CASE REPORT

Significant clinical response induced by vismodegib in advanced sarcoma: Hedgehog pathway inhibition

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Pazopanib increases pathologic necrosis rates in STS
Gemcitabine plus pazopanib a potential alternative in STS
rEECur trial finding optimal chemotherapy regimen for Ewing sarcoma
Abemaciclib meets primary endpoint in phase 2 trial of DDLS
nab-Sirolimus provides benefit in advanced malignant PEComa
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IN BRIEF

Adolescent and young adult survival trends

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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 liposarcoma²

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%).¹

OS=overall survival; CI=confidence interval.

HALAVEN was studied in patients with dedifferentiated, myxoid/round cell, and pleomorphic liposarcoma subtypes¹

**Selected Safety Information**

**Peripheral Neuropathy:** Grade 3 peripheral neuropathy occurred in 3.1% of patients with liposarcoma and leiomyosarcoma receiving HALAVEN and neuropathy lasting more than 60 days occurred in 58% (38/65) of patients who had neuropathy at the last treatment visit. Patients should be monitored for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy until resolution to Grade 2 or less.
Treatment effects of HALAVEN® were demonstrated in patients with advanced liposarcoma based on the preplanned, exploratory subgroup analysis of OS and PFS1

![Graph showing Median OS for HALAVEN and Dacarbazine](image)

- **There was no evidence of efficacy of HALAVEN in patients with advanced or metastatic leiomyosarcoma in this trial1**

**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.
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.

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 B) 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 C) is 0.7 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.

- 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 non-hematological toxicities.

- The Day 8 dose may be delayed for a maximum of 1 week.
  - If toxicities do not resolve or improve to ≥ Grade 2 severity by Day 15, omit the dose.

- If a dose has been delayed, re-escalate HALAVEN at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

Dose Reductions:

- If a dose has been delayed, do not re-escalate HALAVEN dose after it has been reduced.

Reference: 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</td>
<td>1.1 mg/m²</td>
</tr>
<tr>
<td>of the following</td>
<td></td>
</tr>
<tr>
<td>ANC &lt;500/mm³ for &gt;7 days</td>
<td></td>
</tr>
<tr>
<td>ANC &lt;1000/mm³ with fever or infection</td>
<td></td>
</tr>
<tr>
<td>Platelets &lt;50,000/mm³</td>
<td></td>
</tr>
<tr>
<td>Platelets &lt;50,000/mm³ with transfusion</td>
<td></td>
</tr>
<tr>
<td>Non-hematologic Grade 3 or 4 toxicities</td>
<td></td>
</tr>
<tr>
<td>Diminished in delay of Day 8 HALAVEN dose in previous</td>
<td></td>
</tr>
<tr>
<td>cycle for toxicity</td>
<td></td>
</tr>
<tr>
<td>Occurrence of any event requiring permanent dose</td>
<td>0.7 mg/m²</td>
</tr>
<tr>
<td>reduction while receiving 1.1 mg/m²</td>
<td></td>
</tr>
<tr>
<td>ANC = absolute neutrophil count</td>
<td></td>
</tr>
<tr>
<td>Toxicities graded in accordance with National Cancer</td>
<td></td>
</tr>
<tr>
<td>Institute Common Terminology Criteria for Adverse</td>
<td></td>
</tr>
<tr>
<td>Events (CTCAE) version 3.0.</td>
<td></td>
</tr>
</tbody>
</table>

WARNINGS AND PRECAUTIONS

Neuropathy: In Study 1, severe neuropenia (ANC < 500/mm³) lasting more than one week occurred in 12% (83/703) of patients with metastatic breast cancer, leading to discontinuation in <1% of patients. Severe neuropenia (ANC < 500/mm³ or platelet count < 50,000/mm³) occurred in 5% (23/503) of patients; two patients (0.4%) died from complications of febrile neutropenia. In Study 1, patients with alimemtine (AIN) or asparate aminotransferase (AST) > 3 × ULN (upper limit of normal) experienced a higher incidence of Grade 4 neuropenia and febrile neutropenia than patients with normal aminotransferase levels. Patients with bilirubin > 15 > ULN also had a higher incidence of Grade 4 neutropenia and febrile neutropenia. In Study 2, severe neuropenia (ANC < 500/mm³) lasting more than one week occurred in 2% (26/1222) 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 patients for toxicities during HALAVEN therapy 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 at least 2 months following treatment.

Table 1: Recommended Dose Reductions

<table>
<thead>
<tr>
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<td>of the following</td>
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<td></td>
</tr>
<tr>
<td>ANC &lt;1000/mm³ with fever or infection</td>
<td></td>
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<tr>
<td>Platelets &lt;50,000/mm³</td>
<td></td>
</tr>
<tr>
<td>Platelets &lt;50,000/mm³ with transfusion</td>
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</tr>
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<td>reduction while receiving 1.1 mg/m²</td>
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<td></td>
</tr>
<tr>
<td>Events (CTCAE) version 3.0.</td>
<td></td>
</tr>
</tbody>
</table>

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 observed in clinical practice. The following adverse reactions are discussed in detail in other sections of the labeling:

- Neutropenia
- Peripheral neuropathy
- QT prolongation

In clinical trials, HALAVEN has been administered to 1963 patients including 487 patients exposed to HALAVEN for 6 months or longer. The majority of the 1983 patients were women (82%) with a mean age of 55 years (range 17 to 88 years). The racial and ethnic distribution was White (77%), Black (4%), Asian (9%), and other (3%).

Metastatic Breast Cancer: The most common adverse reactions (25%) reported in patients receiving HALAVEN were nausea, vomiting, diarrhea, alopecia, peripheral neuropathy, paresthesia, asthenia, fatigue, dyspnea, anemia, and constipation. The most common serious adverse reactions reported in patients receiving HALAVEN were febrile neutropenia (4%) and neuropathy (2%). The most common adverse reaction leading to 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 simple agent treatment chosen by their physician (control group). A total of 535 patients received HALAVEN and 247 patients in the control group received therapy consisting of chemotherapy (total 59% [anthracyclines 16%, capecitabine 19%, gemcitabine 19%, taxanes 15%, capecitabine 25%, other chemotherapies 10%] or hormonal therapy (3%). The median duration of exposure was 118 days for patients receiving HALAVEN and 63 days for patients receiving control therapy. Table 2 reports the most common adverse reactions occurring in at least 10% of patients in either group.

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>HALAVEN</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>62%</td>
<td>53%</td>
</tr>
<tr>
<td>Nausea</td>
<td>56%</td>
<td>55%</td>
</tr>
<tr>
<td>Dry skin</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19%</td>
<td>15%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19%</td>
<td>15%</td>
</tr>
<tr>
<td>Rash</td>
<td>18%</td>
<td>11%</td>
</tr>
<tr>
<td>Constipation</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>Anemia</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia/Myalgia</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td>Nausea</td>
<td>35%</td>
<td>28%</td>
</tr>
<tr>
<td>Constipation</td>
<td>25%</td>
<td>21%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>Dermatitis and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nails</td>
<td>35%</td>
<td>28%</td>
</tr>
<tr>
<td>Constipation</td>
<td>18%</td>
<td>15%</td>
</tr>
<tr>
<td>Anemia</td>
<td>20%</td>
<td>12%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>16%</td>
<td>12%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16%</td>
<td>10%</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dysuria, abdominal pain, stomatitis, dry mouth</td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>peripheral edema</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>upper respiratory tract infection</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>40%</td>
<td>24%</td>
</tr>
<tr>
<td>Nails</td>
<td>30%</td>
<td>28%</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
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</tr>
<tr>
<td>Alopecia</td>
<td>40%</td>
<td>24%</td>
</tr>
</tbody>
</table>

* Listed Common Adverse Reactions: The following additional adverse reactions were reported in >5% to >10% of the HALAVEN-treated group:

