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Official Journal of the Sarcoma Foundation of America™

EpSSG: Maintenance chemotherapy improved 5-year survival in pediatric rhabdomyosarcoma

Plus, reports on the results of 13 other sarcoma studies presented at ASCO 2018.

Sarcoma Foundation of America
finding the cure in our time

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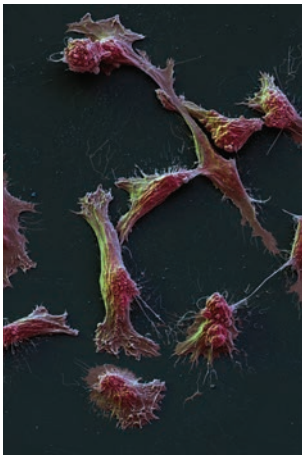
Official Journal of the Sarcoma Foundation of America™

SUMMER 2018



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FROM ASCO 2018

Sarcoma Foundation of America SFA finding the cure in our time

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

EpSSG: Maintenance chemo boosted 5-year survival in pediatric rhabdomyosarcoma

Six months of maintenance chemotherapy prolongs overall survival in youth with high-risk rhabdomyosarcoma, finds a phase 3 randomized controlled trial of the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG).

Rhabdomyosarcoma is a rare but very aggressive tumor, lead study author Gianni Bisogno, MD, PhD, a professor at the University Hospital of Padova, Italy, and chair of the EpSSG, noted in a press briefing at the annual meeting of the American Society of Clinical Oncology, where the findings were reported. Among pediatric patients who achieve complete response to standard therapy, "we know that after 1 or 2 years, one-third of these children relapse, and most of them die," he said.

The EpSSG trial, which took about 10 years to conduct, enrolled 371 patients aged 0-21 years with high-risk rhabdomyosarcoma who had had a complete response to standard intensive therapy. They were randomized evenly to stop treatment or to receive 6 months of maintenance treatment consisting of low-dose vinorelbine and cyclophosphamide.

Results reported in the meeting's plenary session showed that giving maintenance chemotherapy improved the 5-year overall survival rate by an absolute 12.8%, which translated to a near halving of the risk of death. And the maintenance regimen used was generally well tolerated.

"At the end of this long, not-easy study, we concluded that maintenance chemotherapy is an effective and well-tolerated treatment for children with high-risk rhabdomyosarcoma," Dr. Bisogno said.

There are three possibilities for its efficacy, he speculated. "It may be the duration, the type of drugs used, or the metronomic approach. Maybe altogether, these three different actions have a benefit to increase survival.

"Our group has decided this is the new standard treatment for patients. At least in Europe, we give standard intensive therapy and then we continue with 6 more months of low-dose chemotherapy," Dr. Bisogno concluded. "We think that this approach – a new way of using old drugs – can be of interest also for other pediatric tumors."

The trial is noteworthy in that it shows "how to successfully conduct large and important trials in rare diseases," said ASCO expert Warren Chow, MD.

The standard therapy for rhabdomyosarcomas is somewhat different in the United States, typically a regimen containing vincristine, actinomycin D, cyclophosphamide, and (more recently) irinotecan, he noted. "We have not been traditionally using maintenance chemo for any of the pediatric sarcomas, so this is a paradigm shift. These results will need to be tested with U.S.-based protocols before becoming standard of care in the United States. Also, we will need to determine if these results are applicable to patients older than 21 years of age who are


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Dr. Gianni Bisogno, a professor at the University Hospital of Padova, Italy, and chair of the European Paediatric Soft Tissue Sarcoma Study Group.


MDedge News

Dr. Warren Chow, medical oncologist and clinical professor, department of medical oncology & therapeutics research at City of Hope, Duarte, Calif.

considered high risk based solely on their age.

"Even with these caveats, this is the first significant treatment advance in this rare cancer in more than 30 years," concluded Dr. Chow, a medical oncologist and clinical professor at City of Hope, Duarte, Calif. "No doubt, this trial was a home run."

