.

There are several limitations to this study. First, the study has a small sample size, which was a direct result of the number of patients who were excluded because an OPNI value could not be calculated for them. Second, we could not determine if the OPNI was more valuable in patients who underwent pre- or post-operative radiation. This study did not look at other nutritional indices such as prealbumin and vitamin levels. Third, the radiation was provided by different providers, so technique was variable, but the patients received nearly equivalent doses and variability in technique is likely limited. Fourth, we were not able to meaningfully analyze the role of chemotherapy in this patient population because there was a significant heterogeneity of patients receiving pre- and post-operative chemotherapy.

Our findings strongly suggest that a preoperative OPNI of <45.4 and being older than 73 years are strong predictors of patients who will experience a wound complication after radiation therapy for soft tissue sarcomas. This study has led us to start measuring preoperative albumin levels and assess complete metabolic panels. Our goal is to identify patients who are at high risk of wound complication and perform interventions to improve nutrition, then to study whether the interventions help lower the rates of wound complications. **TSJ**

#### CORRESPONDENCE

Tae Won B Kim, MD; kim-taewon@cooperhealth.edu.

#### REFERENCES

- Ormsby MV, Hilaris BS, Nori D, Brennan MF. Wound complications of adjuvant radiation therapy in patients with soft-tissue sarcomas. *Ann Surg.* 1989;210(1):93-99.

2. Greene KA, Wilde AH, Stulberg BN. Preoperative nutritional status of total joint patients: relationship to postoperative wound complications. *J Arthroplasty*. 1991;6(4):321-325.
3. Nozoe T, Kimura Y, Ishida M, Saeki H, Korenaga D, Sugimachi K. Correlation of pre-operative nutritional condition with post-operative complications in surgical treatment for oesophageal carcinoma. *Eur J Surg Oncol*. 2002;28(4):396-400.
4. Nozoe T, Kohno M, Iguchi T, et al. The prognostic nutritional index can be a prognostic indicator in colorectal carcinoma. *Surg Today*. 2012;42(6):532-535.
5. Nozoe T, Ninomiya M, Maeda T, Matsukuma A, Nakashima H, Ezaki T. Prognostic nutritional index: a tool to predict the biological aggressiveness of gastric carcinoma. *Surg Today*. 2010;40(5):440-443.
6. O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet*. 2002;359(9325):2235-2241.
7. Peat BG, Bell RS, Davis A, et al. Wound-healing complications after soft-tissue sarcoma surgery. *Plast Reconstr Surg*. 1994;93(5):980-987.
8. Kunisada T, Ngan SY, Powell G, Choong PF. Wound complications following pre-operative radiotherapy for soft tissue sarcoma. *Eur J Surg Oncol*. 2002;28(1):75-79.
9. Saddegh MK, Bauer HC. Wound complication in surgery of soft tissue sarcoma: analysis of 103 consecutive patients managed without adjuvant therapy. *Clin Orthop Relat Res*. 1993;289:247-253.
10. Tseng JF, Ballo MT, Langstein HN, et al. The effect of preoperative radiotherapy and reconstructive surgery on wound complications after resection of extremity soft-tissue sarcomas. *Ann Surg Oncol*. 2006;13(9):1209-1215.
11. Smale BF, Mullen JL, Buzby GP, Rosato EF. The efficacy of nutritional assessment and support in cancer surgery. *Cancer*. 1981;47(10):2375-2381.
12. Mohri Y, Inoue Y, Tanaka K, Hiro J, Uchida K, Kusunoki M. Prognostic nutritional index predicts postoperative outcome in colorectal cancer. *World J Surg*. 2013;37(11):2688-2692.
13. Jiang N, Deng JY, Ding XW, et al. Prognostic nutritional index predicts postoperative complications and long-term outcomes of gastric cancer. *World J Gastroenterol*. 2014;20(30):10537-10544.
14. Pinato DJ, North BV, Sharma R. A novel, externally validated inflammation-based prognostic algorithm in hepatocellular carcinoma: the prognostic nutritional index (PNI). *Brit J Cancer*. 2012;106(8):1439-1445.
15. Yao ZH, Tian GY, Wan YY, et al. Prognostic nutritional index predicts outcomes of malignant pleural mesothelioma. *J Cancer Res Clin Oncol*. 2013;139(12):2117-2123.
16. Jian-Hui C, Iskandar EA, Cai Sh I, et al. Significance of Onodera's prognostic nutritional index in patients with colorectal cancer: a large cohort study in a single Chinese institution. *Tumour Biol*. 2016;37(3):3277-3283.
17. Hong S, Zhou T, Fang W, et al. The prognostic nutritional index (PNI) predicts overall survival of small-cell lung cancer patients. *Tumour Biol*. 2015;36(5):3389-9337.
18. Mohil RS, Agarwal A, Singh N, Arora J, Bhatnagar D. Does nutritional status play a role in patients undergoing emergency laparotomy? *E Spen Eur E J Clin Nutr Metab*. 2008;3(5):e226-e231.
19. Kay SP, Moreland JR, Schmitter E. Nutritional status and wound healing in lower extremity amputations. *Clin Orthop Relat Res*. 1987;(217):253-256.
20. Dickhaut SC, DeLee JC, Page CP. Nutritional status: importance in predicting wound-healing after amputation. *J Bone Joint Surg Am*. 1984;66(1):71-75.
21. Casey J, Flinn WR, Yao JS, Fahey V, Pawlowski J, Bergan JJ. Correlation of immune and nutritional status with wound complications in patients undergoing vascular operations. *Surgery*. 1983;93(6):822-827.
22. Gu Q, Wang D, Cui C, Gao Y, Xia G, Cui X. Effects of radiation on wound healing. *J Environ Pathol Toxicol Oncol*. 1998;17(2):117-123.

