Chromoplexy linked to aggressive Ewing sarcomas

Plus, the progression to targeted therapies, and more reports from ASCO 2018.
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, bronchospasms, 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 at least 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 (53% vs 35%; 9% vs 2%), neutropenia (65% vs 63%; 50% vs 41%), vomiting (45% vs 19%; 0% vs 0%), diarrhea (34% vs 29%; 13% vs 0%), hypophosphatemia (21% vs 7%; 5% vs 3%), and hypokalemia (21% vs 15%; 8% vs 3%).

- 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 79%; 44% vs 37%), neutropenia (65% vs 63%; 48% vs 38%) and thrombocytopenia (63% vs 44%; 6% vs 13%), hyperglycemia (52% vs 28%; 2% vs 3%), elevated aPTT (33% vs 13%; 5% vs 0%), hypokalemia (21% vs 19%; 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 19OCT2016
LARTRUVO + DOXORUBICIN: THE 1ST AND ONLY FRONT-LINE ADVANCEMENT FOR STS IN MORE THAN 4 DECADES1

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

OBJECTIVE RESPONSE RATE (ORR)*

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

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)

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

*ORR=complete response (CR) + partial response (PR). LARTRUVO + doxorubicin: CR=4.5%, PR=13.6%; doxorubicin alone: CR=15%, PR=6%. Based on independent review; assessed according to RECIST criteria v1.1.

†LARTRUVO + doxorubicin led to 37 (56%) total events compared to 34 (51%) events with doxorubicin alone. HR=0.74 (95% CI: 0.46, 1.19)

NUMBER AT RISK
LARTRUVO + Doxorubicin  
66 62 60 57 52 51 50 47 43 41 41 39 33 32 29 26 16 15 8 3 1 1 0

Doxorubicin Alone  
67 61 51 46 43 37 34 32 28 23 19 19 15 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.

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 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, synovial sarcoma, and additional histologies.

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

VISIT LARTRUVO.COM/HCP TO LEARN MORE


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LARTRUVÒ™ (olaratumab) injection

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

INDICATIONS AND USAGE
LARTRUVÒ 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 LARTRUVÒ 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 some 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 LARTRUVÒ 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 LARTRUVÒ infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Immediately and permanently discontinue LARTRUVÒ for Grade 3 or 4 IRR.

Embryo-Fetal Toxicity
Based on animal data and its mechanism of action, LARTRUVÒ can cause fetal harm when administered to a pregnant woman. Animal knockout models link disruption of 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 LARTRUVÒ 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 LARTRUVÒ in 485 patients from three randomized, open-label, active-controlled clinical trials, which enrolled 296 patients with various tumors who received LARTRUVÒ in combination with chemotherapy (191 patients) or LARTRUVÒ as a single agent (65 patients); four open-label single-arm trials which enrolled 96 patients with various tumors who received LARTRUVÒ 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 LARTRUVÒ at doses of 15 to 20 mg/kg in combination with doxorubicin (103 patients) or LARTRUVÒ as a single agent (30 patients). Among the 485 patients, 25% were exposed to LARTRUVÒ for ≥6 months and 6% were exposed for ≥12 months. The data described below reflect exposure to LARTRUVÒ in 64 patients with metastatic soft tissue sarcoma enrolled in Trial 1, a multicenter, randomized (1:1), open-label, active-controlled trial comparing LARTRUVÒ plus doxorubicin with doxorubicin as a single agent. LARTRUVÒ 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/m² 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 96); 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 LARTRUVÒ was 6 months (range: 21 days to 29.4 months) with 36 (56%) patients receiving LARTRUVÒ for ≥6 months and 10 (16%) patients receiving LARTRUVÒ for ≥12 months. The median cumulative doxorubicin dose was 488 mg/m² in the LARTRUVÒ plus doxorubicin arm and 300 mg/m² in the doxorubicin arm. In Trial 1, adverse reactions resulting in permanent discontinuation of LARTRUVÒ occurred in 8% (564) of patients. The most common adverse reaction leading to LARTRUVÒ discontinuation was infusion-related reaction (3%). Dose reductions of LARTRUVÒ 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 LARTRUVÒ 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 LARTRUVÒ in the randomized portion of the study. The most common adverse reactions reported in at least 20% of patients receiving LARTRUVÒ 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 LARTRUVÒ 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)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LARTRUVÒ plus Doxorubicin N=64</th>
<th>Doxorubicin N=65</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>73</td>
<td>2</td>
</tr>
<tr>
<td>Mucositis</td>
<td>53</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td><strong>General Disorders and Administrative Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>69</td>
<td>9</td>
</tr>
<tr>
<td>Infusion-Related Reactions</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>64</td>
<td>8</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>52</td>
<td>0</td>
</tr>
<tr>
<td><strong>Metabolic and Nutritional Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychiatric Disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td><strong>Eye Disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Eyes</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