Study details

Patients enrolled in the EpSSG trial had had a complete response to the standard intensive therapy used in Europe: high-dose chemotherapy (ifosfamide, vincristine, and actinomycin D, with or without doxorubicin), radiation therapy, and surgery.

The maintenance chemotherapy consisted of a combination of low-dose intravenous vinorelbine given weekly and oral cyclophosphamide given daily. The 6-month duration was somewhat arbitrary, according to Dr. Bisogno. "We had to start somewhere. So when we started, we decided to use 6 months because there was some evidence in the past for regimens that long. In our next European trial, we are going to test different kinds and durations of maintenance because this is very important."

The maintenance regimen was well tolerated, compared with the regimen given during standard intensive therapy, with, for example, lower rates of grade 3 and 4 anemia (8.9% vs. 48.9%), neutropenia (80.6% vs. 91.6%), and thrombocytopenia (0.6% vs. 26.0%), which translated to less need for transfusions, and a lower rate of grade 3 or 4 infection (29.4% vs. 56.4%), Dr. Bisogno reported. There were no cases of grade 3 or 4 cardiac, hepatobiliary/pancreatic, or renal toxicity.

Relative to peers who stopped treatment after standard intensive therapy, patients who received maintenance treatment tended to have better disease-free survival (77.6% vs. 69.8%; hazard ratio, 0.68; P = .0613) and had significantly better overall survival (86.5% vs. 73.7%; hazard ratio, 0.52; P = .0111).

Dr. Bisogno disclosed that he has a consulting or advisory role with Clinigen Group and receives travel, accommodations, and/or expenses from Jazz Pharmaceuticals. The study received funding from Fondazione Città della Speranza, Italy.

SOURCE: Bisogno et al. ASCO 2018, Abstract LBA2.

ENLIVEN: Pexidartinib improved symptoms, function in patients with advanced tenosynovial giant cell tumors

Pexidartinib significantly improved overall response rates and functioning in patients with advanced tenosynovial giant cell tumors (TGCT), based on the final results of the ENLIVEN study.

"Pexidartinib, a novel CSF1 receptor inhibitor, may offer a relevant treatment option for patients with TGCT, which is associated with severe morbidity or functional limitations, and for which surgery is not recommended," said William Tap, MD, of Memorial Sloan Kettering Cancer Center, New York.

Compared with placebo in patients with advanced, symptomatic TGCT, pexidartinib significantly improved overall response rates; Response Evaluation Criteria in Solid Tumors (RECIST) was 39% with pexidartinib and 0% with placebo. Tumor volume score improvement was 56% with pexidartinib and 0% with placebo. Both results were significant at *P* less than .0001.

"Importantly, these responses correlated with improved patient symptoms and function," Dr. Tap said. "Pexidartinib was generally well tolerated with serious, nonfatal liver toxicity with increased bilirubin in 4% of patients." The majority of other adverse events with pexidartinib (hair color changes, vomiting, fatigue, dysgeusia, and periorbital edema) were less than grade 3.

The primary treatment for these patients is surgery; there are currently no approved systemic therapies for advanced tenosynovial giant cell tumor. In previous studies by others, imatinib, evaluated in 27 patients, was associated with a 19% overall response rate (ORR). Nilotinib, evaluated in 51 patients, was associated with a 0% ORR at week 12.

ENLIVEN is a double-blind, randomized, placebo-controlled international, phase 3 study whose participants had histologically confirmed, advanced, symptomatic TGCT of greater than 2 cm. Several had previous surgeries, but further surgical resection would have been associated with the potential for worsening functional limitations or severe morbidity.

In ENLIVEN, 61 patients were randomized to pexidartinib and 59 to placebo. All had recurrent or inoperable TGCT. Patients received placebo or pexidartinib 1,000 mg/day (split b.i.d. for 2 weeks) then 800 mg/day (split b.i.d. for 22 weeks).

Nine patients in the active treatment group and 11 in the placebo group discontinued therapy. Eight patients discontinued pexidartinib because of hepatic adverse events; all serious hepatic events appeared in the first 2 months of treatment.

