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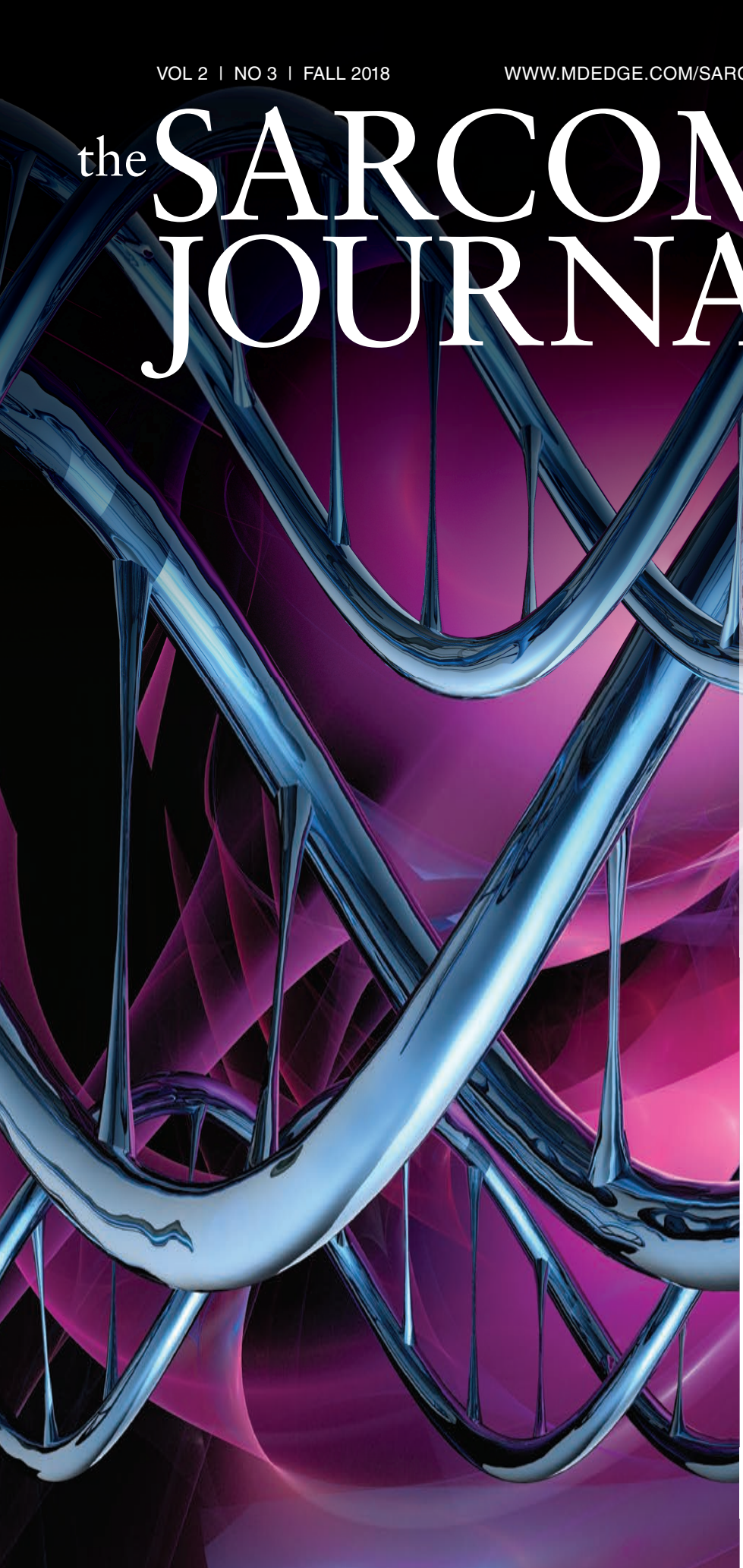


TRANSLATIONAL MEDICINE

Chromoplexy linked to aggressive Ewing sarcomas

PAGE 5

Plus, the progression to targeted therapies, and more reports from ASCO 2018.

Sarcoma SFA Foundation of America
finding the cure in our time

START WITH A BREAKTHROUGH

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

INDICATION

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

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

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

IMPORTANT SAFETY INFORMATION FOR LARTRUVO

Warnings and Precautions

Infusion-Related Reactions

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

Embryo-Fetal Toxicity

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

Most Common Adverse Reactions/Lab Abnormalities

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

Use in Specific Populations

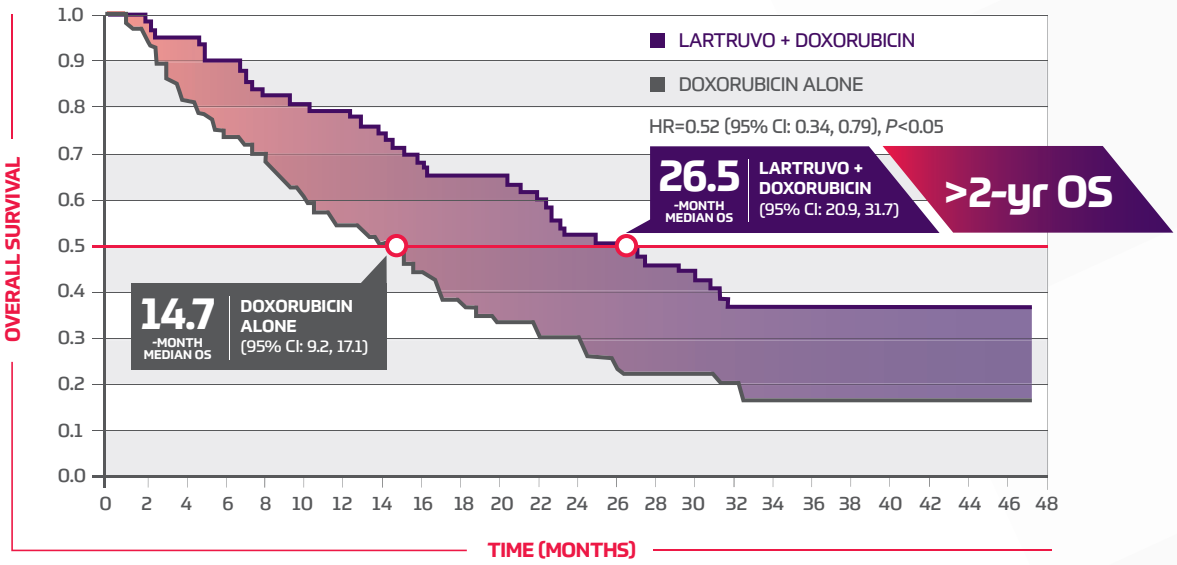
- Lactation: Because of the potential risk for serious adverse reactions in breastfeeding infants, advise women not to breastfeed during treatment with LARTRUVO and for at least 3 months following the last dose.

Please see Brief Summary of Prescribing Information on adjacent pages.

OR HCP ISI 19OCT2016

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

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



NUMBER AT RISK

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

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

CI=confidence interval; HR=hazard ratio.

OBJECTIVE RESPONSE RATE (ORR)*

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

- VS -

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

PROGRESSION-FREE SURVIVAL (PFS)†

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

- VS -

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

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

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

ORR does not include stable disease.

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

PFS based on independent review.

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

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

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

VISIT LARTRUVO.COM/HCP TO LEARN MORE

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

Lartruvo®
(OLARATUMAB)
Injection 10 mg/mL

Lilly

LARTRUVO™ (olaratumab) injection

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

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

Embryo-Fetal Toxicity

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

ADVERSE REACTIONS

Clinical Trials Experience

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

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

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

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

[b] Fatigue includes: asthenia and fatigue.