- Eye Disorders: increased lacrimation
- Gastrointestinal Disorders: Dysphagia, abdominal pain, stomatitis, dry mouth
- General Disorders and Administration Site Conditions: peripheral edema
- Infections and infestations: upper respiratory tract infection
- Respiratory, thoracic, and mediastinal disorders: cough, respiratory infection
- Musculoskeletal and Connective Tissue Disorders: muscle spasms, muscle weakness
- Nervous System Disorders: dyspnea, dizziness
- Psychiatric Disorders: insomnia, depression
- Skin and Subcutaneous Tissue Disorders: rash

3/27/18 3:13 PM

TSJ_17.indd 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 and of 27-day cycle or dacarbazine as single-agent of 500 mg/m2 (28%), 1000 mg/m2 (34%), or 1200 mg/m2 (16%) every 3 weeks. A total of 223 patients received HALAVEN and 221 patients received dacarbazine. Patients were required to have received at least two prior systemic chemotherapy regimens; the trial excluded patients with previous ≥ Grade 2 peripheral neuropathy, known central nervous system metastasis, elevated serum bilirubin or significant chronic liver disease, history of myocardial infarction within 6 months, history of New York Heart Association Class II or IV heart failure, or cardiac arrhythmia requiring treatment. The median age of the safety population in Study 2 was 56 years (range: 24 to 83 years); 67% female, 73% White, 3% Black or African American, 8% Asian/Pacific Islander, and 15% unknown; 89% received prior anthracycline-containing regimen; and 99% received ≥ 2 prior regimens. The median duration of exposure was 2.3 months (range: 21 days to 26 months) for patients receiving HALAVEN.

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

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

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

<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>6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>General disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>28%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Abdominal pain†</td>
<td>29%</td>
<td>18%</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>30%</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3%</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Adverse reactions were graded per National Cancer Institute Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety data from one study site enrolling six patients were excluded.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Includes peripheral sensorimotor neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paresthesia.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Includes abdominal pain, upper abdominal pain, lower abdominal pain, abdominal distention.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Not applicable; (grading system does not specify &gt; Grade 2 for alopecia).</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- **Gastrointestinal disorders:** nausia (11%), vomiting (19%), diarrhea (17%)
- **General Disorders:** asthenia/fatigue (82%), peripheral edema (12%)
- **Metabolism and Nutrition Disorders:** decreased appetite (13%)
- **Musculoskeletal and Connective Tissue Disorders:** arthralgia/myalgia (16%)

Males and females of reproductive potential were required to use effective contraception during treatment with HALAVEN and for at least 12 weeks 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. For a lower starting dose of 1.1 mg/m2 for patients with mild hepatic impairment (Child-Pugh A) and 0.7 mg/m2 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 micronucleus assay.
- Fertility studies have not been conducted with eribulin mesylate in humans or animals; however, nonclinical findings in repeat-dose dog and rat toxicology studies suggest that male fertility may be compromised by treatment with eribulin mesylate. Rates exhibited testicular toxicity (hypocellularity of seminiferous epithelium with hypoplasia/aspermia) following dosing with eribulin mesylate at above 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 3 out of 5 weeks, for up to 3 weeks, and repeated for 8 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, for repeated for 8 cycles.

**PATIENT COUNSELING INFORMATION**
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- **Neuropathy:** Advise patients to contact their health care provider for a fever of 100.5°F or greater or other signs of infection such as chills, cough, or purulent or pain on urination.
- **Peripheral Neuropathy:** Advise patients to inform their healthcare providers of new or worsening numbness, tingling and pain in their extremities.
- **Embolism/Fetal Toxicity:**
  - 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 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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Clinical trials in sarcoma bring hope and promise

In this issue of The Sarcoma Journal, we highlight research and developments presented at the 2019 ASCO annual meeting. Despite the rarity of sarcoma, it was not lost among the thousands of abstracts, posters, and talks presented during the four-and-a-half days of the meeting.

In the past 5 years, there has been a resurgence of phase 3 clinical trials in sarcoma, including several large first-line studies comparing combination therapies to doxorubicin—the gold standard since the mid-1970s. None have shown superiority. Despite this, there has been a gradual improvement in overall survival. This is attributed to advances in the multidisciplinary management of sarcomas and available supportive care services as well as a better understanding of and emergent therapies for individual sarcoma subtypes.

In the United States, we have seen the approval of several agents in sarcoma: pazopanib, with a 3-month improvement in progression-free survival (PFS) over placebo; trabectedin in liposarcoma and leiomyosarcoma, with a 2.7-month improvement in PFS over dacarbazine; and eribulin, based on a liposarcoma subgroup analysis that showed a 7-month improvement in overall survival over dacarbazine.

None of these therapies are approved in the US in the front-line setting; rather, all after a patient generally receives a doxorubicin-based therapy.

We have learned a great deal from these studies. They highlight some of the challenges in designing clinical trials in a rare and heterogeneous group of malignancies. The sarcoma community is very much focused on overcoming these challenges by designing clinical trials appropriate to the disease and the therapy that is being studied. This includes the incorporation of novel endpoints, imaging modalities, patient-reported outcome measures, and statistical methodologies to best serve the patient and to determine whether and how the therapy is helping them.

There is tremendous hope and promise in sarcoma due to significant advancements in our understanding of mesenchymal biology and of the genetic diversity in these diseases. This has led to an influx of promising agents and trials, many of which have transformed treatment paradigms on specific sarcoma subtypes. This issue provides a glimpse into the progress being made.

From Dr. Tap’s plenary presentation at ASCO 2019
Significant clinical response induced by vismodegib in advanced sarcoma: Hedgehog pathway inhibition

Spindle cell sarcomas are part of a rare, heterogeneous family of connective tissue tumors. These tumors are primarily treated with surgery and have a high risk of recurrence and distant metastasis with elevated mortality rates.1 Other than the evidence for first-line therapy with doxorubicin in advanced soft tissue sarcoma, little evidence exists to point to an optimal second-line therapy. This is due to the diversity of soft tissue sarcomas, which encompass approximately 70 different histologic subtypes that can each respond differently to treatment.2 As such, newer strategies, including immunotherapy and targeted molecular drugs, are being developed.

Quiescent in most adult tissues, the Hedgehog signaling pathway, when inappropriately activated, has been implicated in the development of multiple types of cancers, including basal cell, breast, prostate, hepatocellular, pancreatic, and brain cancer.3 The Hedgehog signaling pathway is an important regulator of cell growth and differentiation in early development, but when inappropriately activated can lead to cell proliferation and increased angiogenic factors, decreased apoptosis, and breakdown of tight junctions promoting cancer growth and metastasis.4 Recent data reveal that the Hedgehog pathway plays a specific role in activation of satellite cells, proliferation of myoblasts, and differentiation of skeletal muscle.5 Activation of this embryonic pathway has been implicated in embryonal rhabdomyosarcoma, osteosarcoma, and chondrosarcoma.5-7

This pathway has recently been recognized as a therapeutic target, with the development of vismodegib, a targeted Hedgehog pathway inhibitor. This novel agent is in active use for treatment of advanced basal cell carcinoma and is currently undergoing trials for various other malignancies. Recently, a phase 2a basket study, called MyPathway, evaluated the use of targeted therapies in 35 different advanced refractory solid tumors harboring specific molecular alterations. Out of 21 patients with mutations in the Hedgehog pathway, 3 had a partial response to vismodegib—one had an unknown primary tumor, another a squamous skin cancer, and the third a salivary gland cancer.8 Vismodegib (GDC-0449) was also evaluated in a phase 2 multicenter clinical trial in patients with progressive advanced chondrosarcoma.7 Although the study did not meet its primary endpoint, the proportion of patients with non-progressive disease was 25.6% at 6 months. Investigators observed that the benefit occurred in the subset of patients with overexpression of the Hedgehog ligand. Genomic studies for mutations in SMO and PTCH genes were available for only 28 and 26 patients, respectively, of the 45 patients enrolled on the trial. While there were no mutations identified, expression data revealed that overexpression of the Hedgehog ligand was present in 65% of cases tested (13 out of 20 patients). In patients with stable disease at 6 months, all had overexpression of the Hedgehog ligand.7 These studies point to the potential use of vismodegib in both bone and soft tissue sarcomas, and more specifical-
ly, to the importance of genomic testing in these cases.