> **"PEXIDARTINIB, A NOVEL CSF1 RECEPTOR INHIBITOR, MAY OFFER A RELEVANT TREATMENT OPTION FOR PATIENTS WITH TGCT."**

At 25 weeks, blinded reviews of MRI scans were performed. A partial response was seen in 12 (52%) patients and stable disease was seen in 7 (30%), based on RECIST 1.1.

Also at week 25, pexidartinib-treated patients did better on scores of functional endpoints related to range of motion, PROMIS physical function, stiffness, and BPI worst pain response. Based on functional endpoints, 9 of 61 (15%) had a complete response and 15 (25%) had a partial response, for an overall response rate of 24 (39%); *P* less than .0001.

None of the 59 patients in the placebo group had a response.

Tumor volume scores at week 25 were complete

in 3 (5%) and partial in 31 (51%); overall response rate was 34 (56%); *P* less than .0001. Disease was stable in 14 (23%), progressive in 1 (2%), and not evaluable in 12 (20%). There were no complete or partial responses in the placebo group; disease was stable in 45 (76%), progressive in 2 (3%), and not evaluable in 12 (20%).

Dr. Tap disclosed consulting or advisory roles with Daiichi Sankyo, the maker of pexidartinib, as well as Adaptimmune, Blueprint Medicines, Eisai, EMD Serono, Immune Design, Janssen, Lilly, Loxo, Novartis, Plexxikon, and TRACON Pharma. Clinical trial information: NCT02371369.

SOURCE: Tap WD et al. ASCO 2018, Abstract 11502.

SARCO24: Regorafenib falls short for treatment-refractory liposarcoma

Regorafenib fell short for improving progression-free survival in patients with treatment-refractory liposarcomas, Richard Reidel, MD, of Duke University Medical Center, Durham, N.C., reported.

In a 48-patient study, the median progression-free survival was not significantly different for regorafenib-treated patients, 1.9 months, and for placebo-treated patients, 2.1 months. None of the regorafenib-treated patients had responses. Median overall survival was not reached for either group of patients.

The most common grade 3-4 adverse events observed with regorafenib included grade 3 abdominal pain (13%), hypertension (13%), rash (13%), anemia (8%), anorexia (8%), generalized weakness (8%), and elevated lipase (8%). Grade 5 events occurred in one patient on regorafenib and three on placebo.

For the study, patients with advanced or metastatic, treatment-refractory liposarcoma were randomized 1:1 to receive either regorafenib 160 mg daily or placebo (3 weeks on, 1 week off). The study was powered to detect a difference of at least 3 months in median progression-free survival. Secondary objectives included adverse event assessments, overall response rate, time to tumor progression, progression-free survival at 8 and 16 weeks, overall survival, and disease-specific survival. Follow-up information was available for 47 patients, with a median follow-up of 3.8 months (0.2-15.3). The analyses included 33 dedifferentiated, 12 myxoid/round cell, and 2 pleomorphic liposarcomas.

Dr. Riedel and some of his coauthors disclosed financial relationships with several drug companies including Bayer, the maker of regorafenib (Stivarga). Clinical trial information: NCT02048371.

SOURCE: Riedel RF et al. ASCO 2018, Abstract 11505.