* Abdominal pain includes: abdominal pain, lower abdominal pain, and upper abdominal pain.

* Fatigue includes: asthenia and fatigue.

* 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.

LARTRUVÒ™ (olaratumab) injection OR HCP BS 21OCT2016
**WARNINGS AND PRECAUTIONS**

**Infusion-related reactions (IRR) occurred in 70 (14%) of 485 patients who received at least one dose of LARTRUVO.**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LARTRUVO plus Doxorubicin(a)</th>
<th>Doxorubicin(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>52 (2) 28 (3)</td>
<td></td>
</tr>
<tr>
<td>Increased aPTT(b)</td>
<td>33 (5) 13 (0)</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>21 (8) 15 (3)</td>
<td></td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>21 (5)  7 (3)</td>
<td></td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>16 (0) 7 (0)</td>
<td></td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>16 (0)  8 (0)</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>77 (44) 73 (37)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>65 (48) 63 (38)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>63 (6)  44 (11)</td>
<td></td>
</tr>
</tbody>
</table>

\(a\) 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**

Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm. There are no available data on LARTRUVO use in pregnant women. No animal studies using olaratumab have been conducted to evaluate its effect on female reproduction and embryo-fetal development. Animal knockout models link disruption of platelet-derived growth factor receptor alpha (PDGFR-\(\alpha\)) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-\(\alpha\) antibody 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.

**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**

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.

**LACTATION**

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.

**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.
TRANSLATIONAL MEDICINE

5 Chromoplexy linked to aggressive Ewing sarcomas

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

FEATURE: NEW THERAPIES

8 Addressing the rarity and complexities of sarcomas

FROM ASCO 2018

21 Predicting treatment response in leiomyosarcoma, liposarcoma

22 SEAL: Selinexor extends PFS in advanced dedifferentiated liposarcoma

24 EPAZ: Pazopanib matches doxorubicin without the neutropenia in elderly patients
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.

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
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 Imieliński 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.
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.

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%. 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).

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.

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.

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. Frequent mutations in several highly targetable tyrosine kinases, notably KIT, which is mutated in around 85% of cases, and platelet-derived growth factor receptor-alpha (PDGFRα) were identified in these tumors.

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.

Imatinib was also shown to benefit patients with surgically resectable disease and was subsequently approved in the adjuvant setting in 2008.
there are some instances where notable differences exist. Japanese males living in the state of California, have a reported osteosarcoma incidence rate of 1.3 per 100,000 males [69]. This rate is relatively high in comparison to incidence rates observed through much of the world. Typically, osteosarcoma incidence rates range from 0.2-0.6 per 100,000 males, depending on geographic region. Osteosarcoma incidence rates of similar magnitude were not observed throughout Japan. However, a high incidence of 1.1 cases per 100,000 was reported among Japanese males living in Hawaii [69]. These findings may suggest that Japanese migrants living in "westernized" regions may be subject to increase osteosarcoma risk due to environmental or lifestyle factors.