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

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

LARTRUVO™ (olaratumab) injection OR HCP BS 21OCT2016

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

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

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

[b] aPTT = activated partial thromboplastin time

Immunogenicity

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Contraception

Females

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

Infertility

Males

Based on animal models, LARTRUVO may impair male fertility.

Pediatric Use

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

Geriatric Use

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

PATIENT COUNSELING INFORMATION

Infusion-Related Reactions

Advise patients to report signs and symptoms of infusion reactions.

Embryo-Fetal Toxicity

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

Lactation

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

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

Lilly

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COVER: LAGUNA DESIGN/Science Source

Sarcoma Foundation of America SFA finding the cure in our time

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Chromoplexy linked to aggressive Ewing sarcomas

Mary Jo M. Dales

FROM SCIENCE

Chromoplexy, a sudden burst of complex, looplike gene rearrangements that gives rise to a fusion gene, appears to be associated with aggressive Ewing sarcomas, based on a study of 124 tumors reported in Science.

Ewing sarcomas with complex karyotypes are associated with a poorer prognosis, compared with those with simpler karyotypes. The new findings show that these complex karyotypes are the product of chromoplexy and that chromoplexy-generated fusions arise early, giving rise to both primary and relapse Ewing sarcoma tumors, which can continue to evolve in parallel.

Analysis of the sequence context surrounding chromoplexy breaks may provide clues and potentially point to a therapeutic vulnerability that could be used to treat Ewing sarcomas. Further, given the preference of chromoplexy events for transcriptionally active regions, Ewing sarcomas that arise from chromoplexy may be responsive to immune checkpoint inhibition.

In a study of the whole genomes of 124 Ewing sarcomas, chromoplexy rather than simple reciprocal translocations defined the gene fusions seen in 52 tumors (42%). Ewing sarcoma involves fusions between *EWSR1*, a gene encoding an RNA-binding protein, and E26 transformation-specific (ETS) transcription factors.

"Our analyses reveal rearrangement bursts (chromoplectic loops) as a source of gene fusion in human bone and soft tissue tumors. Ewing sarcomas with complex karyotypes are associated with a poorer prognosis than are those with simpler karyotypes, and here we show chromoplexy as the mechanism in 42% of tumors. It is possible that the chromoplectic tumor's additional gene disruptions and fusions contribute to the difference in patient survival," wrote Nathaniel D. Anderson of the Hospital for Sick Children, Toronto, and the University of Toronto, and his colleagues.

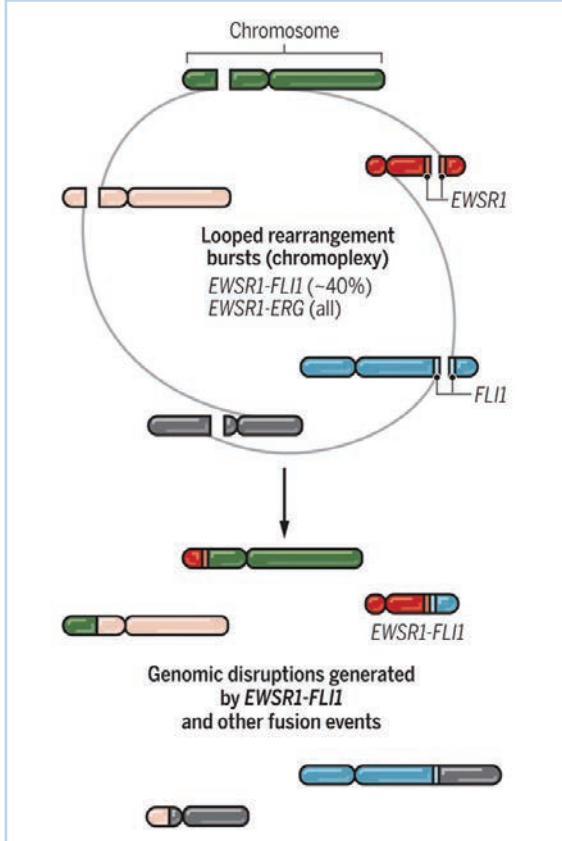

FIGURE Fusions via chromoplexy: Bursts of complex rearrangements can generate Ewing sarcoma oncogenic fusion genes and are associated with genomic complexity, more frequent TP53 mutations, and increased risk of relapse.

Adapted by A. Kitterman/Science

Standard reciprocal translocations involve DNA breaks in two fusion partners. Chromoplexy involves three or more breakpoints in the genome. A loop pattern emerges as these three or more broken chromosome ends are forced to find a new partner. The result is the formation of

functional *EWSR1-FLI1* or *EWSR1-ERG* fusions that, upon expression, provide a selective growth or survival advantage.

The researchers found that the loop rearrangements always contained the disease-defining fusion at the center, but they disrupted multiple additional genes. The loops occurred preferentially in early replicating and transcriptionally active genomic regions.

They found similar loops forming canonical fusions in three other sarcoma types.

"Our whole-genome sequence data support a model in which there is an early clone of (Ewing sarcoma), containing *EWSR1-ETS* and chromoplexy, arising at least 1 year before diagnosis, which gives rise to both the primary and metastatic or relapse tumors. Whether the bursts ... are chance events or driven by specific mutational processes, akin to the RAG machinery operative in leukemia, remains to be established. As an increasing and diverse number of tumor genome sequences become available, we may be able to define further rearrangement processes that underlie fusion genes and thus unravel the causes of fusion-driven human cancers," the researchers wrote.

The clinical features and demographics of the study patients were typical of Ewing sarcoma patients. Average patient age at diagnosis was 14.8 years (2.8-36.6 years); the male-to-female ratio was 1.38:1; and 14 patients had relapsed, with 13 having died from their disease.

About half of fusions between the EWS RNA binding protein 1 (*EWSR1*) gene on chromosome 22 and an E26 transformation-specific (ETS) family transcription factor gene, either *FLI1* at 11q24 or *ERG* at 21q11 arose via chromoplexy.

mdales@mdedge.com

SOURCE: Anderson et al. Science 2018 Aug 31. doi: 10.1126/science.aam8419.

VIEWS

Time for whole genome sequencing in Ewing sarcoma?

The contribution of genetic analysis to the current standard of care for Ewing sarcoma is limited to confirmation of the diagnostic *EWSR1-FLI1* or *EWSR1-ERG* fusions. The discovery of genomic patterns associated with subsets of Ewing sarcomas raises the question of whether additional molecular diagnostic modalities are warranted. If chromoplexy events are important clinical biomarkers for disease aggressiveness in this tumor, as the authors suggest, their findings may support a new indication for clinical whole genome sequencing.

Analysis of additional patient samples will be needed, however, to confirm that the presence of chromoplexy is an independent prognostic predictor in Ewing sarcoma. This is because the researchers find that chromoplexy-driven Ewing sarcoma more likely contains tumor protein 53 (*TP53*) mutations. Because TP53 and stromal antigen 2 (*STAG2*) mutations and genomic complexity have each been associated with more aggressive Ewing sarcoma, dissecting the contribution of these factors to poor clinical outcomes in chromoplexy-derived Ewing sarcoma will be an important area of future work.

More generally, the study has important clinical implications for the genomic diagnosis of these and other cancers, as well as the expanding biological role of complex rearrangements in cancer evolution.

Could chromoplexy events in Ewing sarcoma be linked, for example, to the activity of an aberrantly expressed endogenous transposase such as PiggyBac transposase 5 (PGBD5), which was recently implicated in the genesis of the pathogenic gene rearrangements in childhood malignant rhabdoid tumors? An alternative possibility is a constitutional or acquired DNA repair defect (Science 2018 Aug 31. doi: 10.1126/science.aau8231).