**CASE PRESENTATION AND SUMMARY**

This report describes the novel use of vismodegib, an oral Hedgehog signaling pathway inhibitor, in the treatment of a patient with metastatic soft tissue sarcoma.

An 18-year-old female with no particular previous illnesses was initially diagnosed with superficial soft tissue sarcoma overlying the right hip in 2013. Due to the complexity of pathology, a second opinion was requested and revealed atypical cellular spindle and epithelioid cells, morphologically and immunohistochemically suggestive of spindle cell sarcoma, not otherwise specified. She underwent negative-margin resection in January 2014. Her course was complicated by two recurrences in the right inguinal lymph nodes in July 2014 and July 2015. She was treated with lymph node dissection in 2014, followed by numerous right lymph node dissections and adjuvant radiation in 2015.

A routine computerized tomography (CT) scan of the thorax-abdomen and pelvis in August 2016 revealed recurrence of disease, with multiple lung nodules as well as metastases in the retroperitoneum. She received 6 cycles of gemcitabine and docetaxel with stability of disease. The patient was then started on a PI3K inhibitor as part of a clinical trial, as genotypic analysis of the tumor revealed an activating mutation of the PI3K gene. The patient’s course was complicated by acute obstructive renal failure requiring a double J stent. She also had transaminitis resulting from a common bile duct stricture treated with a biliary stent and worsening ascites requiring regular paracentesis. This was all in the context of new or growing metastatic implants.

At this time, the result of the FoundationOne genomic testing revealed PTCH1 loss of exons 1-24 and CDKN2A/B loss. Mutation of tumor suppressor gene PTCH1 leads to Hedgehog pathway activation and therefore the patient was started on vismodegib on January 22, 2018. She was discharged from the hospital in stable condition a day later, on January 23.

Repeat imaging revealed disease progression, and the patient was then switched to liposomal doxorubicin alone for 4 months and then in combination with olaratumab. She received the combined treatment for a total of 3 months, which was then stopped when she was found to have new peritoneal implants and worsening ascites. At this time, tissue was sent for FoundationOne® next generation sequencing (NGS)-based genomic testing, and the patient received one dose of nivolumab.

In January 2018, 2 days after receiving her first dose of nivolumab, the patient required admission for worsening abdominal pain secondary to progression of her disease (**FIGURE 1**). She was found to have acute kidney injury on top of chronic kidney disease due to hydronephrosis requiring a left-sided double J stent. She also had transaminitis resulting from a common bile duct stricture treated with a biliary stent and worsening ascites requiring regular paracentesis. This was all in the context of new or growing metastatic implants.

At this time, the result of the FoundationOne genomic testing revealed PTCH1 loss of exons 1-24 and CDKN2A/B loss. Mutation of tumor suppressor gene PTCH1 leads to Hedgehog pathway activation and therefore the patient was started on vismodegib on January 22, 2018. She was discharged from the hospital in stable condition a day later, on January 23.

The patient’s clinical status subsequently improved, with significant reduction in her chronic abdominal pain and very minimal side effects. Clinically, the patient’s acute kidney injury resolved (from a creatinine of 272 µmol/L at discharge to 85 µmol/L after a week of treatment) and her liver enzymes normalized (from an alkaline phosphatase of 301 U/L to 83 U/L, and alanine transaminase of 111 U/L to 38 U/L). CT scan of her chest
and abdomen, which was performed 1 month post treatment, revealed stability of disease with absence of ascites (Figure 2). The patient continued to have a good response to treatment for 6 months, with no recurrence of pain or ascites.

Six months later, in July 2018, the patient developed increasing pain and a CT scan revealed worsening of abdominopelvic carcinomatosis. In this context, vismodegib was discontinued on July 17. In the next 5 months, she went on to receive carboplatin and paclitaxel, gemcitabine, and nivolumab consecutively with no response. She was admitted to hospital on December 30 for a pain crisis. She passed away on January 9, 2019, from fecal peritonitis.

**DISCUSSION**

To the best of our knowledge, this is the first patient with metastatic sarcoma to receive vismodegib, a Hedgehog signaling pathway inhibitor. She achieved an excellent clinical response with progression-free disease for approximately 6 months after starting treatment.

There is no current standard second-line treatment for metastatic soft tissue sarcoma. The choice of systemic therapy is histology-driven and therefore treatment is individualized for each patient. The future of oncology is heading towards an even more personalized approach with molecular profiling. Our case report highlights the relevance of genomic testing and targeted therapies, especially in cases of diverse clinical and biological disease behavior.

Molecular targeting is even more necessary in patients with advanced cancer who have failed multiple lines of treatment. As in our study, these patients can obtain a significant response with meaningful improvement in their quality of life. Future research is currently focusing on identifying new molecular targets in patients with advanced refractory cancers. Further studies will need to be done to determine whether these molecular targeting agents, such as vismodegib, lead to significant outcome changes in these patients.

**REFERENCES**


**EDITORIAL NOTE:**

**FIGURE 2.** CT scan of the patient’s abdomen-pelvis performed on March 14 revealed stability of disease with an absence of ascites.
SFA awards grants to 15 researchers

Since its inception, the Sarcoma Foundation of America (SFA) has awarded research grants for the best, most promising research to cure sarcoma. This year SFA awarded $750,000 in research funds to 15 scientists as part of its 2019 SFA Research Grant program. The grants, worth $50,000 each, explore numerous sarcoma subtypes, multiple strategies, and different approaches to find effective treatments for many forms of the disease. Research projects are listed below alphabetically by investigator last name. More details are available on the SFA’s grant pages, available at https://www.curesarcoma.org/grant.

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<td>Claudio Brancolini, PhD¹</td>
<td>University of Udine, Italy</td>
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<td>Eleanor Chen, MD, PhD²</td>
<td>University of Washington, USA</td>
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<td>Enrique De Alava, MD, PhD³</td>
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<td>David Scadden, MD⁸</td>
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<td>Juan Manuel Schwartzman, MD, PhD⁶</td>
<td>Memorial Sloan Kettering Cancer Center, USA</td>
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<td>Uncovering polygenic signatures of Ewings sarcoma drug sensitivity during the evolution of resistance</td>
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<td>David Shultz, MD, PhD³</td>
<td>Princess Margaret Cancer Centre, Canada</td>
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<td>Joshua Waterfall, PhD⁹</td>
<td>Institut Curie, France</td>
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<tr>
<td>Lai Man Natalie Wu, PhD⁷</td>
<td>Cincinnati Children’s Hospital Medical Center, USA</td>
<td>Single-cell transcriptomics and epigenomics to identify tumor-microenvironment interactions for targeted treatment of MPNST</td>
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Awards received:
1. Spring for Sarcoma York, PA, Research Award
2. STL Cure Sarcoma Research Award
3. Race to Cure Sarcoma Research Award
4. Dr. Richard and Valerie Aronsohn Memorial Research Award
5. Sarcoma Foundation of America Research Award
6. Christopher Langbein Research Award
7. Zach Cohen Memorial Research Award
8. Pittsburgh Cure Sarcoma Research Award
9. Jay Vernon Jackson Memorial Research Award
This issue of The Sarcoma Journal features reports from the annual meeting of the American Society of Clinical Oncology (ASCO), held in Chicago, May 31 – June 4, 2019.