Malignant bone tumors

Soft tissue sarcomas

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.19

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Mechanism of action</th>
<th>Most advanced clinical setting (clinicaltrials.gov identifier)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abemaciclib (Verzenio)</td>
<td>Eli Lilly</td>
<td>CDK inhibitor</td>
<td>Phase 2 (NCT02846987)</td>
</tr>
<tr>
<td>Ribociclib (Kisqali)</td>
<td>Novartis</td>
<td>CDK inhibitor</td>
<td>Phase 2 (NCT03114527, NCT03009201, NCT03096912)</td>
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<tr>
<td>Palbociclib</td>
<td>Pfizer</td>
<td>CDK inhibitor</td>
<td>Phase 2 (PalboSarc/NCT03242382, NCT03526250)</td>
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<tr>
<td>Sarcoma-specific CAR T-cells</td>
<td>Various</td>
<td>Immunotherapy</td>
<td>Phase 1/2 (NCT03356782, NCT0902044)</td>
</tr>
<tr>
<td>CMB305</td>
<td>Immune Design</td>
<td>Immunotherapy (vaccine)</td>
<td>Phase 3 (Synovate/NCT03520959)</td>
</tr>
<tr>
<td>Nivolumab (Opdivo)</td>
<td>Bristol-Myers Squibb</td>
<td>Immunotherapy (immune checkpoint inhibitor)</td>
<td>Phase 1/2 (NCT03190174, NCT03138161, NCT03277924, NCT03282344, NCT02982486)</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>Merck</td>
<td>Immunotherapy</td>
<td>Phase 2 (SARCO28/NCT02301039, SARCO32/ NCT03092323, PEBRO SARC/NCT02406781)</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq)</td>
<td>Genentech</td>
<td>Immunotherapy</td>
<td>Phase 2 (NCT03474094, NCT03141684, NCT02609984)</td>
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<tr>
<td>Anlotinib</td>
<td>Advenchen</td>
<td>Multitargeted TKI</td>
<td>Phase 3 (APROMISS/NCT03016819, ALTER0203/NCT02449343)</td>
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<tr>
<td>Cediranib</td>
<td>AstraZeneca</td>
<td>VEGFR inhibitor</td>
<td>Phase 2 (NCT01391962, NCT01337401/CASPS)</td>
</tr>
<tr>
<td>Pazopanib (Votrient)</td>
<td>Novartis</td>
<td>Multitargeted TKI</td>
<td>FDA approved for advanced soft tissue sarcoma Phase 2 (PASART-2/NCT02575066, NCT02357810, NCT01956669, NCT01462630, NCT0300545)</td>
</tr>
<tr>
<td>Regorafenib (Stivarga)</td>
<td>Bayer</td>
<td>Multitargeted TKI</td>
<td>FDA approved for GIST Phase 2 (REGISTRI/NCT02638766, REGOBONE/ NCT02389244, NCT02048722, NCT02048371)</td>
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<tr>
<td>Sorafenib (Nexavar)</td>
<td>Bayer</td>
<td>Multitargeted TKI</td>
<td>Phase 2 (NCT00822848)</td>
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<tr>
<td>Sunitinib (Sutent)</td>
<td>Pfizer</td>
<td>Multitargeted TKI</td>
<td>FDA approved for imatinib-resistant or -intolerant GIST Phase 2 (NCT01391962)</td>
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<tr>
<td>Imatinib (Gleevec)</td>
<td>Novartis</td>
<td>Multitargeted TKI</td>
<td>FDA approved for GIST Phase 3 (NCT02413736)</td>
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<tr>
<td>Olaratumab (Lartruvo)</td>
<td>Eli Lilly</td>
<td>PDGF-Rx-targeting mAb</td>
<td>FDA approved for soft tissue sarcoma Phase 1/2 (NCT03283696, NCT03126591)</td>
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<tr>
<td>Avapritinib (PLX9486)</td>
<td>Plexxicon</td>
<td>c-KIT inhibitor</td>
<td>Phase 1/2 (NCT02401815)</td>
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<tr>
<td>Sapanisertib (TAK-228)</td>
<td>Millennium</td>
<td>mTOR inhibitor</td>
<td>Phase 2 (NCT02987959)</td>
</tr>
<tr>
<td>Carotuximab (TRC105)</td>
<td>Tracon</td>
<td>Endoglin-targeting antibody</td>
<td>Phase 3 (TAPPAS; NCT02979899)</td>
</tr>
<tr>
<td>Niraparib (Zejula)</td>
<td>Tesaro</td>
<td>PARP inhibitor</td>
<td>Phase 1 (NCT02044120)*</td>
</tr>
<tr>
<td>Talazoparib (BMN673)</td>
<td>Pfizer</td>
<td>PARP inhibitor</td>
<td>Phase 1 (NCT02392793)</td>
</tr>
<tr>
<td>Olaparib (Lynparza)</td>
<td>AstraZeneca</td>
<td>PARP inhibitor</td>
<td>Phase 1 (RADIOSARP/NCT02787642, NCT02044120*, TOMAS/NCT02398058)</td>
</tr>
<tr>
<td>Vorinostat (Zolinza)</td>
<td>Merck</td>
<td>HDAC inhibitor</td>
<td>Phase 2 in uterine sarcoma (NCT03509207, NCT01879085)</td>
</tr>
<tr>
<td>Tazemetostat</td>
<td>Epizyme</td>
<td>EZH2 inhibitor</td>
<td>Phase 2 (NCT02601950, NCT03213665*, NCT02875548, NCT03155620)</td>
</tr>
<tr>
<td>Selinexor</td>
<td>Karyopharm</td>
<td>XPO-1 inhibitor</td>
<td>Phase 2/3 (SEAL; NCT02606461)</td>
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<tr>
<td>TK216</td>
<td>Oncenternal</td>
<td>ETS inhibitor</td>
<td>Phase 1 (NCT02657005)</td>
</tr>
<tr>
<td>Larotrectinib (LOX3-101)</td>
<td>Loxo</td>
<td>TRK inhibitor</td>
<td>Phase 2 (NCT03213704, NAVIGATE/NCT02576431)</td>
</tr>
<tr>
<td>Denosumab (Xgeva)</td>
<td>Amgen</td>
<td>RANKL inhibitor</td>
<td>FDA approved for giant cell tumor of the bone Phase 2 (NCT02470091)</td>
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<tr>
<td>Entrectinib (RXDX-101)</td>
<td>Roche</td>
<td>TRK, ALK, ROS inhibitor</td>
<td>Phase 2 (STARTRK-2/NCT02568267)</td>
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<tr>
<td>ADI-PEG20</td>
<td>Polaris</td>
<td>Pegylated arginine deaminase</td>
<td>Phase 2 (NCT03449901)</td>
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</tbody>
</table>