Marcin Imielinski is with the Meyer Cancer Center, Cornell University, and the New York Genome Center, New York. Marc Ladanyi is with Memorial Sloan Kettering Cancer Center, New York. They made their remarks in an editorial in Science that accompanied the study.

Novel molecular assay: Promising results in bone and soft tissue tumor evaluation

Andrew D. Bowser

FROM THE JOURNAL OF MOLECULAR DIAGNOSTICS

A novel method for detection of translocations appears to be superior to conventional molecular assays in the evaluation of bone and soft tissue tumor samples, according to researchers.

The technique of anchored multiplex polymerase chain reaction (AMP)–based targeted next-generation sequencing (NGS) had a failure rate of 14% but, nonetheless, worked favorably when compared with conventional techniques, which were associated with several false positives in this study, the researchers reported in the Journal of Molecular Diagnostics.

Two new fusion partners for the USP6 gene were found using AMP-based targeted NGS in this study, which thus contributed to the "further unraveling of the molecular landscape" for these tumors, added corresponding author Judith V.M.G. Bovée, MD, PhD, of the department of pathology at Leiden (the Netherlands) University Medical Center and her colleagues.

While the genetics of bone and soft tissue tumors have diagnostic value in clinical practice, standard fluorescence in situ hybridization (FISH) and reverse transcriptase PCR are associated with several drawbacks, such as a high false-negative rate in the case of FISH, Dr. Bovée and her coauthors wrote.

Accordingly, the researchers evaluated the applicability of a targeted sequencing assay (Archer FusionPlex Sarcoma kit, which was developed by ArcherDX) aimed at 26 genes relevant to bone and soft tissue tumor diagnostics.

Besides allowing for assessment of multiple target genes in a single assay, this technique circumvents the need to know both fusion partners for translocation detection, which opens up the possibility of identifying novel or rare fusion partners, investigators noted.

AMP-based targeted NGS was used to evaluate 81 bone and soft tissue tumor samples, and of those, 48 cases showed a fusion. For the remaining 33 cases in which no fusion was detected, 22 were considered truly negative because samples met all criteria for good quality, while the remaining 11 (14%) were considered not reliable because of insufficient quality.

The samples were also evaluated through use of FISH, reverse transcriptase PCR, or both in 58 cases and use of immunohistochemistry in 16 cases; for the remaining 7 cases, no assay or immunohistochemistry could be applied because of a lack of availability.

Among the 48 entities that were fusion positive according to AMP-based targeted NGS, 29 were validated using standard molecular assays, and of those, 25 had concordant results. Further analysis of the four discordant cases with a third independent technique confirmed the AMP-based targeted NGS findings.

Among the 22 fusion-negative high-quality samples, 19 were validated using FISH, and one case was found to be discordant; however, despite use of a third independent technique, this discrepancy could not be resolved.

The AMP-based targeted NGS technique identified COL1A1 and SEC31A as novel fusion partners for USP6 in two cases of nodular fasciitis.

Conventional methods were sufficient in this study to confirm translocations in straightforward cases and ordinary rearrangements, according to the investigators. "Both reverse transcription PCR and FISH are not only quick and easy to conduct but are also of low cost and high analytical validity and accuracy, which make them attractive methods," they wrote.

The study was supported by Leiden University Medical Center, which receives royalties from Kreatech/Leica, the source of a COL1A1/PDGFB fusion probe used in the research.

SOURCE: Lam SW et al. J Mol Diagn. 2018 Aug 20;20(5):653-63.

Addressing the rarity and complexities of sarcomas

Jane de Lartigue, PhD

The rarity and complexities of bone and soft tissue sarcomas pose a major challenge to effective treatment. Historically, there has been a blanket approach to treatment, but more recently that has begun to change, thanks to genome profiling studies and novel clinical trial strategies. Here, we discuss the resulting enrichment of the therapeutic armamentarium with molecularly targeted and immune therapies.

A challenging tumor type

Sarcomas are a large group of histologically diverse cancers that arise in the mesenchymal cells. They can be broadly divided into bone and soft tissue sarcomas (STS) but are further subdivided according to the type of cell from which they derive; osteosarcomas in the bone, rhabdomyosarcomas in the skeletal muscle, liposarcomas in the fat tissues, leiomyosarcomas in the smooth muscle, and chondrosarcomas in the cartilaginous tissue, for example.

Each sarcoma subtype itself encompasses a range of different cancers with unique biology. Under the umbrella of liposarcoma, for example, are well/dedifferentiated liposarcomas and myxoid liposarcomas, which have very different pathologies and clinical courses.

As a whole, sarcomas are extremely rare tumors, accounting for less than 1% of all adult cancers, although they disproportionately affect children and young adults, with a prevalence closer to 15%.[1,2] Certain sarcoma subtypes are exceptionally rare, with only a few cases diagnosed worldwide each year, whereas liposarcomas are at the other end of the spectrum, comprising the most common form of STS (Figure 1).[3]

In the early stages, sarcomas are generally highly treatable with a combination of surgical resection, chemotherapy, and radiation therapy. However, many patients develop advanced metastatic disease, which presents much more of a challenge.[4,5]

Magic bullet for GIST

Despite their clear heterogeneity and complexity, sarcomas have tended to be treated as a single entity. Chemotherapy has played a central role in the treatment of advanced sarcomas and continues to do so, with two newer drugs approved by the United States Food and Drug Administration (FDA) in the past several years.[6,7]

The development of targeted therapy, on the other hand, for the most part proved unsuccessful. In general, studies examining the somatic mutation landscape in sarcomas found very few that were highly recurrent. The exception was gastrointestinal stromal tumors (GIST), which represent around 8% of STS.[8] Frequent mutations in several highly targetable tyrosine kinases, notably KIT, which is mutated in around 85% of cases,[9] and platelet-derived growth factor receptor-alpha (PDGFRα) were identified in these tumors.[10]

This prompted the development of tyrosine kinase inhibitors (TKIs), targeting these and other kinases, for the treatment of patients with GIST, and culminated in the approval of imatinib for this indication in 2002. This revolutionized the treatment of GIST, which had a poor prognosis and were resistant to chemotherapy, extending median overall survival in patients with metastatic disease almost to 5 years.[11-13]

Imatinib was also shown to benefit patients with surgically resectable disease and was subsequently approved in the adjuvant setting in 2008.

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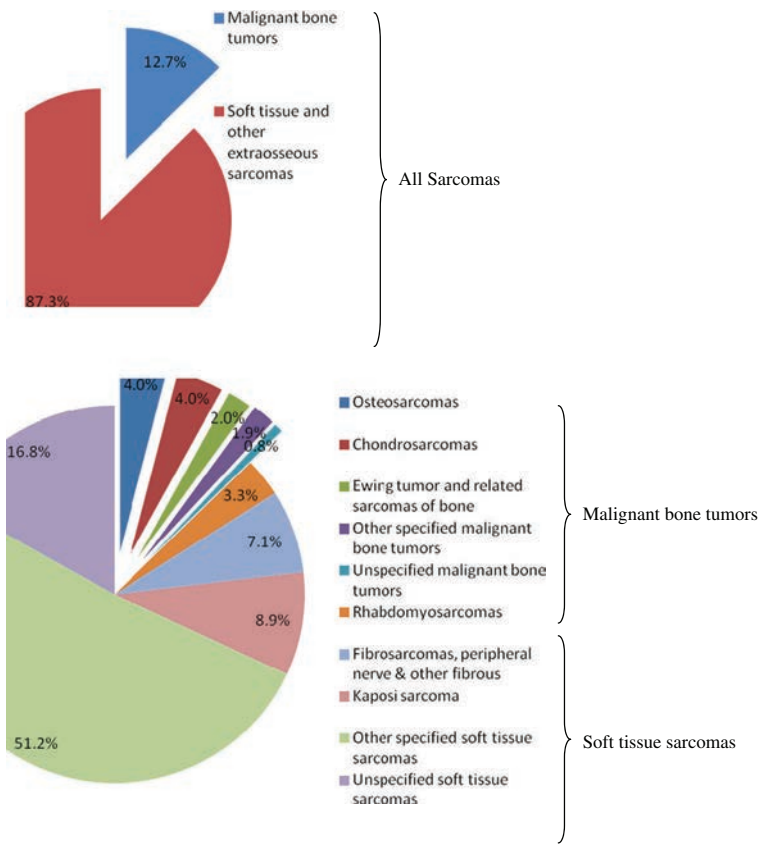