> OUR FINDINGS STRONGLY SUGGEST THAT A PREOPERATIVE OPNI OF <45.4 AND BEING OLDER THAN 73 YEARS ARE STRONG PREDICTORS OF PATIENTS WHO WILL EXPERIENCE A WOUND COMPLICATION AFTER RADIATION THERAPY FOR SOFT TISSUE SARCOMAS.

# Tumor lysis syndrome in an adolescent with recurrence of abdominal rhabdomyosarcoma: A case report and literature review

Sabrina Solorzano, DO<sup>1</sup>;  
Matteo Trucco, MD<sup>1,2</sup>; John M.  
Goldberg, MD<sup>1,2</sup>; Fernando F.  
Corrales-Medina, MD<sup>1,2</sup>

1. Holtz Children's Hospital  
- Jackson Memorial Health  
System, Miami, FL.

2. Division of Pediatric  
Hematology-Oncology,  
Department of Pediatrics.  
University of Miami-Miller  
School of Medicine, Miami,  
FL.

## DISCLOSURES

The authors declared having  
no relevant conflicts of  
interest.

DOI: 10.12788/sarcj.0001

## INTRODUCTION

Tumor lysis syndrome (TLS) is a life-threatening oncologic emergency that results when massive cell breakdown occurs either spontaneously or in response to cytotoxic chemotherapy. TLS is characterized by metabolic derangements, including hyperkalemia and hyperphosphatemia, secondary to the release of intracellular components into the systemic circulatory system. In addition, purine degradation can lead to hyperuricemia, and precipitation of calcium phosphate can result in hypocalcemia. Lactate dehydrogenase (LDH) levels are often elevated, especially in higher risk patients; however, this finding is not a specific marker for TLS.

TLS more commonly occurs in patients with rapidly proliferating hematological malignancies, such as acute leukemias with a high white blood cell count and Burkitt's lymphoma, and is a relatively rare event in patients with solid malignancies.<sup>1-3</sup> It is even more rare in patients with tumor recurrence.

There are few reported cases of TLS in children with solid malignancies. To our knowledge, only one case of TLS has previously been reported in a pediatric patient with abdominal rhabdomyosarcoma. We report the second such case, and what we believe to be the only reported case of TLS occurring in a pediatric patient with recurrence of a solid tumor.