**Notes:**
- 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 κappa-B ligand; TKI, TRK, tropomyosin receptor kinase; VEGFR, vascular endothelial growth factor receptor; XPO-1, exportin-1.
- *Trial is ongoing, but not actively recruiting participants. †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. 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.

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). 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.

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

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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 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...
**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/mm³) 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.
The first and only single agent to show a significant survival advantage in a Phase III study of patients with advanced liposarcoma

**OVERALL SURVIVAL ANALYSIS (LIPOSARCOMA STRATUM):**

**MEDIAN OS, MONTHS (95% CI)**

**HALAVEN**

- **15.6 months**
  - (10.2, 18.6)
  - Deaths=52

**Dacarbazine**

- **8.4 months**
  - (5.2, 10.1)
  - Deaths=63

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/m² administered intravenously on Days 1 and 8 of a 21-day cycle or to dacarbazine at a dose of 850 mg/m², 1,000 mg/m², or 1,200 mg/m² 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%).

**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. Withdraw 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 PFS¹

**Secondary endpoint: PFS¹**

- 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.

A reduction in starting dose is recommended for patients with mild or

were the most common serious adverse reactions. The most common adverse reactions resulting in

most common (≥5%) Grade 3-4 laboratory abnormalities reported in patients receiving HALAVEN were

(35%), constipation (32%), peripheral neuropathy (29%), abdominal pain (29%), and pyrexia (28%). The

QT Prolongation:

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was

HALAVEN and for 3.5 months following the /f_inal dose.

with female partners of reproductive potential to use effective contraception during treatment with

potential risk to a fetus. Advise females of reproductive potential to use effective contraception

studies, eribulin mesylate caused embryo-fetal toxicity when administered to pregnant rats during

Based on /f_indings from an animal reproduction study and its mechanism

Monitor patients closely for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN

27 days to 29 months).

percent (41/65) had not recovered within a median follow-up duration of 6.4 months (range:

Twenty-two percent (109/503) of patients developed a new or worsening neuropathy that had not

24/503) in Study 1. Neuropathy lasting more than one year occurred in 5% (26/503) of patients.