FIGURE 1 Distribution of sarcoma cases by histology (2008). According to data from the Surveillance, Epidemiology and End Results (1973-2008), soft tissue sarcomas occur much more frequently than malignant bone tumors. Osteosarcomas and chondrosarcomas are the most commonly diagnosed malignant bone tumors, and "other specified soft tissue sarcoma" accounted for roughly 51% of all sarcomas diagnosed in 2008. Citation: Burningham et al.[8] Reproduced under a Creative Commons Attribution License.

A recent trial demonstrated that 3-year continuation of adjuvant imatinib resulted in a significantly longer progression-free survival (PFS), compared with 1 year of adjuvant imatinib, and even longer time periods are now being evaluated.[14,15] The TKIs sunitinib and regorafenib have also been approved for the treatment of patients who become resistant to imatinib.[16,17] Avapritinib, a newer, more specific inhibitor of KIT is also being evaluated in patients with GIST (see Table, page 10).

Long-sought success for STS

Sunitinib and regorafenib include PDGFRα and the vascular endothelial growth factor receptors (VEGFRs) among their targets, receptors that play crucial roles in the formation of new blood vessels (angiogenesis). Many types of non-GIST sarcomas have been shown to be highly vascularized and express high levels of both of those receptors and other angiogenic proteins, which sparked interest in the development of multitargeted TKIs and other antiangiogenic drugs in patients with STS.[18]

In 2012, pazopanib became the first FDA-approved, molecularly targeted therapy for the treatment of non-GIST sarcomas. Approval in the second-line setting was based on the demonstration of a 3-month improvement in PFS, compared with placebo.[19] Four years later, the monoclonal antibody olaratumab, a more specific inhibitor of PDGFRα, was approved in combination with doxorubicin, marking the first front-line approval for more than four decades.[20]

Numerous other antiangiogenic drugs continue to be evaluated for the treatment of advanced STS. Among them, anlotinib is being tested in phase 3 clinical trials, and results from the ALTER0203 trial were presented at the 2018 annual meeting of the American Society of Clinical Oncology (ASCO).[21] After failure of chemotherapy, 223 patients were randomly assigned to receive either anlotinib or placebo. Anlotinib significantly improved median PFS across all patients, compared with placebo (6.27 vs 1.4 months, respectively; hazard ratio, 0.33; $P < .0001$), but was especially effective in patients with alveolar soft part sarcoma (ASPS; mPFS: 18.2 vs. 3 months) and was well tolerated.[21]

Sarcoma secrets revealed

Advancements in genome sequencing technologies have made it possible to interrogate the molecular underpinnings of sarcomas in greater detail. However, their rarity presents a significant technical challenge, with a dearth of samples available for genomic testing. Large-scale worldwide collaborative efforts have facilitated the collection of sufficiently large patient populations to provide statistically robust data in many cases. The Cancer Genome Atlas has established a rare tumor characterization project to facili-

TABLE Targeted therapies in sarcoma

Drug	Manufacturer	Mechanism of action	Most advanced clinical setting (clinicaltrials.gov identifier)
Abemaciclib (Verzenio)	Eli Lilly	CDK inhibitor	**Phase 2** (NCT02846987)
Ribociclib (Kisqali)	Novartis	CDK inhibitor	**Phase 2** (NCT03114527, NCT03009201, NCT03096912)
Palbociclib	Pfizer	CDK inhibitor	**Phase 2** (PalboSarc/NCT03242382, NCT03526250)
Sarcoma-specific CAR T-cells	Various	Immunotherapy (adoptive cell therapy)	**Phase 1/2** (NCT03356782, NCT00902044)
CMB305	Immune Design	Immunotherapy (vaccine)	**Phase 3** (Synovate/NCT03520959)
Nivolumab (Opdivo)	Bristol-Myers Squibb	Immunotherapy (immune checkpoint inhibitor)	**Phase 1/2** (NCT03190174, NCT03138161, NCT03277924, NCT03282344, NCT02982486)
Pembrolizumab (Keytruda)	Merck	Immunotherapy (immune checkpoint inhibitor)	**Phase 2** (SARC028/NCT02301039, SARC032/NCT03092323, PEMBROSARC/NCT02406781)
Atezolizumab (Tecentriq)	Genentech	Immunotherapy (immune checkpoint inhibitor)	**Phase 2** (NCT03474094, NCT03141684, NCT02609984)
Anlotinib	Advenchen	Multitargeted TKI	**Phase 3** (APROMISS/NCT03016819, ALTER0203/NCT02449343[a])
Cediranib	AstraZeneca	VEGFR inhibitor	**Phase 2** (NCT01391962, NCT01337401/CASPS)
Pazopanib (Votrient)	Novartis	Multitargeted TKI	**FDA approved** for advanced soft tissue sarcoma **Phase 2** (PASART-2/NCT02575066, NCT02357810, NCT01956669, NCT01462630, NCT02300545)
Regorafenib (Stivarga)	Bayer	Multitargeted TKI	**FDA approved** for GIST **Phase 2** (REGISTRI/NCT02638766, REGOBONE/NCT02389244, NCT02048722, NCT02048371)
Sorafenib (Nexavar)	Bayer	Multitargeted TKI	**Phase 2** (NCT00822848)
Sunitinib (Sutent)	Pfizer	Multitargeted TKI	**FDA approved** for imatinib-resistant or -intolerant GIST **Phase 2** (NCT01391962)
Imatinib (Gleevec)	Novartis	Multitargeted TKI	**FDA approved** for GIST **Phase 3** (NCT02413736)
Olaratumab (Lartruvo)	Eli Lilly	PDGFRα-targeting mAb	**FDA approved** for soft tissue sarcoma **Phase 1/2** (NCT03283696, NCT03126591)
Avapritinib (PLX9486)	Plexxicon	c-KIT inhibitor	**Phase 1/2** (NCT02401815)
Sapanisertib (TAK-228)	Millennium	mTOR inhibitor	**Phase 2** (NCT02987959)
Carotuximab (TRC105)	Tracon	Endoglin-targeting antibody	**Phase 3** (TAPPAS; NCT02979899)
Niraparib (Zejula)	Tesaro	PARP inhibitor	**Phase 1** (NCT02044120)[a]
Talazoparib (BMN673)	Pfizer	PARP inhibitor	**Phase 1** (NCT02392793)
Olaparib (Lynparza)	AstraZeneca	PARP inhibitor	**Phase 1** (RADIOSARP/NCT02787642, NCT02044120[a], TOMAS/NCT02398058)
Vorinostat (Zolinza)	Merck	HDAC inhibitor	**Phase 2** In uterine sarcoma (NCT03509207, NCT01879085)
Tazemetostat	Epizyme	EZH2 inhibitor	**Phase 2** (NCT02601950, NCT03213665[b], NCT02875548, NCT03155620)
Selinexor	Karyopharm	XPO-1 inhibitor	**Phase 2/3** (SEAL; NCT02606461)
TK216	Oncternal	ETS inhibitor	**Phase 1** (NCT02657005)
Larotrectinib (LOXO-101)	Loxo	TRK inhibitor	**Phase 2** (NCT03213704, NAVIGATE/NCT02576431)
Denosumab (Xgeva)	Amgen	RANKL inhibitor	**FDA approved** for giant cell tumor of the bone **Phase 2** (NCT02470091)
Entrectinib (RXDX-101)	Roche	TRK, ALK, ROS inhibitor	**Phase 2** (STARTRK-2/NCT02568267)
ADI-PEG20	Polaris	Pegylated arginine deaminase	**Phase 2** (NCT03449901)