## CASE DESCRIPTION

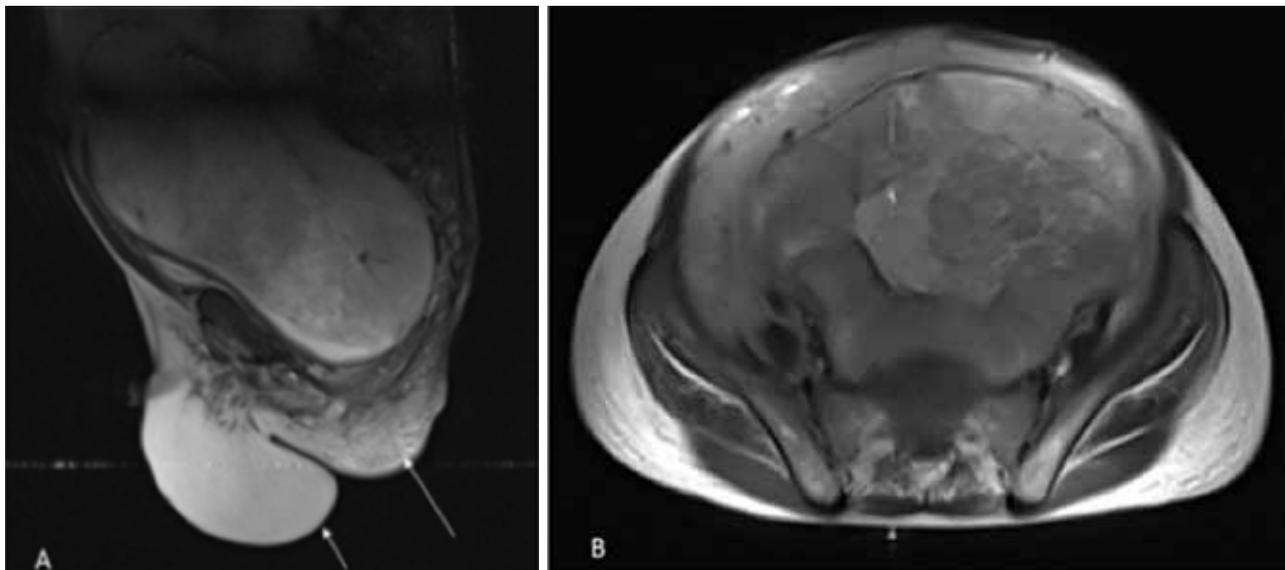
A 15-year-old male from Saudi Arabia presented to our hospital with confirmed stage IV abdominal rhabdomyosarcoma

and lung metastases diagnosed in 2012. His initial treatment consisted of complete surgical resection, lung irradiation, and chemotherapy with intercalating cycles of ifosfamide/etoposide and vincristine/doxorubicin/cyclophosphamide, as per the COG-ARST0431 high-risk sarcoma protocol (NCT00354744). He completed treatment without any reported TLS in Saudi Arabia in June 2014. He had no residual tumor at the end of therapy, but six months later he was found to have an abdominal recurrence and started treatment with single-agent topotecan chemotherapy. He experienced worsening abdominal distention, pain, and difficulty voiding, prompting his family to seek further treatment options abroad.

The patient was admitted to our hospital in March 2015. Despite being severely malnourished, he was in stable condition. He was noted to have a markedly enlarged, firm, distended abdomen with dilated veins, abdominal and lower back pain, lower extremity pitting edema, and difficulty urinating.

Initial laboratory findings were unremarkable except for elevated levels of BUN (29 mg/dL), creatinine (1.69 mg/dL), and phosphorus (5.6 mg/dL). MRI revealed a large pelvic mass measuring 15.3 x 15.2 x 21.3 centimeters in transverse, anterior-posterior, and cranio-caudal dimensions, respectively; with concomitant severe bilateral hydronephrosis (FIGURE 1).

Three days following admission, the patient's urine output decreased and his creatinine level rose rapidly. His worsening abdominal distention was attributed



**FIGURE 1.** Sagittal (A) and Axial (B) T2-weighted MR images of the pelvis (prior to initiating therapy) demonstrating a large heterogeneous mass occupying the entire pelvis. There is evidence of edema involving the soft tissues of the perineum (long arrow) and a large associated hydrocele (short arrow).

to growing tumor bulk and obstructive nephropathy. He required emergency placement of bilateral nephrostomy tubes. Urine output subsequently improved; although, serum creatinine remained persistently elevated.