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.


Please see all Selected Safety Information throughout and adjacent brief summary of HALAVEN full Prescribing Information.
HALAVEN® (eribulin mesylate) Injection, for intravenous use
BRIEF SUMMARY – See package insert for full prescribing information.

DOSEAGE AND ADMINISTRATION
Recommended Dose: The recommended dose of HALAVEN is 1.4 mg/m² 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/m² 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 0.9 mg/m² 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 severe or moderate renal impairment (creatinine clearance [CrCl] 15-49 mL/min) is 1.1 mg/m² 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/mm³
  – Platelets < 75,000/mm³
  – Grade 3 or 4 hematologic toxicities.
• The Day 8 dose may be delayed for a maximum of 1 week.
• If toxicities do not resolve or improve to ≤ Grade 2 severity by Day 15, omit the dose, if possible, and do not start HALAVEN until the next cycle.
Recommended dose reductions
• HALAVEN has been administered at reduced dose and initiation of the next cycle no sooner than 2 weeks later.
• Do not re-escalate HALAVEN dose after it has been reduced.

Table 1: Recommended Dose Reductions

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Recommended HALAVEN Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanently reduce the 1.4 mg/m² HALAVEN dose for any of the following:</td>
<td></td>
</tr>
<tr>
<td>ANC &lt;500/mm³ for &gt;7 days</td>
<td>1.1 mg/m²</td>
</tr>
<tr>
<td>ANC &lt;1,000/mm³ with fever or infection</td>
<td></td>
</tr>
<tr>
<td>Platelets &lt;50,000/mm³</td>
<td></td>
</tr>
<tr>
<td>Neutrophils &lt;0.5 × 10⁹/L requiring transfusion</td>
<td></td>
</tr>
<tr>
<td>Nonhematologic Grade 3 or 4 toxicities</td>
<td></td>
</tr>
<tr>
<td>Diminishing in delay of Day 8 HALAVEN dose in previous cycle for toxicity</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occurrence of any event requiring permanent dose reduction while receiving 1.1 mg/m²</th>
<th>Discontinue HALAVEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-limiting toxicity</td>
<td></td>
</tr>
</tbody>
</table>

WARRANTS AND PRECAUTIONS
Neuropathy: In Study 1, severe neuropathy (ANC < 500/mm³) lasting more than one week occurred in 12% (82/503) of patients with metastatic breast cancer, leading to discontinuation in <1% of patients. Fever and chills (fever >38.9°C for >3 days) 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 alamine 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/mm³) lasting more than one week occurred in 5% (26/522) of patients with liposarcoma or leiomyosarcoma. Febrile neutropenia occurred in 0.3% of patients treated with HALAVEN and fatal neutropenic sepsis in 0.9%.
Monitor early-onset neutropenia more than anterior; 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 included patients with baseline neutrophil counts below 1,500/mm³.

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 resolved 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.

QT Prolongation: Monitor for prolonged QT intervals 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.

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Study 1</th>
<th>ADRS (≥2%)</th>
<th>Study 2</th>
<th>ADRS (≥2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>68%</td>
<td>53%</td>
<td>68%</td>
<td>53%</td>
</tr>
<tr>
<td>Nerve system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>35%</td>
<td>8%</td>
<td>45%</td>
<td>10%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>19%</td>
<td>&lt;1%</td>
<td>19%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td>54%</td>
<td>10%</td>
<td>21%</td>
<td>9%</td>
</tr>
<tr>
<td>Sedation</td>
<td>19%</td>
<td>15%</td>
<td>18%</td>
<td>10%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18%</td>
<td>18%</td>
<td>18%</td>
<td>18%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>35%</td>
<td>28%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Constipation</td>
<td>25%</td>
<td>21%</td>
<td>21%</td>
<td>17%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18%</td>
<td>11%</td>
<td>15%</td>
<td>13%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18%</td>
<td>0%</td>
<td>18%</td>
<td>0%</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia/Athralgia</td>
<td>23%</td>
<td>&lt;1%</td>
<td>17%</td>
<td>2%</td>
</tr>
<tr>
<td>Back pain</td>
<td>16%</td>
<td>1%</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>12%</td>
<td>1%</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>11%</td>
<td>1%</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>Nutritional and metabolic disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased weight</td>
<td>21%</td>
<td>14%</td>
<td>14%</td>
<td>15%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>20%</td>
<td>1%</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16%</td>
<td>13%</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Cough</td>
<td>14%</td>
<td>9%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10%</td>
<td>9%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>General Adverse Reactions: The following additional adverse reactions were reported in ≥5% to &lt;10% of the HALAVEN-treated group:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye Disorders: increased lacrimation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders: Dysphagia, abdominal pain, stomatitis, dry mouth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic and Lymphohematopoietic Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Hematologic and Lymphohematopoietic Disorders: 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 (15%).