ALK, anaplastic lymphoma kinase; CAR, chimeric antigen receptor; CDK, cyclin-dependent kinase; ETS, E26 transformation-specific; EZH2, enhancer of zeste homolog 2; GIST, gastrointestinal stromal tumor; HDAC, histone deacetylase; mTOR, mammalian target of rapamycin; NTRK, neurotropic; PARP, poly(ADP) ribose polymerase; PDGFR, platelet-derived growth factor receptor; RANKL, receptor activator of nuclear factor kappa-B ligand; TKI, TKI; TRK, tropomyosin receptor kinase; VEGFR, vascular endothelial growth factor receptor; XPO-1, exportin-1

[a]Trial is ongoing, but not actively recruiting participants. [b]Trial is currently under a clinical hold by the US Food and Drug Administration.

tate the genomic sequencing of rare cancer types like sarcomas.

Genome sequencing studies have revealed two types of sarcomas: those with relatively stable genomes and few molecular alterations, exemplified by Ewing sarcoma, which has a mutational load of 0.15 mutations/Megabase (Mb); and those that are much more complex with frequent somatic mutations, the prime example being leiomyosarcoma. The latter are characterized by mutations in the *TP53* gene, dubbed the "guardian of the genome" for its essential role in genome stability.

The two types are likely to require very different therapeutic strategies. Although genomically complex tumors offer up lots of potential targets for therapy, they also display significant heterogeneity and it can be challenging to find a shared target across different tumor samples. The p53 protein would make a logical target but, to date, tumor suppressor proteins are not readily druggable.

The most common type of molecular alterations in sarcomas are chromosomal translocations, where part of a chromosome breaks off and becomes reattached to another chromosome. This can result in the formation of a gene fusion when parts of two different genes are brought together in a way in which the genetic code can still be read, leading to the formation of a fusion protein with altered activity.[22-25]

In sarcomas, these chromosomal translocations predominantly involve genes encoding transcription factors and the gene fusion results in their aberrant expression and activation of the transcriptional programs that they regulate.

Ewing sarcoma is a prime example of a sarcoma that is defined by chromosomal translocations. Most often, the resulting gene fusions occur between members of the ten-eleven translocation (TET) family of RNA-binding proteins and the E26 transformation-specific (ETS) family of transcription factors. The most common fusion is between the *EWSR1* and *FLI1* genes, observed in between 85% and 90% of cases.

Significant efforts have been made to target *EWSR1-FLI1*. Since direct targeting of transcription factors is challenging, those efforts focused on targeting the aberrant transcriptional programs that they initiate. A major downstream target is the insulinlike growth factor receptor 1 (*IGF1R*) and numerous *IGF1R* inhibitors were developed and tested in patients with Ewing sarcoma, but unfortunately success was limited. Attention turned to the mammalian target of rapamycin (mTOR) as a potential mechanism of resistance to *IGF1R* inhibitors and explanation for the limited responses. Clinical trials combining mTOR and *IGF1R* inhibitors also proved unsuccessful.[26]

Although overall these trials were deemed failures, they were notable for the dramatic responses that were seen in one or two patients. Researchers are probing these "exceptional responses" using novel N-of-1 clinical trial designs that focus on a single patient (Figure 2).[27-30] More recently, the first drug to specifically target the *EWSR1-FLI1* fusion protein was developed. TK216 binds to the fusion protein and prevents it from binding to RNA helicase A, thereby blocking its function.[31]

Another type of gene fusion, involving the neurotrophic tropomyosin receptor kinase (*NTRK*) genes, has recently come into the spotlight for the treatment

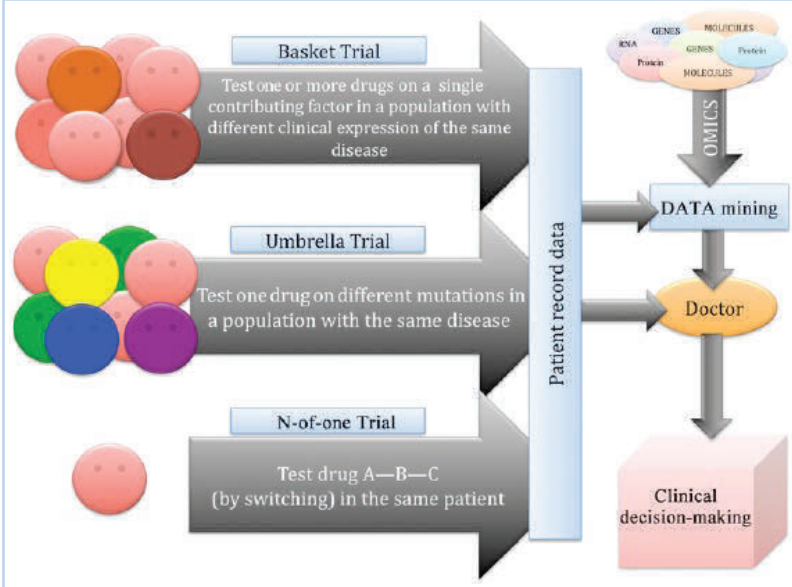


FIGURE 2 Novel personalized clinical trial designs. Several novel clinical trial designs have been developed that can be useful for the study of rare cancers that are often difficult to study in randomized controlled trials. Citation: Savoia et al.[27] Reproduced under a Creative Commons Attribution License 4.0 (CC BY).

of lung cancer. According to a recent study, *NTRK* fusions may also be common in sarcomas. They were observed in 8% of patients with breast sarcomas, 5% with fibrosarcomas, and 5% with stomach or small intestine sarcomas.[32]

The *NTRK* genes encode TRK proteins and several small molecule inhibitors of TRK have been developed to treat patients with *NTRK* fusion-positive cancers. Another novel clinical trial design – the basket trial – is being used to test these inhibitors. This type of trial uses a tumor-agnostic approach, recruiting patients with all different histologic subtypes of cancer that are unified by the shared presence of a specific molecular alteration.[33]

The safety and efficacy of TRK inhibitor larotrectinib were demonstrated in a study presented at the annual meeting of the Connective Tissue Oncology Society in November 2017. The phase 1/2 trial enrolled 11 patients with infantile fibrosarcoma or another sarcoma subtype, among other tumor types, who received larotrectinib before surgery. The partial response (PR) rate was 91%, and three after four to six cycles of larotrectinib, two of whom achieved a complete response that was still ongoing at the time of presentation.[34]

Results from the ongoing STARTRK-2 basket trial of entrectinib were also presented at the same meeting. Among patients with STS who were treated with entrectinib, three achieved a confirmed clinical response of 30% tumor reduction or more.[35]

Repurposing gynecologic cancer drugs

More recently, a third group of sarcomas was categorized, with intermediate genomic complexity. These tumors, including well/dedifferentiated liposarcomas, were characterized by amplifications of chromosome 12, involving genes such as cyclin-dependent kinase 4 (*CDK4*). In fact, more than 90% of patients with well/dedifferentiated sarcomas display *CDK4* amplification, making it a logical therapeutic target.[36]

CDK4 encodes CDK4 protein, a cell cycle-associated protein that regulates the transition from G1-S phase, known as the restriction point, beyond which the cell commits to undergoing mitosis. Aberrant expression of *CDK4* in cancer drives the hallmark process of unchecked cellular proliferation.