The meeting included developments in research and treatment approaches for sarcoma, highlighting a wide-ranging array of agents, disease subtypes, and therapeutic strategies. The studies below were presented in oral abstract sessions, except for the late-breaking abstract reported in the plenary session, which kicks off the conference coverage that follows. Note: Information presented at the meeting may differ from the corresponding abstract.

BEHIND OLARATUMAB’S PHASE 3 DISAPPOINTMENT

ANNOUNCE, the phase 3 trial designed to confirm the clinical benefit of olaratumab in patients with advanced soft tissue sarcoma (STS), failed to meet its primary endpoint of overall survival (OS) in all STS histologies and the leiomyosarcoma population. The previous phase 1b/2 signal-finding study of olaratumab had achieved an unprecedented improvement in OS, and the US Food and Drug Administration (FDA) awarded olaratumab accelerated approval in October 2016. By December 2018, olaratumab received additional accelerated, conditional, and full approvals in more than 40 countries worldwide. William D. Tap, MD, chief of the Sarcoma Medical Oncology Service at Memorial Sloan Kettering Cancer Center in New York, presented the phase 3 results and provided some explanations for the findings during the plenary session at ASCO.

ANNOUNCE (NCT02451943), which was designed and enrolled prior to olaratumab receiving accelerated approval, opened in September 2015 and completed accrual 10 months later in July 2016. Investigators randomized and treated 509 patients with advanced STS not amenable to curative therapy, 258 patients in the olaratumab-doxorubicin arm and 251 in the placebo-doxorubicin arm. Most patients (46%) had leiomyosarcoma, followed by liposarcoma (18%), pleomorphic sarcoma (13%), and 24% of the patient population had 26 unique histologies. Three-quarters of the patients had no prior systemic therapy.

Results

As of the data cutoff on December 5, 2018, there were no survival differences in the intention-to-treat population, in the total STS population nor in the leiomyosarcoma subpopulation, with olaratumab-doxorubicin compared to placebo-doxorubicin. For the total STS population, median OS with olaratumab was 20.4 months and with placebo-doxorubicin 19.7 months. “This is the highest survival rate described to date in any phase 3 sarcoma study,” Dr. Tap said. “It is of particular interest as ANNOUNCE did not mandate treatment in the first line.” In the leiomyosarcoma population, median OS was 21.6 months with olaratumab and 21.9 months with placebo. The secondary endpoints of progression-free survival (PFS), overall response rate, and disease control rate did not favor olaratumab either.

Investigators are examining the relationship between PDGFRα expression and OS in ANNOUNCE. PDGFRα-positive tumors tended to do worse with olaratumab than PDGFRα-negative tumors. The investigators noticed a 6-month difference in OS between these populations favoring PDGFRα-negative tumors. Additional biomarker analyses are ongoing.

A large and concerted effort is underway, Dr. Tap said, to understand the re-
results of the ANNOUNCE study alone and in context with the phase 1b/2 study. “There are no noted discrepancies in study conduct or data integrity which could explain these findings or the differences between the two studies.”

**Possible explanations**

The designs of the phase 1b/2 and phase 3 studies had some important differences. The phase 1b/2 study was a small, open-label, US-centric study (10 sites) that did not include a placebo or subtype-specified analyses. Its primary endpoint was PFS; it did not have a loading dose of olaratumab, and it specified the timing of dexrazoxane administration after 300 mg/m² of doxorubicin.

ANNOUNCE, on the other hand, was a large (n=509), international (110 study sites), double-blind, placebo-controlled trial that had outcomes evaluated in STS and leiomyosarcoma. Its primary endpoint was OS; it had a loading dose of olaratumab of 20 mg/kg, and there was no restriction as to the timing of dexrazoxane administration.

Dr. Tap pointed out that in ANNOUNCE it was difficult to predict or control for factors that may have had an unanticipated influence on outcomes, such as albumin levels as a surrogate for disease burden and behavior of PDGFRα status. It is possible, he said, that olaratumab has no activity in STS and that the phase 1b/2 results were due to, among other things, the small sample size, numerous represented histologies with disparate clinical behavior, and the effect of subtype-specific therapies on overall survival, given subsequently or even by chance. On the other hand, it is also possible, he said, that olaratumab has some activity in STS, with outcomes being affected by the heterogeneity of the study populations, differences in trial design, and the performance of the ANNOUNCE control arm. Whatever the case, he said, accelerated approval allowed patients to have access to a potentially life-prolonging drug with little added toxicity.

**Discussion**

In the expert discussion following the presentation, Jaap Verweij, MD, PhD, of Erasmus University Medical Center in Rotterdam, The Netherlands, congratulated the investigators for performing the study at an unprecedented pace. He commented that lumping STS subtypes together is problematic, as different histological subtypes behave as though they are different diseases. Small numbers of each tumor subtype and subtypes with slow tumor growth can impact trial outcomes. In the phase 1b/2 and phase 3 trials, 26 different subtypes were represented in each study. Dr. Verweij pointed out this could have made a big difference in the phase 1b/2 study, in which there were only 66 patients in each arm.

It is striking to note, he said, that without exception, phase 2 randomized studies in STS involving doxorubicin consistently overestimated and wrongly predicted PFS in the subsequent phase 3 studies. And the situation is similar for OS. The results of the ANNOUNCE study are no exception, he added. “Taken together, these studies indicate that phase 2 studies in soft tissue sarcomas, certainly those involving additions of drugs to doxorubicin, even if randomized, should be interpreted with great caution,” he said. **TSJ**

**SOURCE:** Tap WD, et al. J Clin Oncol 37, 2019 (suppl; abstr LBA3)

The study was sponsored by Eli Lilly and Company.

Dr. Tap reported research funding from Lilly and Dr. Verweij had nothing to report related to this study. Abstract coauthors disclosed numerous financial relationships, including consulting/advisory roles and/or research funding from Lilly, and several were employed by Lilly.

**THE PHASE 3 STUDY OF OLARATUMAB HAD NO NOTED DISCREPANCIES IN STUDY CONDUCT OR DATA INTEGRITY THAT COULD EXPLAIN THE FINDINGS OR DIFFERENCES BETWEEN IT AND THE PHASE 1b/2 STUDY.**

**ADDITION OF TEMOZOLOMIDE MAY IMPROVE OUTCOMES IN RMS**

Investigators from the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) found that the addition of temozolomide (T) to vincristine and irinotecan (VI) may improve outcomes in adults and children with relapsed or refractory rhabdomyosarcoma (RMS). Principal investigator of the study, Anne Sophie Defachelles, MD, pediatric oncologist at the...
**The Addition of Temozolomide to Treatment with Vincristine and Irinotecan Achieved a “Large and Significant Reduction in Risk of Death.”**

Centre Oscar Lambret in Lille, France, presented the results on behalf of the EpSSG.

The primary objective of the study was to evaluate the efficacy of VI and VIT regimens, defined as objective response (OR)—complete response (CR) plus partial response (PR)—after 2 cycles. Secondary objectives were progression-free survival (PFS), overall survival (OS), and safety in each arm, and the relative treatment effect of VIT compared to VI in terms of OR, survival, and safety.

The international, randomized (1:1), open-label, phase 2 trial (VIT-0910; NCT01355445) was conducted at 37 centers in 5 countries. Patients ages 6 months to 50 years with RMS were eligible. They could not have had prior irinotecan or temozolomide. A 2015 protocol amendment limited enrollment to patients at relapse and increased the enrollment goal by 40 patients. After the 2015 amendment, patients with refractory disease were no longer eligible.

From January 2012 to April 2018, investigators enrolled 120 patients, 60 on each arm. Two patients in the VI arm were not treated. Patients were a median age of 10.5 years in the VI arm and 12 years in the VIT arm. 92% (VI) and 87% (VIT) had relapsed disease, 8% (VI) and 13% (VIT) had refractory disease, and 55% (VI) and 68% (VIT) had metastatic disease at study entry.