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

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

Indication

Liposarcoma

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

Selected Safety Information

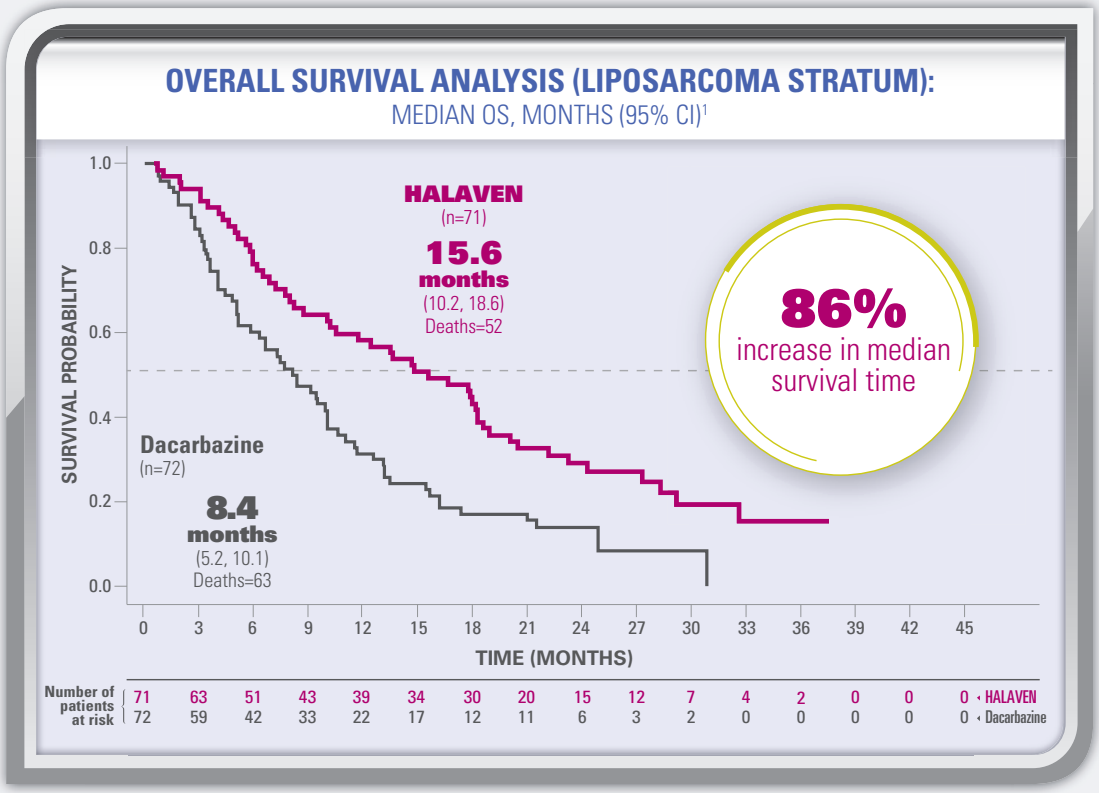
Warnings and Precautions

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

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

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

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



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

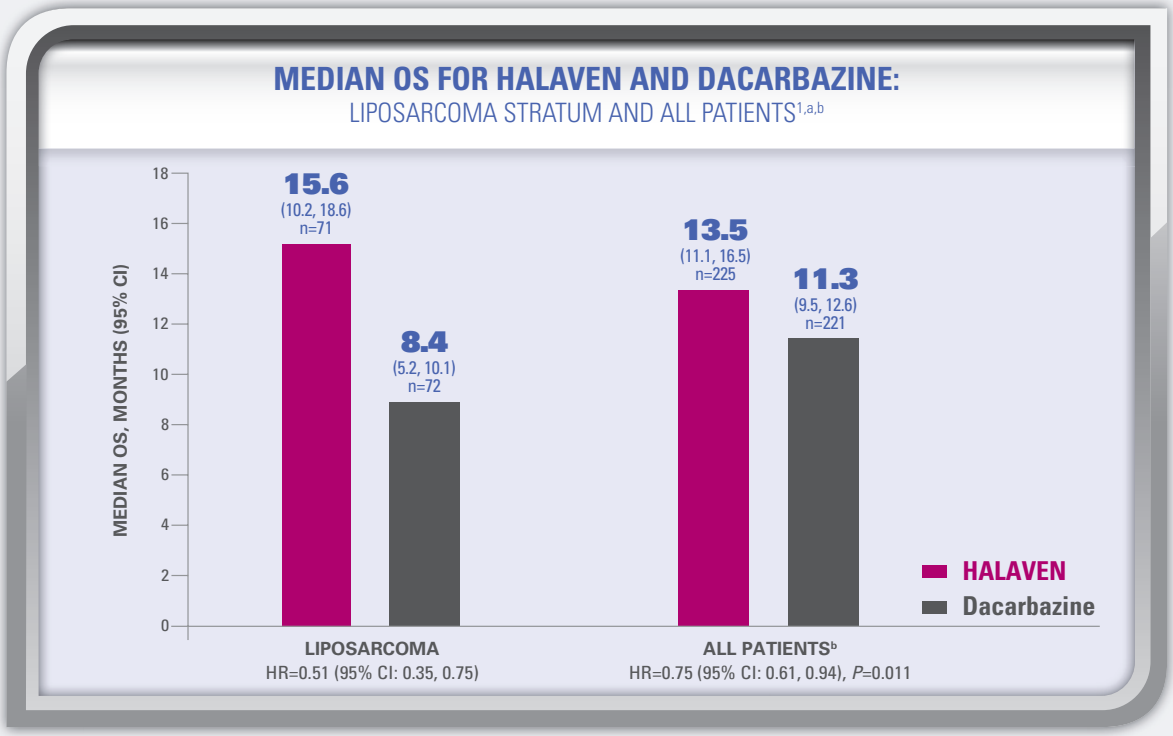
OS=overall survival; CI=confidence interval.