Some small molecule CDK4/6 inhibitors have been developed and have shown significant promise in the treatment of breast cancer. They are also being evaluated in patients with sarcoma whose tumors display CDK4 overexpression. In a recently published phase 2 trial of palbociclib in 60 patients with well/dedifferentiated liposarcomas, there was 1 CR.[37]

Another group of drugs that has advanced the treatment of gynecologic cancers comprises the poly (ADP-ribose) polymerase (PARP) inhibitors. In this context, PARP inhibitors are used in patients with mutations in the breast cancer susceptibility genes, *BRCA1/2*. The BRCA and PARP proteins are both involved in DNA repair pathways and the inhibition of PARP in patients who already have a defective BRCA pathway renders a lethal double blow to the cancer cell. According to the Broad Institute Cancer Cell Line Encyclopedia, Ewing sarcomas express high levels of the PARP1 enzyme, which could render them sensitive to PARP inhibition. Preclinical studies seemed to confirm that sensitivity, however, so far this has yet to translate into success in clinical trials, with no objective responses observed as yet.[38]

Expanding the field

Other treatment strategies being tested in patients with sarcoma are moving the field beyond conventional targeted therapies. There has been substantial focus in recent years on epigenetic alterations and their potential role in the development of cancer. Epigenetics is the secondary layer of regulation that acts on the genome and directs the spatial and temporal expression of genes.

Both DNA and the histone proteins they are packaged up with to form chromatin in nondividing cells can be modified by the attachment of chemical groups, such as acetyl and methyl groups, which can alter access to the DNA for transcription.

EZH2 is an enzyme that participates in histone methylation and thereby regulates transcriptional repression. Some types of sarcoma are characterized by a loss of expression of the *INI1* gene, also known as *SMARCB1.* The INI1 protein is part of a chromatin remodeling complex that relieves transcriptional repression and when INI1 is lost, cells become dependent upon EZH2.[39]

Clinical trials of the EZH2 inhibitor tazemetostat are ongoing in several types of sarcoma. Results from a phase 2 study in adults with *INI1*-negative tumors were presented at ASCO in 2017. Among 31 patients treated with 800 mg tazemetostat in continuous 28-day cycles, mPFS was 5.7 months, disease control rate was 10%, and confirmed overall response rate

Continued on page 19

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

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

Indication

Liposarcoma

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

Selected Safety Information

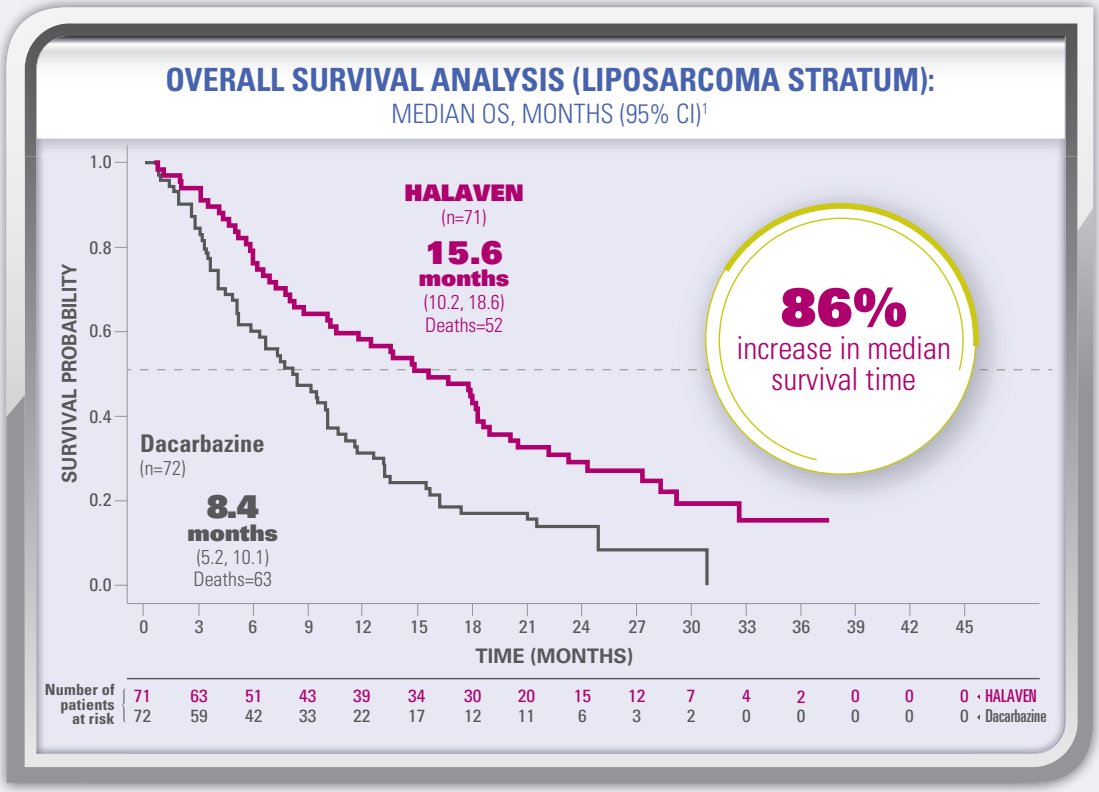
Warnings and Precautions

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

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

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

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



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

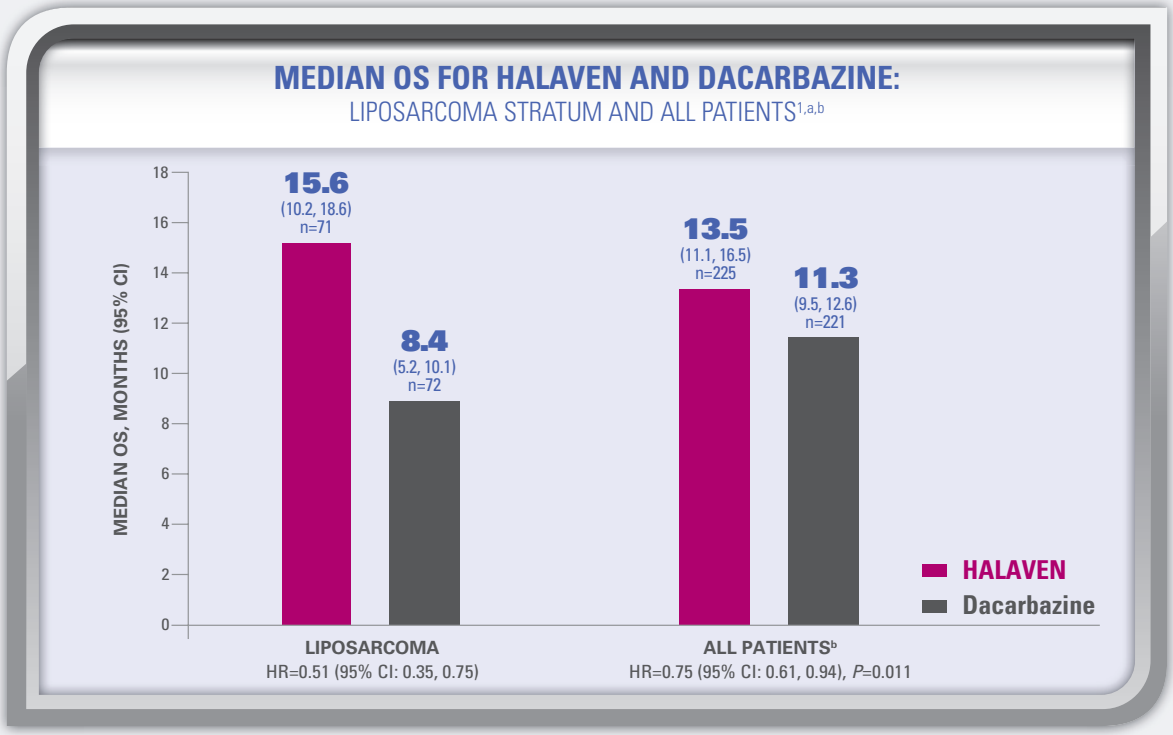
OS=overall survival; CI=confidence interval.