**Results**

Patients achieved an OR rate of 44% (VIT) and 31% (VI) for the whole population, one-sided $P$ value <.0001. The adjusted odds ratio for the whole population was 0.50, $P=.09$. PFS was 4.7 months (VIT) and 3.2 months (VI), “a nearly significant reduction in the risk of progression,” Dr. Defachelles noted. Median OS was 15.0 months (VIT) and 10.3 months (VI), which amounted to “a large and significant reduction in the risk of death,” she said. The adjusted hazard ratio was 0.55, $P=.006$.

Adverse events of grade 3 or higher were more frequent in the VIT arm, with hematologic toxicity the most frequent (81% for VIT, 59% for VI), followed by gastrointestinal adverse events. “VIT was significantly more toxic than VI,” Dr. Defachelles observed, “but the toxicity was manageable.”

“VIT is now the standard treatment in Europe for relapsed rhabdomyosarcoma and will be the control arm in the multi-arm, multistage RMS study for relapsed patients,” she said.

In a discussion following the presentation, Lars M. Wagner, MD, of Cincinnati Children’s Hospital, pointed out that the study was not powered for the PFS and OS assessments. These were secondary objectives that should be considered exploratory. Therefore, he said, the outcome data is not conclusive. The role of temozolomide in RMS is also unclear, given recent negative results in patients with newly diagnosed metastatic RMS (Malempati et al, Cancer 2019). And he said it’s uncertain how these results apply to patients who received irinotecan upfront for RMS.

**Pazopanib Increases Pathologic Necrosis Rates in STS**

Pazopanib added to a regimen of preoperative chemoradiation in non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) significantly increased the rate of near-complete pathologic response in both children and adults with intermediate or high-risk disease. Pazopanib, a multtargeted receptor tyrosine kinase inhibitor, works in multiple signaling pathways involved in tumorigenesis—VEGFR-1, -2, -3, PDGFRα/β, and c-kit. A phase 3 study demonstrated significant improvement in progression-free survival (PFS) in advanced STS patients and was the basis for its approval in the US.
and elsewhere for treatment of this patient population. Preclinical data suggest synergy between pazopanib and cytotoxic chemotherapy, forming the rationale for the current trial with neoadjuvant pazopanib added to chemoradiation.

According to the investigators, the trial (ARST1321) is the first ever collaborative study codeveloped, written, and conducted by pediatric (Children’s Oncology Group) and adult (NRG Oncology) cancer cooperative groups (NCT02180867). Aaron R. Weiss, MD, of the Maine Medical Center in Portland and study cochair, presented the data for the chemotherapy arms at ASCO. The primary objectives of the study were to determine the feasibility of preoperative chemoradiation with or without pazopanib and to compare the rates of complete pathologic response in patients receiving radiation or chemoradiation with or without pazopanib. Pathologic necrosis rates of 90% or better have been found to be predictive of outcome in STS.

Patients with metastatic or non-metastatic NRSTS were eligible to enroll if they had initially unresectable extremity or trunk tumors with the expectation that they would be resectable after therapy. Patients had to be 2 years or older—there was no upper age limit—and had to be able to swallow a tablet whole. The dose-finding phase of the study determined the pediatric dose to be 350 mg/m² and the adult dose to be 600 mg/m², both taken orally and once daily. Patients in the chemotherapy cohort were then randomized to receive chemotherapy—ifosfamide and doxorubicin—with or without pazopanib. At week 13, patients in the pazopanib arm showed significant improvement, with 14 (58%) of those evaluated having pathologic necrosis of at least 90%, compared with 4 (22%) in the chemoradiation-only arm (P = .02). The study was closed to further accrual.

Eighteen patients were not evaluable for pathologic response and 21 were pending pathologic evaluation at week 13. Radiographic response rates were not statistically significant on either arm. No complete responses (CR) were achieved in the pazopanib arm, but 14 patients (52%) achieved a partial response (PR) and 12 (44%) had stable disease (SD). In the chemoradiation-only arm, 2 patients (8%) achieved a CR, 12 (50%) a PR, and 8 (33%) SD. Fifteen patients in each arm were not evaluated for radiographic response.

The pazopanib arm experienced more febrile neutropenia and myelotoxicity during induction and continuation phases than the chemoradiation-only arm. In general, investigators indicated pazopanib combined with chemoradiation was well tolerated and no unexpected toxicities arose during the trial.

In the post-presentation discussion, Dr. Raphael E. Pollock, MD, PhD, of The Ohio State University, called it a tremendous challenge to interdigitate primary local therapies in systemic approaches, particularly in the neoadjuvant context. He pointed out that in an earlier study, a 95% to 100% necrosis level was needed to achieve a significant positive impact on outcomes and perhaps a subsequent prospective trial could determine the best level. He questioned whether the availability of only 60% of patient responses could affect the conclusions and whether the high number of toxicities...
THE COMBINATION OF GEMCITABINE PLUS PAZOPANIB ACHIEVED A HIGHER RESPONSE RATE THAN SINGLE-AGENT GEMCITABINE OR PAZOPANIB, BUT NOT HIGHER THAN THE GEMCITABINE-DOCETAXEL COMBINATION.

(73.8% grade 3/4 with pazopanib) might be too high to consider the treatment for most patients, given the intensity of the regimen. TSJ


The study was sponsored by the National Cancer Institute.

Drs. Weiss and Pollock had no relationships with commercial interests to disclose. A few investigators disclosed advisory, consulting, or research roles with pharmaceutical companies, including one who received institutional research funding from Novartis (pazopanib).

GEMCITABINE PLUS PAZOPANIB A POTENTIAL ALTERNATIVE INSTS

In a phase 2 study of gemcitabine with pazopanib (G+P) or gemcitabine with docetaxel (G+D), investigators concluded the combination with pazopanib can be considered an alternative to that with docetaxel in select patients with advanced soft tissue sarcoma (STS). They reported similar progression-free survival (PFS) and rate of toxicity for the two regimens. Neeta Somaiah, MD, of the University of Texas MD Anderson Cancer Center in Houston, presented the findings of the investigator-initiated effort (NCT01593748) at ASCO.

The objective of the study, conducted at 10 centers across the United States, was to examine the activity of pazopanib when combined with gemcitabine as an alternative to the commonly used gemcitabine plus docetaxel regimen. Pazopanib is a multi-tyrosine kinase inhibitor with efficacy in non-adipocytic STS. Adult patients with metastatic or locally advanced non-adipocytic STS with ECOG performance of 0 or 1 were eligible. Patients had to have received prior anthracycline exposure unless it was contraindicated. The 1:1 randomization included stratification for pelvic radiation and leiomyosarcoma histology, which was felt to have a higher response rate with the pazopanib regimen.

The investigators enrolled 90 patients, 45 in each arm. Patients were a mean age of 56 years, and there was no difference in age or gender distribution between the arms. Patients with leiomyosarcoma (31% overall) or prior pelvic radiation (11% overall) were similar between the arms. The overall response rate using RECIST 1.1 criteria was partial response (PR) in 8 of 44 evaluable patients (18%) in the G+D arm and 5 of 43 evaluable patients (12%) in the G+P arm. Stable disease (SD) was observed in 21 patients (48%) in the G+D arm and 24 patients (56%) in the G+P arm. This amounted to a clinical benefit rate (PR + SD) of 66% and 68% for the G+D and G+P arms, respectively (Fisher’s exact test, P > .99). The median PFS was 4.1 months on both arms and the difference in median overall survival—15.9 months in the G+D arm and 12.4 months in the G+P arm—was not statistically significant.