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 (15%).

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/m²) 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 16%, capecitabine 19%, 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.

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 the rates in other clinical trials and may not reflect the rates of reaction in clinical practice.

The following adverse reactions are discussed in detail in other sections of the labeling:
- Neutropenia
- Neutropenic fever
- QT prolongation

In clinical trials, HALAVEN has been administered to 1,963 patients including 467 patients exposed to HALAVEN for 6 months or longer. The majority of the 1,853 patients were women (82%) with a mean age of 55 years (range: 17 to 88 years). The racial and ethnic distribution was White (74%) Black (4%), Asian (9%), and other (3%).
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/m2 on Days 1 and 8 of a 21-day cycle or dacarbazine at doses of 500 mg/m2 (50%), 800 mg/m2 [84%], or 1200 mg/m2 [16%] every 3 weeks. A total of 273 patients received HALAVEN and 221 patients received dacarbazine. Patients were required to have received at least two prior systemic chemotherapeutic regimens. The trial excluded patients with pre-existing Grade 2 or greater 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 III 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; 39% received prior anthracycline-containing regimens; and 59% 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 reaction (>2%) 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 hyperglycemia. 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%).

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>HALAVEN</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>29%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>19%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>General disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>28%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>22%</td>
<td>9%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>29%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>34%</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Laboratory abnormalities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>70%</td>
<td>59%</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>Respiratory disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>18%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eyes</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Nervous System disturbances</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory polyneuropathy, peripheral sensory neuropathy, and sensory neuropathy</td>
<td>29%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual field defect</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Neoplasms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>39%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
| **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 unknown size, it is not possible to reliably estimate their frequency or establish a causation relationship to drug exposure.

- Blood and Lympathic System Disorders: lymphopения
- Gastrointestinal Disorders: pancreatitis
- Hepatobiliary Disorders: hepatitis, cholestasis
- Immune System Disorders: drug hypersensitivity
- Infections and Infestations: pneumonia, sepsis/septicemia
- Metabolism and Nutrition Disorders: hypoglycemia, 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 is associated with an increased risk of fetal malformations and can cause fetal harm when administered to a pregnant woman. There is 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 infusions 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/m2 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 as high as 2.0 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/m2 to patients with mild hepatic impairment and 0.7 mg/m2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m2 to patients with normal hepatic function. Therefore, a lower starting dose of 1.1 mg/m2 is recommended for patients with mild hepatic impairment (Child-Pugh A) and of 0.7 mg/m2 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/m2.

### 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 microsomal assay. Fertility studies have not been conducted with eribulin mesylate in humans or animals; however, nonclinical findings in repeat-dose dog and rat toxicity studies suggest that male fertility may be compromised by treatment with eribulin mesylate. Rats exhibited testicular toxicity (hypercellularity of seminiferous epithelium with hypospermatogenesis/aplasia) 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 every 3 weeks for 5 weeks, and repeated for 6 cycles. Testicular toxicity was also observed in dogs given 0.84 times the recommended human dose (based on body surface area) weekly for 3 out of 5 weeks, repeated for 8 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 (ADIP-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 reactivate tumor-infiltrating T cells, could be a beneficial strategy.43

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.44

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-1.45

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.46

References
FEATURE: New Therapies

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; \( P = .03 \)).

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.

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.”
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.


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.”

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 dedifferentiated liposarcoma 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.

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/m² 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.

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.

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