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

Selected Safety Information

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

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



PFS=progression-free survival; HR=hazard ratio.
[a]Efficacy data from 1 study site enrolling 6 patients were excluded.
[b]All patients=liposarcoma and leiomyosarcoma.

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

Secondary endpoint: PFS[1]

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

Selected Safety Information

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

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

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

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

by visiting **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

Selected Safety Information

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

Adverse Reactions

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

Use in Specific Populations

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

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

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

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

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

HALAVEN® (eribulin mesylate) Injection, for intravenous use

BRIEF SUMMARY – See package insert for full prescribing information.

DOSAGE AND ADMINISTRATION

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

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

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

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

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

Recommended dose delays

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

Recommended dose reductions

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

Table 1: Recommended Dose Reductions

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

- Neutropenia
- Peripheral neuropathy
- QT prolongation

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

Data

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

Females and Males of Reproductive Potential

Contraception

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

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

Infertility

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

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

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

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

OVERDOSAGE

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

There is no known antidote for HALAVEN overdose.

NONCLINICAL TOXICOLOGY

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

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

PATIENT COUNSELING INFORMATION

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

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

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

Embryo-Fetal Toxicity

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

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

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was 13%. The FDA has granted tazemetostat orphan drug designation in this indication.[40]

A pediatric basket trial of tazemetostat also is ongoing, but the FDA recently placed it under a clinical hold as a result of a safety update from the trial in which a pediatric patient with advanced poorly differentiated chordoma developed a secondary T-cell lymphoma.[41]

Targeting the unique metabolism of sarcomas may offer a promising therapeutic strategy, although this is in the preliminary stages of evaluation. A recent study showed that the expression of the argininosuccinate synthase 1 enzyme, which is involved in the generation of arginine through the urea cycle, was lost in up to 90% of STS. A pegylated arginine deaminase (ADI-PEG20), is being evaluated in a phase 2 clinical trial.[42]

Finally, the concept of using immunotherapy to boost the antitumor immune response also is being examined in sarcomas. A significant number of cases of STS, osteosarcoma and GIST have been shown to express programmed cell death protein-ligand 1, therefore the use of immune checkpoint inhibitors that block this ligand or its receptor and help to reactive tumor-infiltrating T cells, could be a beneficial strategy.

Limited activity has been observed in studies conducted to date, however combination therapies, especially with inhibitors of the indoleamine 2,3-dioxygenase (IDO) enzyme, which plays a key role in immunosuppression, could help to harness the power of these drugs. Studies have suggested that sarcomas may be infiltrated by immunosuppressive macrophages that express IDO.[43]

It is generally believed that immunotherapy is most effective in tumors that are highly mutated because that allows a large number of cancer antigens to provoke an antitumor immune response. However, a single highly expressed antigen can also be strongly immunogenic. Synovial sarcomas have a relatively low mutational burden but they do express high levels of the cancer-testis antigen NY-ESO-1.

NY-ESO-1 has provided a useful target for the development of adoptive cell therapies and vaccines for the treatment of sarcomas. CMB305 is an NY-ESO-1 vaccine that also incorporates a toll-like receptor 4 agonist. It is being evaluated in the phase 3 Synovate study as maintenance monotherapy in patients with locally advanced, unresectable or metastatic synovial sarcoma. In a phase 1 study, at a median follow-up of just under 18 months, the median OS for all 25 patients was 23.7 months.[44]

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This issue of *The Sarcoma Journal* features brief summaries of some of the leading sarcoma studies presented in June at the 2018 annual meeting of the American Society of Clinical Oncology.

Predicting treatment response in leiomyosarcoma, liposarcoma

Aberrations in oncogenic pathways and immune modulation influence treatment response in patients with metastatic leiomyosarcoma or liposarcoma, based on an analysis of whole-exome sequencing of tumor samples from patients in a completed phase 3 randomized trial that compared trabectedin and dacarbazine.

In that trial, trabectedin benefit was mostly seen in patients with leiomyosarcoma, as well as in patients with myxoid/round cell sarcomas, and less so in those with dedifferentiated and pleomorphic liposarcomas.

Gurpreet Kapoor, PhD, of LabConnect, Seattle, and colleagues examined aberrations in oncogenic pathways (DNA damage response, PI3K, MDM2-p53) and in immune modulation and then correlated the genomic aberrations with prospective data on clinical outcomes in the trial.

For the study, archival tumor samples were collected from 456 of the 518 patients; 180 had uterine leiomyosarcomas, 149 had nonuterine leiomyosarcomas, 66 had dedifferentiated liposarcomas, 46 had myxoid liposarcomas, and 15 had pleomorphic liposarcomas.

Peripheral blood samples from a subset of 346 patients were also analyzed as matched normal to filter noise from nonpathogenic variants in the whole-exome sequencing.

Consistent with sarcoma data from The Cancer Genome Atlas, frequent homozygous gene deletions with relatively low mutational load were noted in these leiomyosarcoma and liposarcoma samples. TP53 and RB1 alterations were more frequent in leiomyosarcomas than in liposarcomas and were not associated with clinical outcomes. Analyses of 103 DNA damage-response genes found somatic alterations exceeded 20% across subtypes and correlated with improved progression-free survival in only uterine leiomyosarcomas (hazard ratio, 0.63; $P = .03$).

> **"THE PATTERN AND PREVALENCE OF GENOMIC ABERRATIONS THAT WE'RE SEEING IN THIS COHORT OF PATIENTS PROSPECTIVELY ANALYZED ON A CLINICAL TRIAL ARE CONSISTENT WITH PRIOR REPORTS. ... INCLUDING CDK4 AND MDM2 IN DEDIFFERENTIATED LIPOSARCOMA, PI3-KINASE IN SOME MYXOID/ROUND CELLS, P53 IN LEIOMYOSARCOMA AND LIPOSARCOMA, AND SO ON."**

Genomic alterations in PI3K pathway genes were noted in 30% of myxoid liposarcomas and were associated with a worse rate of progression-free survival (HR, 3.0; $P = .045$).

A trend toward better overall survival was noted in dedifferentiated liposarcoma patients with MDM2 amplification as compared with normal MDM2 copy number.

Certain subtype-specific genomic aberrations in immune modulation pathways were associated with worse clinical outcomes in patients with uterine leiomyosarcoma or dedifferentiated liposarcoma. Alterations in immune suppressors were associated with improved clinical outcomes in nonuterine leiomyosarcomas and alterations in lipid metabolism were associated with improved clinical outcomes in dedifferentiated liposarcomas.

The invited discussant for the study, Mark Andrew Dickson, MD, of Memorial Sloan Kettering Cancer Center, New York, noted that "the real take-home here is that the TMBs (tumor mutation burdens) are relatively low across all of the L-type sarcomas.