Adverse events (AEs) of grade 3 or higher occurred in 19.9% of patients on G+D and 20.6% on G+P. Serious AEs occurred in 33% (G+D) and 22% (G+P). Dose reductions were necessary in 80% of patients on G+P and doses were held in 93%. Dr. Somaiah explained that this may have been because the starting dose of gemcitabine and pazopanib (1000 mg/m² of gemcitabine on days 1 and 8 and 800 mg of pazopanib) was “probably higher than what we should have started at.” The rate of doses held was also higher in the pazopanib arm (93%) compared with the docetaxel arm (58%). This was likely because pazopanib was a daily dosing, so if there was a toxicity it was more likely to be held than docetaxel, she observed. Grade 3 or higher toxicities occurring in 5% or more of patients in either arm consisted generally of cytopenias and fatigue. The G+P arm experienced a high amount of neutropenia, most likely because this arm did not receive granulocyte-colony stimulating factor (GCSF) support, as opposed to the G+D arm.

Dr. Somaiah pointed out that the 12% response rate for the G+P combination is similar to what has been previously presented and higher than single-agent gemcitabine or pazopanib, but not higher than the G+D combination. The PFS of 4.1 months was less than anticipated, she added, but it was similar on both arms.
The "DROP-A-LOSER" TRIAL IS DESIGNED TO FIND THE STANDARD OF CARE FOR EWING SARCOMA. 

The investigators believe the G+P combination warrants further exploration. TSJ


The study was sponsored by the Medical University of South Carolina, with Novartis as collaborator.

Dr. Somaiah disclosed Advisory Board roles for Blueprint, Deciphera, and Bayer. Abstract coauthors disclosed advisory/consulting roles or research funding from various commercial interests, including Novartis (pazopanib) and Pfizer (gemcitabine).

rEECur TRIAL FINDING OPTIMAL CHEMOTHERAPY REGIMEN FOR EWING SARCOMA

Interim results of the first and largest randomized trial in patients with refractory or recurrent Ewing sarcoma (ES), the rEECur trial, are guiding the way to finding the optimal chemotherapy regimen to treat the disease. Until now, there has been little prospective evidence and no randomized data to guide treatment choices in relapsed or refractory patients, and hence no real standard of care, according to the presentation at ASCO. Several molecularly targeted therapies are emerging, and they require a standardized chemotherapy backbone against which they can be tested.

The rEECur trial (ISRCTN36453794) is a multi-arm, multistage phase 2/3 "drop-a-loser" randomized trial designed to find the standard of care. The trial compares 4 chemotherapy regimens to each other and drops the least effective one after 50 patients per arm are enrolled and evaluated. The 3 remaining regimens continue until at least 75 patients on each arm are enrolled and evaluated, and then another arm would be dropped. The 2 remaining regimens continue to phase 3 evaluation. Four regimens are being tested at 8 centers in 17 countries: topotecan/cyclophosphamide (TC), irinotecan/temozolomide (IT), gemcitabine/docetaxel (GD), and ifosfamide (IFOS). The primary objective is to identify the optimal regimen based on a balance between efficacy and toxicity. Martin G. McCabe, MB BChir, PhD, of the University of Manchester in the United Kingdom, presented the results on behalf of the investigators of the rEECur trial.

Results

Two hundred twenty patients 4 years or older and younger than 50 years with recurrent or refractory histologically confirmed ES of bone or soft tissue were randomized to receive GD (n=72) or TC, IT, or IFOS (n=148). Sixty-two GD patients and 123 TC/IT/IFOS patients were included in the primary outcome analysis. Patients were predominantly male (70%), with a median age of 19 years (range, 4 to 49). About two-thirds (67.3%) were post-pubertal. Most patients (85%) were primary refractory or experienced their first disease recurrence, and 89% had measurable disease.

Investigators assessed the primary outcome of objective response after 4 cycles of therapy and found 11% of patients treated with GD responded compared to 24% in the other 3 arms combined. When they subjected the data to Bayesian analysis, there was a 25% chance that the response rate in the GD arm was better than the response in Arm A, a 2% chance that it was better than Arm B, and a 3% chance that it was better than Arm C. Because this study was still blinded at the time of the presentation, investigators didn’t know which regimen constituted which arm. The probability that response favored GD, however, was low.

The investigators observed no surprising safety findings. Eighty-five percent of all patients experienced at least 1 adverse event. Most frequent grade 3-5 events consisted of pneumonitis (50%, 60%), neutropenic fever (17%, 25%), and diarrhea (0, 12%) in GD and the combined 3 arms, respectively. Grade 3 events in the GD arm were lower than in the other 3 arms combined. There was 1 toxic death attributed to neutropenic sepsis in 1 of the 3 blinded arms.

Median progression-free survival (PFS) for all patients was approximately 5 months. Bayesian analysis suggested there was a low probability that GD was more effective than the other 3 arms: a 22% chance that GD was better than Arm A, a 3% chance that it was better than
Arm B, and a 7% chance that it was better than Arm C. Bayesian analysis also suggested there was a probability that OS favored GD. Because the trial directs only the first 4 or 6 cycles of treatment and the patients receive more treatment after trial-directed therapy, investigators were not fully able to interpret this.

Data suggested GD is a less effective regimen than the other 3 regimens both by objective response rate and PFS, so GD has been dropped from the study. Investigators already had more than 75 evaluable patients in each of the 3 arms for the second interim analysis to take place. In a discussion following the presentation, Jayesh Desai, FRACP, of Peter MacCallum Cancer Centre in Melbourne, Australia, called this study a potentially practice-changing trial at this early stage, noting that the GD combination will be de-prioritized in practice based on these results.

**Results**

Thirty patients, 29 evaluable, with metastatic or recurrent DDLS were enrolled and treated with abemaciclib 200 mg orally twice daily between August 2016 and October 2018. Data cutoff for the presentation was the first week of May 2019. Patients were a median of 62 years, 60% were male, and half had no prior systemic treatment. Prior systemic treatments for those previously treated included doxorubicin, olaratumab, gemcitabine, docetaxel, ifosfamide, eribulin, and trabectedin. For 87%, the primary tumor was in their abdomen or retroperitoneum.

Toxicity was as expected with this class of agent, according to the investigators. The most common grades 2 and 3 toxicities, respectively, possibly related to the study drug, occurring in more than 1 patient included anemia (70%, 37%), thrombocytopenia (13%, 13%), neutropenia (43%, 17%), and lymphocyte count decreased (23%, 23%). Very few of these adverse events were grade 4—none for anemia, and 3% each for thrombocytopenia, neutropenia, and lymphocyte count decreased. Diarrhea of grades 2 and 3 occurred in 27% and 7% of patients, respectively, and was managed well with loperamide.

In addition to reaching the primary endpoint of 15 patients or more achieving PFS at 12 weeks, 1 patient had a confirmed partial response (PR) and another

**ABEMACICLIB MEETS PRIMARY ENDPOINT IN PHASE 2 TRIAL OF DDLS**

The newer and more potent CDK4 inhibitor, abemaciclib, met its primary endpoint in the investigator-initiated, single-center, single-arm, phase 2 trial in patients with advanced progressive dedifferentiated liposarcoma (DDLS). Twenty-two patients (76%) achieved progression-free survival (PFS) at 12 weeks for a median PFS of 30 weeks. A subset of patients experienced prolonged clinical benefit, remaining on study with stable disease for over 900 days. The study (NCT02846987) was conducted at Memorial Sloan Kettering Cancer Center (MSKCC) in New York and Mark A. Dickson, MD, presented the results at ASCO.

Of three agents in the clinic with the potential to target CDK4 and CDK6—palbociclib, ribociclib, and abemaciclib—abemaciclib is more selective for CDK4 than CDK6. CDK4 amplification occurs in more than 90% of well-differentiated and dedifferentiated liposarcomas. Abemaciclib also has a different side effect profile, with less hematologic toxicity than the other 2 agents. The current study was considered positive if 15 patients or more of a 30-patient sample size were progression-free at 12 weeks.
an unconfirmed PR. At data cutoff, 11 patients remained on study with stable disease or PR. The investigators conducted correlative studies that indicated all patients had CDK4 and MDM2 amplification with no loss of retinoblastoma tumor suppressor. They observed an inverse correlation between CDK4 amplification and PFS—the higher the level of CDK4 amplification, the shorter the PFS. They also found additional genomic alterations, including JUN, GLI1, ARID1A, TERT, and ATRX. TERT amplification was also associated with shorter PFS. Based on these findings, the investigators believe a phase 3 study of abemaciclib in DDLS is warranted.