Given his worsening condition, chemotherapy was begun three days after nephrostomy tube placement with vinorelbine, cyclophosphamide, and temsirolimus, as per COG-ARST0921 (NCT01222715), at renal-adjusted doses. Laboratory studies approximately 24 hours after chemotherapy initiation demonstrated the presence of TLS (TABLE 1). Potassium level was at the upper end of normal at 4.9 mmol/L, calcium level was decreased to 7.1 mg/dL, phosphorus level elevated to 12 mg/dL, uric acid level was markedly elevated to 19.5 mg/dL, and LDH elevated to 662 unit/L. A dose of 0.15 mg/kg of rasburicase was immediately given with a second dose repeated 14 hours later, after which the uric acid level decreased to less than 0.5 mg/dL. Sevelamer, sodium polystyrene, calcium carbonate, and magnesium gluconate were also administered to treat other electrolyte imbalances. The patient remained at clinical baseline throughout, and the TLS laboratory derangements

normalized by three days after the TLS diagnosis; LDH level normalized after one week. The patient continued with chemotherapy, per protocol, with no further TLS-related complications. Over subsequent weeks, his tumor continued to shrink dramatically. Pain related to intra-abdominal compression, lower extremity edema, and difficulty voiding resolved.

## DISCUSSION

A literature search was performed using Pubmed/Medline and Scopus from 1950 to July 2016 using key words “TLS,” “tumor lysis syndrome,” “pediatric tumor lysis syndrome,” “tumor lysis syndrome in solid malignancies,” “recurrence,” “solid tumor,” “sarcoma,” “rhabdomyosarcoma,” and their combinations. The references of relevant articles were reviewed. Baeksgaard and Sorensen,<sup>3</sup> and Vodopivec, et al<sup>4</sup> provide an organized review of reported cases of TLS in solid tumors until 2002 and 2011 respectively; their articles are supported by the 2014 literature review by Mirrakhimov, et al.<sup>1</sup> Excluding our case, 13 cases of TLS have been described in pediatric patients with solid tumors, with only one occurring in patient with abdominal rhabdomyosar-

TUMOR LYSIS SYNDROME IN AN ADOLESCENT:  
A CASE REPORT AND LITERATURE REVIEW

**TABLE 1** Tabulation of TLS laboratory values and renal function, as measured with creatinine level, from day of admission to resolution of acute TLS

Labs	Admission	- 3 days	AM before chemo given	+1 day am/ pm ↓	+2 days am/pm ↓	+3 days	+4 days
Potassium (3.5 -5.0 mmol/L)	4.9	3.9	3.0	3.6/ 4.6	4.4/ 3.3	3.1/2.4	2.5
Calcium (8- 11 mg/dL)	9.1	8.7	8.3	<b>7.2/ 7.1</b>	<b>7.0/ 6.7</b>	<b>6.7/ 6.2</b>	<b>7.4</b>
Phosphorus (2.5- 4.5 mg/dL)	<b>5.6</b>	<b>5.5</b>	<b>6.8</b>	<b>7.0/ 12.0</b>	<b>11.6/ 16.6</b>	<b>9.8/ 6.0</b>	3.6
Uric Acid (3.5-8.5 mg/dL)	-	-	-	-/ <b>19.5</b>	<b>13.6/</b> 0.6	<0.5	<0.5
Creatinine (0.5 -1 mg/dL)	<b>1.7</b>	<b>2.2</b>	<b>2.1</b>	<b>1.6/ 1.9</b>	<b>2.2/ 2.1</b>	<b>2.1/ 1.5</b>	1.0
LDH (313-618 unit/L)	592	-	-	-/ <b>662</b>	<b>621/1211</b>	<b>1502/1592</b>	<b>1505</b>

“-“ indicates level was not collected. “↓” indicates Rasburicase was given. **Bold** indicates an abnormal laboratory value.