"The pattern and prevalence of genomic aberrations that we're seeing in this cohort of patients prospectively analyzed on a clinical trial are consistent with prior reports. ... including CDK4 and MDM2 in dedifferentiated liposarcoma, PI3-kinase in some myxoid/round cells, p53 in leiomyosarcoma and liposarcoma, and so on."

Generally, tumor mutation burden is low in L-type sarcomas, and there are some intriguing associations with benefit to therapies, such as PI3-kinase pathway and potential resistance to trabectedin and high tumor mutation burden and potential sensitivity to trabectedin, that need to be explored and validated in another larger cohort, he said.

"I also am increasingly coming to terms with the fact that the tumors like leiomyosarcoma, which have low tumor mutation burden and which so far have proven fairly immune to immunotherapy, based on all of the negative PD-1 data that we've seen, and that also have recurrent, relatively unactionable mutations, like p53 and Rb, remain very difficult to treat," Dr. Dickson concluded.

SOURCE: Kapoor G et al. ASCO 2018, Abstract 11513.

SEAL: Selinexor extends PFS in advanced dedifferentiated liposarcoma

The investigational drug selinexor appears to be improving progression-free survival in patients with advanced dedifferentiated liposarcoma, based on phase 2 results from the randomized, placebo-controlled SEAL study.

But the statistical significance of the improvements varied depending on whether progression-free survival (PFS) was assessed by the World Health Organization criteria, which looks at two-dimensional measurements of these irregular three-dimensional objects, or RECIST v1.1 criteria, which only looks at a unidimensional measure, reported Mrinal M. Gounder, MD, of Memorial Sloan Kettering Cancer Center, New York. When tumor response was based on WHO criteria, there was no difference in median PFS for the 24 patients on active therapy (1.4 months) and the 27 patients on placebo (1.8 months). By RECIST v1.1 criteria, however, median PFS was 5.6 months with selinexor.

Dedifferentiated liposarcoma is incurable, and palliative therapies are associated with an overall survival of 11-20 months in these patients. Selinexor is an oral selective inhibitor of exportin-1 which exports proteins from the nucleus into the cytoplasm. The drug appears to prevent p53 from leaving the nucleus, thereby protecting it from overexpressed MDM2, which is a negative regulator of p53, but the drug might have other potential mechanisms of action.

The double-blind study included 56 evaluable patients who had progressive dedifferentiated liposarcoma and had received at least one prior systemic therapy. Patients' median age was 61 years and they had received a median of two prior therapies. Patients were randomized to get either 60 mg of selinexor (26 patients) or placebo (30 patients) twice weekly until their disease progressed or they were no longer able to tolerate therapy. Patients whose disease progressed on placebo (24 patients) were allowed to cross over to open-label selinexor therapy.

Treatments were unblinded for 51 of the patients, 24 on selinexor and 27 on placebo. Disease progression as confirmed by Independent Central Radiological Review using WHO criteria was the main reason for ending blinded treatment.

Grade 1/2 adverse events for selinexor versus placebo, respectively, were nausea (85% vs. 31%), anorexia (62% vs. 14%), and fatigue (58% vs. 45%). The comparable rates of grade 3/4 adverse events were hyponatremia (15% vs. 0%), anemia (15% vs. 7%), and thrombocytopenia (12% vs. 0%). Selinexor dose was reduced because of adverse events in 12 patients.

In a discussion of the study's implications, Mark Andrew Dickson, MD, also of Memorial Sloan Kettering Cancer Center, called the adverse events profile "mostly manageable but predictable grade 1/2 adverse events ... and median progression-free survival of 5 and a half months is quite encouraging.

"Changing response assessment method midtrial in a study with progression-free survival as the primary endpoint is obviously problematic, but it also highlights how difficult it is to measure three-dimensional tumors like complex retroperitoneal liposarcomas, which move and change and grow and shrink over time," he said. "And I would conclude that RECIST is probably the worst method of tumor assessment for sarcoma, except for all the other methods of tumor assessment."

To illustrate the difficulty of measuring tumor response, Dr. Dickson presented examples of different tumor shapes and scenarios in which one method would indicate tumor progression and the other would indicate stable disease.

"There can be differences between the two methods in how progression responds and is determined. And you can do this experiment with a number of different shapes and find scenarios where one method would call it progression at a different time than the other. So this is really critically important when we look at the results of the clinical trial, because it was designed to look at WHO PFS. And you can see that, based on that, there was no significant difference between the selinexor and placebo arm," he said.

› **"THERE CAN BE DIFFERENCES BETWEEN THE TWO METHODS IN HOW PROGRESSION RESPONDS AND IS DETERMINED. AND YOU CAN DO THIS EXPERIMENT WITH A NUMBER OF DIFFERENT SHAPES AND FIND SCENARIOS WHERE ONE METHOD WOULD CALL IT PROGRESSION AT A DIFFERENT TIME THAN THE OTHER."**

Additionally, he reviewed cases from the study in which "either way you measure this, you can see that [the] tumor is getting smaller over time," as well as cases where the tumor grew in patients on placebo first, but decreased in size after switching to the active therapy.

"The improvement in progression-free survival is promising and ... selinexor probably does have activity in dediff lipo compared to historical data," said Dr. Dickson, adding that he looks forward to selinexor progressing to a randomized, phase 3 trial and "seeing those data perhaps next year."

Dr. Gounder disclosed financial relationships with multiple drug companies including Karyopharm Therapeutics, the maker of selinexor. Dr. Dickson disclosed a consult or adviser role with Celgene and research funding from Eli Lilly.

SOURCE: Gounder M et al. ASCO 2018, Abstract 11512.

EPAZ: Pazopanib matches doxorubicin without the neutropenia in elderly patients

Pazopanib can be considered as a first-line alternative treatment to doxorubicin in patients older than age 60 years with advanced, inoperable soft tissue sarcomas, based on the results of the phase 2 EPAZ study.

Pazopanib outcomes compared to those with doxorubicin in the study; but unlike doxorubicin, pazopanib was not associated with neutropenia, reported Viktor Grünwald, MD, of the Medical School Hanover, Germany. "The distinct AE (adverse event) profile may be used to counsel patients and tailor therapy to individual needs."

In the randomized study with a median 12-month follow-up of previously untreated patients with a median age of 71 years, the incidence of grade 4 neutropenia and neutropenic fever were 56% and 10% for 39 patients given doxorubicin and 0% and 0% for 81 patients given pazopanib, respectively. Overall survival was 14.3 months and 12.3 months, a nonsignificant difference. The most frequent adverse events for doxorubicin were fatigue (64.9%), alopecia (56.8%), and nausea (48.6%), and for pazopanib they were fatigue (58%), nausea (43.2%), and diarrhea (43.2%). Similar outcomes were reported for global EORTC QLQ-C30 measures.

EPAZ included patients aged 60 years and older (median 71 years) with no prior systemic treatment for soft tissue sarcoma, progressive disease, ECOG 0-2, and adequate organ function. After 1:2 randomization, patients received either doxorubicin 75 mg/m^2 every 3 weeks for a total of six cycles or oral pazopanib 800 mg/day given continuously. ECOG 2 and liposarcoma histology were used for stratification.

> "THE DISTINCT AE (ADVERSE EVENT) PROFILE MAY BE USED TO COUNSEL PATIENTS AND TAILOR THERAPY TO INDIVIDUAL NEEDS."

Dr. Grunwald and several of his co-authors disclosed financial relationships with various drug companies including Novartis, the maker of pazopanib (Votrient). Clinical trial information: NCT01861951.

SOURCE: Grunwald V et al. ASCO 2018, Abstract 11506.

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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.