Winette van der Graaf, MD, PhD, of the Netherlands Cancer Institute in Amsterdam, in the discussion following the presentation, concurred that it is certainly time for a multicenter phase 3 study of CDK4 inhibitors in DDLS, and a strong international collaboration is key to conducting such studies, particularly in rare cancers. On a critical note, Dr. van der Graaf expressed concern that no patient-reported outcomes were measured after 120 patients, including those in previous studies, were treated on palbociclib and abemaciclib. Given that the toxicities of the CDK4 inhibitors are quite different, she recommended including patient-reported outcomes in future studies using validated health-related quality-of-life instruments. TSJ

SOURCE: Dickson MA, et al. J Clin Oncol 37, 2019 (suppl; abstr 11004)

The study was sponsored by Memorial Sloan Kettering Cancer Center, with the study collaborator, Eli Lilly and Company.

Dr. Dickson disclosed research funding from Lilly, the company that provided the study drug. Dr. van der Graaf had no relevant relationships to disclose. Abstract coauthors had consulting/advisory roles or research funding from various companies, including Lilly.

nab-SIROLIMUS PROVIDES BENEFIT IN ADVANCED MALIGNANT PEComA

In a prospective phase 2 study of nab-sirolimus in advanced malignant perivascular epithelioid cell tumor (PEComa), the mTOR inhibitor achieved an objective response rate (ORR) of 42% with an acceptable safety profile, despite using relatively high doses of nab-sirolimus compared to other mTOR inhibitors. Activation of the mTOR pathway is common in PEComa, and earlier case reports had indicated substantial clinical benefit with mTOR inhibitor treatment. nab-Sirolimus (ABI-009) is a novel intravenous mTOR inhibitor consisting of nanoparticles of albumin-bound sirolimus. It has significantly higher anti-tumor activity than oral mTOR inhibitors and greater mTOR target suppression at an equal dose. Andrew J. Wagner, MD, PhD, of the Dana-Farber Cancer Institute in Boston, presented the findings of AMPECT (NCT02494570)—Advanced Malignant PEComa Trial—at ASCO.

Investigators enrolled 34 patients 18 years or older with histologically confirmed malignant PEComa. Patients could not have had prior mTOR inhibitors. They received infusions of 100 mg/m² nab-sirolimus on days 1 and 8 every 21 days until progression or unacceptable toxicity. Patients were a median age of 60 years and 44% were 65 or older; 82% were women, which is typical of the disease. Most patients (88%) had no prior systemic therapy for advanced PEComa.

Results

The drug was well tolerated, with toxicities similar to those of oral mTOR inhibitors. Treatment-related adverse events (TRAEs) occurring in 25% or more of patients were mostly grade 1 or 2 toxicities. Hematologic TRAEs included anemia (47%) and thrombocytopenia (32%) of any grade. Nonhematologic events of any grade included stomatitis/mucositis (74%), dermatitis/rash (65%), fatigue (59%), nausea (47%), and diarrhea (38%), among others. A few grade 3 events occurred on study, most notably stomatitis/mucositis (18%). Severe adverse events (SAEs) were also uncommon, occurring in 7 of 34 patients (21%). Pneumonitis is common in orally administered mTOR inhibitors; 6 patients (18%) treated with nab-sirolimus...
had grade 1 or 2 pneumonitis. Of the 31 evaluable patients, 13 (42%) had an objective response, all of which were partial responses (PR). Eleven (35%) had stable disease and 7 (23%) had progressive disease. The disease control rate, consisting of PR and stable disease, was 77%. The median duration of response had not been reached as of the data cutoff on May 10, 2019. At that time, it was 6.2 months (range, 1.5 to 27.7+). The median time to response was 1.4 months and the median progression-free survival (PFS) was 8.4 months. The PFS rate at 6 months was 61%. Three patients had received treatment for over a year and another 3 patients for more than 2 years.

Correlation with biomarkers
Of the 25 patients who had tissue suitable for next-generation sequencing, 9 had TSC2 mutations, 5 had TSC1 mutations, and 11 had neither mutation. Strikingly, 9 of 9 patients with TSC2 mutations developed a PR, while only 1 with a TSC1 mutation responded. One patient with no TSC1/2 mutation also responded and 2 patients with unknown mutational status responded. The investigators also analyzed pS6 status by immunohistochemistry—pS6 is a marker of mTOR hyperactivity. Twenty-five patient samples were available for analysis. Eight of 8 patients who were negative for pS6 staining did not have a response, while 10 of 17 (59%) who were pS6-positive had a PR.

In the discussion that followed, Winette van der Graaf, MD, of the Netherlands Cancer Institute in Amsterdam, noted that this study showed that biomarkers can be used for patient selection, although TSC2 mutations are not uniquely linked with response. She indicated a comparator with sirolimus would have been of great interest. TSJ


The study was sponsored by Aadi Bioscience, Inc., and funded in part by a grant from the FDA Office of Orphan Products Development (OOPD).

Disclosures relevant to this presentation include institutional research funding from Aadi Bioscience for Dr. Wagner and a few other abstract co-authors. Several coauthors are employed by Aadi Bioscience and have stock or other ownership interests. Dr. van der Graaf had nothing to disclose.

CABOZANTINIB ACHIEVES DISEASE CONTROL IN GIST
The phase 2 EORTC 1317 trial, known as CaboGIST (NCT02216578), met its primary endpoint of progression-free survival (PFS) at 12 weeks in patients with metastatic gastrointestinal stromal tumor (GIST) treated with the tyrosine kinase inhibitor (TKI) cabozantinib. Twenty-four (58.5%) of the 41 patients in the primary study population, and 30 (60%) of the entire 50-patient population, were progression-free at 12 weeks. The study needed 21 patients to be progression-free for cabozantinib to warrant further exploration in GIST patients.

Cabozyantinib is a multtargeted TKI inhibiting KIT, MET, AXL, and VEGFR2, which are potentially relevant targets in GIST. In patient-derived xenografts of GIST, cabozantinib demonstrated activity in imatinib-sensitive and -resistant models and inhibited tumor growth, proliferation, and angiogenesis. Additional preclinical experience suggested that cabozantinib could potentially be used as a potent MET inhibitor, overcoming upregulation of MET signaling that occurs with imatinib treatment of GIST, known as the kinase switch.

This investigator-initiated study had as its primary objective assessment of the safety and activity of cabozantinib in patients with metastatic GIST who had progressed on imatinib and sunitinib. The patients could not have been exposed to other KIT- or PDGFR-directed TKIs, such as regorafenib. Secondary objectives included the assessment of cabozantinib in different mutational subtypes of GIST. Patients received cabozantinib tablets once daily until they experienced no further clinical benefit or became intolerant to the drug or chose to discontinue therapy. Fifty patients started treatment between February 2017 and August 2018. All were evaluable for the primary endpoint, and one-third of patients contin-
TRK FUSION CANCER IS A RARE MALIGNANCY SEEN IN A WIDE VARIETY OF ADULT AND CHILDHOOD TUMOR TYPES.

LAROTRECTINIB EFFECTIVE IN TRK FUSION CANCERS

Pediatric patients with tropomyosin receptor kinase (TRK) fusions involving **NTRK1**, **NTRK2**, and **NTRK3** genes had a high response rate with durable responses and a favorable safety profile when treated with larotrectinib, according to a presentation at ASCO. In this pediatric subset of children and adolescents from the SCOUT and NAVIGATE studies, the overall response rate (ORR) was 94%, with a 35% complete response (CR), 59% partial response (PR), and 6% stable disease as of the data cutoff at the end of July 2018.