**TABLE 2** Reported cases of tumor lysis syndrome occurring in pediatric solid tumors, not including presented case

Patient Age/ Gender	Tumor	Onset of TLS	Reference
9 years, female	Abdominal RMS	Following chemotherapy initiation	5
14 years, male	Disseminated RMS; No localized primary tumor	Spontaneous with DIC	6
14.5 years, female	Disseminated RMS; Primary tumor: intracranial parietal region	Spontaneous with DIC	6
14 years, male	Disseminated RMS; No localized primary tumor	Spontaneous	7
2 weeks, female	Neuroblastoma	Following radiotherapy	8
3.5 months, female	Neuroblastoma	Following radiotherapy	8
2 days, female	Neuroblastoma	Spontaneous	8
4 months, male	Neuroblastoma	Following chemotherapy initiation	8
22 months, female	Neuroblastoma	Following chemotherapy initiation	9
7 months, male	Hepatoblastoma	Following chemotherapy initiation	10
7 months, female	Hepatoblastoma	Intra-operatively	11
23 years, male	Medulloblastoma	Following chemotherapy initiation	3
5 years, male	Wilm’s Tumor	Intra-operatively	12

“RMS” indicates rhabdomyosarcoma

coma<sup>5</sup>. Patients’ ages ranged from 2 days to 23 years; the cases are summarized in the following table (TABLE 2). To our knowledge, ours is the first case of TLS reported in association with a pediatric solid tumor recurrence.

It is important to note that the three

reported cases of disseminated rhabdomyosarcoma<sup>6,7</sup> were initially believed to be hematologic malignancies because of their presentation with lymphadenopathy, metastases to the bone marrow, and spontaneous onset of TLS. Rhabdomyosarcoma with bone marrow involvement

**TABLE 3** Guidelines for prophylactic treatment of hyperuricemia in TLS based on risk assessment

Low Risk	Manage with close observation of fluid status and laboratory results
Intermediate Risk	Offer up to seven days of allopurinol prophylaxis with increased hydration post initiation of treatment or until risk of TLS has resolved
High Risk	Treat prophylactically with a single dose of 0.2 mg/kg of rasburicase
Established TLS	Treat with rasburicase 0.2 mg/kg/day - duration to depend on clinical response.
Note:	<ul style="list-style-type: none"> <li>- If the patient is receiving rasburicase, the addition of allopurinol is not recommended, as it has the potential to reduce the effectiveness of rasburicase.</li> <li>- Rasburicase is to be avoided in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.</li> </ul>

Adapted from Jones G, Will A, Jackson GH, et al. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. *Br J Haematol.* 2015;169:661-671.

without an obvious primary tumor is easily confused with acute leukemia, particularly of the lymphoblastic type.<sup>12</sup> However, this disseminated-hematologic presentation of rhabdomyosarcoma differs from the solid abdominal-pelvic tumor, which we describe.

Cairo and Bishop<sup>13</sup> categorize patients as either laboratory TLS, depicted by metabolic abnormalities alone, or clinical TLS, occurring when laboratory imbalances lead to significant, life-threatening clinical manifestations. Hyperkalemia may lead to cardiac arrhythmias such as torsades de pointes and cardiac arrest. Obstructive nephropathy can occur from the precipitation of calcium phosphate or uric acid crystals in the renal tubules. Hypocalcemia may cause neuromuscular irritability including tetany, convulsions, and altered mental status.<sup>13, 14</sup>

The 2015 “Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology”<sup>4</sup> state there are well-recognized risk factors for the development of TLS including, but not limited to, high tumor burden, tumors with rapid cell turnover, and pre-existing renal impairment. Cairo and Bishop, on behalf of the TLS expert panel consensus of 2010<sup>2</sup>, classify patients as having low-risk disease (LRD), intermediate-risk disease (IRD), or high-risk disease (HRD) based on the risk factors and type of malignancy. All patients with solid tumors are classified

into LRD, unless the tumors are bulky or sensitive to chemotherapy, mentioning specifically that neuroblastomas, germ-cell tumors and small cell lung cancers are classified as IRD. Cairo and Bishop take into account the risk factor of renal dysfunction/ involvement, which if present, increases the risk by one level. For example, if the patient has IRD and has renal dysfunction, risk increases to HRD<sup>2</sup>. However, these guidelines do not mention or address the significance of recurrence in any kind of malignancy with regards to assessing risk for TLS.

The British Committee’s 2015 Guidelines for management of TLS in hematologic malignancies<sup>14</sup> provide recommendations for treatment based on the patient’s risk classification (TABLE 3). Children with HRD are recommended to be treated prophylactically with a single dose of 0.2 mg/kg of rasburicase. Patients with IRD are recommended to be offered up to 7 days of allopurinol prophylaxis with increased hydration post initiation of treatment or until risk of TLS has resolved. Patients with LRD are recommended to be managed essentially with close observation. Patients with established TLS should receive rasburicase 0.2 mg/kg/day - duration to depend on clinical response. If the patient is receiving rasburicase, the addition of allopurinol is not recommended, as it has the potential to reduce the effectiveness of rasburicase. Further, rasburicase is to be avoided in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency<sup>14</sup>.

➤ PATIENTS WITH ESTABLISHED TLS SHOULD RECEIVE RASBURICASE 0.2 MG/KG/DAY-DURATION TO DEPEND ON CLINICAL RESPONSE.

› OUR PATIENT LIKELY DEVELOPED TLS BECAUSE OF A FAST GROWING TUMOR THAT CAUSED SIGNIFICANT TUMOR BURDEN AND RENAL INVOLVEMENT, INDICATED BY AN ELEVATED PHOSPHORUS LEVEL.

Our patient likely developed TLS because of a fast growing tumor that caused significant tumor burden and renal involvement, indicated by an elevated phosphorus level. Despite these risk factors, TLS was not anticipated in the case presented; therefore, a uric acid level was not collected at the time of admission. Review of the literature indicates that the incidence of TLS in a solid tumor recurrence is either unheard of, or is likely under-reported and truly unknown. Further, the TLS expert panel consensus of 2010<sup>2</sup>, which provides guidelines on risk assessment for TLS, does not address the risk of TLS in a malignancy recurrence. The British Committee's 2015 guidelines<sup>14</sup> also do not address hyperuricemia prophylaxis in a solid tumor recurrence.

Our case presents a question regarding the degree of risk for the development of TLS in a solid tumor recurrence. If the guidelines had existed at the time of the case presentation and had been applied, our patient would likely be classified as having IRD because of his renal involvement. This classification would have lead to a different course of management when initiating chemotherapy, likely prevented laboratory TLS, and provided more cost effective treatment, as rasburicase is known to be expensive.

On the other hand, it can also be argued that our patient classifies as LRD, considering the rarity of TLS in a solid tumor recurrence, that the patient had no TLS complication with his initial course of therapy, and also had a normal LDH on admission. LDH is sometimes used to assess risk in hematological malignancies, although it is not used to make the diagnosis of TLS<sup>2</sup>. However, with such an argument, it is assumed that the risk of TLS in a solid tumor malignancy recurrence, with no previous TLS complication, is less than the risk associated with a new-onset solid tumor malignancy when, truly, the actual risk is not known. Again, the question is raised of the degree of risk for the development of TLS in a case of a malignancy recurrence, and also in a pediatric patient with risk factors.

In our patient's case, close observa-

tion allowed for prompt diagnosis, appropriate treatment of laboratory TLS, and prevented clinical symptoms from developing. However, a screening or baseline uric acid level may have lead to a more conservative approach towards hyperuricemia prophylaxis, similar to treating the patient as IRD. Therefore, we recommend that a screening or baseline uric acid level and LDH level be obtained when initiating chemotherapy, even in patients with LRD.