TRK fusion cancer is a rare malignancy seen in a wide variety of adult and childhood tumor types. Among pediatric malignancies, infantile fibrosarcoma and congenital mesoblastic nephroma are rare, but have high **NTRK** gene fusion frequency. Other sarcomas and pediatric high-grade gliomas, for example, are less rare but have low **NTRK** gene fusion frequency. Larotrectinib, a first-in-class and the only selective TRK inhibitor, has high potency against the 3 **NTRK** genes that encode the neurotrophin receptors. It is highly selective and has limited inhibition of the other kinases. The US Food and Drug Administration approved larotrectinib for the treatment of patients with solid tumors harboring **NTRK** fu-

Results

Patients were a median age of 63 years. Virtually all patients (92%) had prior surgery and only 8% had prior radiotherapy. The daily cabozantinib dose was a median 47.2 mg and duration of treatment was a median 20.4 weeks. No patient discontinued treatment due to toxicity, but 88% discontinued due to disease progression.

Safety signals were the same as for other indications in which cabozantinib is used. Almost all patients (94%) had at least 1 treatment-related adverse event of grades 1-4, including diarrhea (74%), palmar-plantar erythrodysesthesia (58%), fatigue (46%), and hypertension (46%), which are typical of treatment with cabozantinib. Hematologic toxicities in this trial were clinically irrelevant, according to the investigators, consisting of small numbers of grades 2-3 anemia, lymphopenia, white blood cell count abnormality, and neutropenia. Biochemical abnormalities included grades 3 and 4 hypophosphatemia, increased grades 3 and 4 gamma-glutamyl transferase, grade 3 hyponatremia, and grade 3 hypokalemia, in 8% or more of patients.

Overall survival was a median 14.4 months, with 16 patients still on treatment at the time of data cutoff. Twenty-four patients were progression-free at week 12, satisfying the study decision rule for clinical benefit. Median duration of PFS was 6.0 months. Seven patients (14%) achieved a confirmed partial response (PR) and 33 (66%) achieved stable disease (SD). Nine patients had progressive disease as their best response, 3 of whom had some clinical benefit. Forty patients (80%) experienced a clinical benefit of disease control (PR + SD).

An analysis of the relationship of genotype, duration, and RECIST response showed objective responses in patients with primary exon 11 mutations, with exon 9 mutations, and with exon 17 mutations, and in 2 patients without any known mutational information at the time of the presentation. Patients with stable disease were spread across all mutational subsets in the trial. The investigators suggested the definitive role of **MET** and **AXL** inhibition in GIST be assessed further in future clinical trials. **TSJ**

**Source:** Schöffski P, et al. J Clin Oncol 37, 2019 (suppl; abstr 11006).

The study was sponsored by the European Organization for Research and Treatment of Cancer (EORTC).

Presenting author, Patrick Schöffski, MD, of KU Leuven and Leuven Cancer Institute in Belgium, disclosed institutional relationships with multiple pharmaceutical companies for consulting and research funding, including research funding from Exelixis, the developer of cabozantinib. No other abstract coauthor disclosed a relationship with Exelixis.
sions. Cornelis Martinus van Tilburg, MD, of the Hopp Children’s Cancer Center, Heidelberg University Hospital, and German Cancer Research Center in Heidelberg, Germany, presented the findings.

Investigators enrolled 38 children and adolescents younger than 18 years from the SCOUT (NCT02637687) and NAVIGATE (NCT02576431) studies of larotrectinib who had non-central nervous system (CNS) TRK fusion cancers. Not all patients had the recommended phase 2 dose, Dr. van Tilburg pointed out, but most did. Hence, 29 of the 38 patients received the 100 mg/m² twice-daily, phase 2 dose until progression, withdrawal, or unacceptable toxicity.

Patients were young, with a median age of 2.3 years (range, 0.1 to 14.0 years). Almost two-thirds (61%) had prior surgery, 11% had prior radiotherapy, and 68% had prior systemic therapy. For 12 patients, larotrectinib was their first systemic therapy. The predominant tumor types were infantile fibrosarcoma (47%) and other soft tissue sarcoma (42%). And 47% of patients had NTRK3 fusions with ETV6, most of which were infantile fibrosarcoma.

Efficacy
Thirty-four patients were evaluable, and 32 had a reduction in tumor size, for an ORR of 94%, CR of 35%, and PR of 59%. Two patients with infantile fibrosarcoma had pathologic CRs—after treatment, no fibroid tissue in the tumors could be found. Median time to response was 1.8 months, median duration of treatment was 10.24 months, and 33 of 38 patients (87%) remained on treatment or underwent surgery with curative intent. As of the data cutoff of July 30, 2018, the secondary endpoints were not yet reached. However, 84% of responders were estimated to have a response duration of a year or more, and progression-free and overall survival looked very promising, according to Dr. van Tilburg.

Adverse events were primarily grades 1 and 2. The grades 3 and 4 treatment-related adverse events were quite few and consisted of increased alanine aminotransferase, decreased neutrophil count, and nausea. Longer follow-up of the patient safety profile is required, particularly since NTRK has multiple roles in neurodevelopment. The investigators recommended that routine testing for NTRK gene fusions in pediatric patients with cancer be conducted in appropriate clinical contexts.

In a discussion after the presentation, Daniel Alexander Morgenstern, MB BChir, PhD, of Great Ormond Street Hospital, London, UK, said that in many ways, the NTRK inhibitors have become the new poster child for precision oncology in pediatrics because of “these really spectacular results” with larotrectinib [and entrectinib]. One of the questions he raised regarding larotrectinib was the issue of CNS penetration, since patients with CNS cancer were not enrolled in the trial and preclinical data suggest limited CNS penetration for larotrectinib. "TSJ"


The studies were funded by Loxo Oncology, Inc., and Bayer AG.

Disclosures relevant to this presentation include consulting or advisory roles for Bayer for Drs. van Tilburg and Morgenstern. A few coauthors also had consulting/advisory roles or research funding from various companies, including Loxo and Bayer.
Adolescent and young adult (AYA) survival trends

**The good news:** AYA survival improvement was at least as large as in younger children and older adults comparing deaths in two time periods, 1988-2000 and 2001-2014, in a California Cancer Registry.

**The bad news:** There was no statistically significant difference in survival between time periods for patients with bone and soft tissue sarcoma.

### Risk of death

**Characteristics of bone/soft tissue sarcoma patients in AYA population during 2001-2014 compared with 1988-2000**

**LOWER RISK**
- No characteristic conferred a lower risk of death for bone/STS patients

**NO DIFFERENCE IN RISK**
- All tumor stages
- Sex – both
- All age groups, except 25-29
- Asian-Pacific Islanders
- Latino whites
- Non-Latino whites
- High socioeconomic status
- Mid-high socioeconomic status
- Mid-low socioeconomic status
- Low socioeconomic status

**HIGHER RISK**
- Age 25-29
- Black
- Other or unknown race/ethnicity
- Middle socioeconomic status

IN BRIEF

Risk of death

All cancer types in AYA population during 2001-2014 compared with 1988-2000 (adjusted for disease stage, sex, age, race, ethnicity, and socioeconomic status)

LOWER RISK
- Brain/CNS
- Breast
- Cervix
- Colorectal
- Kaposi sarcoma
- Kidney
- Leukemias: ALL, AML, CML
- Lip/Oral cavity
- Lung
- Lymphoma: Hodgkin, NHL
- Melanoma
- Other*

NO DIFFERENCE IN RISK
- Bone/STS
- Ovary carcinoma
- Ovary-Germ cell
- Stomach
- Testis
- Thyroid
- Uterus

HIGHER RISK

No cancer had a higher risk of death in the later time period

* All noncategorized invasive cancers and benign intracranial tumors. Includes chondrosarcoma, other specified and unspecified bone tumors, rhabdomyosarcoma, unspecified soft tissue sarcoma


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