Our patient was never hyperkalemic, likely because of concomitant administration of furosemide in an attempt to improve his decreased urine output. Hyperuricemia dropped from 19.5 mg/dL to less than 0.5 mg/dL within 24 hours, following two doses of 0.15 mg/kg of rasburicase, confirming the efficacy of this therapy in cases of established TLS, as is recommended by the British Committee's 2015 guidelines.<sup>14</sup>

## CONCLUSION

TLS is a relatively rare event in patients with solid malignancies and even more rare in a tumor recurrence. While there is only one previously reported case of TLS occurring in a pediatric patient with abdominal rhabdomyosarcoma, there are not any reported cases to date of TLS occurring in pediatric solid tumor recurrence. This may be because the incidence is truly rare or because cases may be under-reported. Thus, a question is raised regarding the risk for TLS in a solid tumor recurrence, and moreover in a pediatric patient with pre-existing risk factors, such as renal involvement.

TLS remains a life-threatening emergency that can be prevented and reversed if a high index of suspicion is maintained. We recommend all patients with malignancies receiving chemotherapy, especially those with risk factors, have a baseline or screening uric acid and LDH level drawn, as part of the assessment and risk-stratification for TLS which should always be performed. **TSJ**

---

## CORRESPONDENCE

Fernando F Corrales-Medina, MD, ffc5@med.miami.edu

## REFERENCES

1. Mirrakhimov AE, Ali AM, Khan M, et al. Tumor lysis syndrome in solid tumors: an up to date review of the literature. *Rare Tumors*. 2014;6:68-74.
2. Cairo MS, Bertrand C, Reiter A, et al. Recommendation for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *Br J Haematol*. 2010;149:578-586.
3. Bæksgaard L, Sørensen JB. Acute tumor lysis syndrome in solid tumors – a case report and review of the literature. *Cancer Chemother Pharmacol*. 2003;51:187-192.
4. Vodopivec D, Rubio J, Fornoni A, et al. An unusual presentation of tumor lysis syndrome in a patient with advanced gastric adenocarcinoma: case report and literature review. *Case Rep Med*. 2012;2012:1-12.
5. Khan J, Broadbent VA. Tumor lysis syndrome complicating treatment of widespread metastatic abdominal rhabdomyosarcoma. *Pediatr Hematol Oncol*. 1993;10:151-155.
6. Bien E, Maciejka-Kapuscinka L, Niedzwiecki M, et al. Childhood rhabdomyosarcoma metastatic to bone marrow presenting with disseminated intravascular coagulation and acute tumour lysis syndrome: review of the literature apropos of two cases. *Clin Exp Metastasis*. 2010;27:399-407.
7. Patiroglu T, Isik B, Unal E, et al. Cranial metastatic alveolar rhabdomyosarcoma mimicking hematological malignancy in an adolescent boy. *Childs Nerv Syst*. 2014;30:1737-1741.
8. Hain RD, Rayner L, Weitzman S, et al. Acute tumour lysis syndrome complicating treatment of stage IVS neuroblastoma in infants under six months old. *Med Pediatr Oncol*. 1994;23:136-139.
9. Kushner BH, LaQuaglia MP, Modak S, et al. Tumor lysis syndrome, neuroblastoma, and correlation between serum lactate dehydrogenase levels and MYCN-amplification. *Med Pediatr Oncol*. 2003;41:80-82.
10. Bercovitz RS, Greffe BS, Hunger SP. Acute tumor lysis syndrome in a 7-month-old with hepatoblastoma. *Curr Opin Pediatr*. 2010;22:113-116.
11. Lobe TE, Karkera MS, Custer MD, et al. Fatal refractory hyperkalemia due to tumor lysis during primary resection for hepatoblastoma. *J Pediatr Surg*. 1990;25:249-250.
12. Sandberg A, Stone J, Czarnecki L, et al. Hematologic Masquerade of Rhabdomyosarcoma. *Am J Hematol*. 2001;68:51-57.
13. Cairo M, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*. 2004;127:3-11.
14. Jones G, Will A, Jackson GH, et al. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. *Br J Haematol*. 2015;169:661-671.



[www.curesarcoma.org](http://www.curesarcoma.org)



@curesarcoma #curesarcoma

— OUR MISSION —

The mission of the Sarcoma Foundation of America (SFA) is to advocate for sarcoma patients by funding research and by increasing awareness about the disease. The organization raises money to privately fund grants for sarcoma researchers and conducts education and advocacy efforts on behalf of sarcoma patients.