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

Selected Safety Information

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

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



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

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

Secondary endpoint: PFS[1]

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

Selected Safety Information

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

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

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

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

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

Learn more about the efficacy of HALAVEN at
www.halaven.com/hcp/advanced-liposarcoma

Selected Safety Information

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

Adverse Reactions

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

Use in Specific Populations

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

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

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

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

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

HALAVEN® (eribulin mesylate) Injection, for intravenous use

BRIEF SUMMARY – See package insert for full prescribing information.

DOSAGE AND ADMINISTRATION

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

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

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

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

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

Recommended dose delays

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

Recommended dose reductions

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

Table 1: Recommended Dose Reductions

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

- Neutropenia
- Peripheral neuropathy
- QT prolongation

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

Data

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

Females and Males of Reproductive Potential

Contraception

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

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

Infertility

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

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

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

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

OVERDOSAGE

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

There is no known antidote for HALAVEN overdose.

NONCLINICAL TOXICOLOGY

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

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

PATIENT COUNSELING INFORMATION

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

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

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

Embryo-Fetal Toxicity

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

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

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REGOBONE: Regorafenib shows activity in metastatic osteosarcoma

Regorafenib appears to be active in patients with metastatic osteosarcomas, based on results from REGOBONE a noncomparative phase 2, double-blind, placebo-controlled trial.

Among 38 efficacy-evaluable patients (12 given placebo and 26 given regorafenib), 17 patients (65.4%) had nonprogressive disease at 8 weeks in the regorafenib arm and 0 in the placebo arm, reported Florence Duffaud, MD, of La Timone University Hospital, Marseille, France.

Median progression-free survival (PFS) was 13.7 weeks for patients given regorafenib and 4 weeks for those given placebo. The PFS rate at 24 weeks was 35% with regorafenib and 0 with placebo. The 1-year overall survival was 53% and 33% for regorafenib and placebo, respectively.

Ten patients in the placebo arm crossed over to the regorafenib arm of the study after centrally confirmed disease progression. The most common adverse events of grade 3 or greater with regorafenib were hypertension (24%), hand-foot skin reaction (17%), asthenia (10%), and diarrhea (7%).

REGOBONE consists of four independent cohorts: patients with metastatic osteosarcoma, Ewing sarcoma, chondrosarcoma, or chordoma. The results were reported for 43 patients with metastatic osteosarcoma who were randomized 2:1 to receive either regorafinib (160 mg/day for 21 days of a 28-day cycle) or to placebo with the option to cross over at the time of confirmed central review of progressive disease.

Dr. Duffaud and several of her coauthors received funding from various drug companies including Bayer, the maker of regorafenib (Stivarga). Clinical trial information: NCT02389244.

SOURCE: Duffaud F et al. ASCO 2018, Abstract 11505.

ALTER0203: Metastatic soft tissue sarcomas respond to anlotinib

Anlotinib was confirmed to be safe and effective for soft tissue sarcoma patients who have progressed after first-line chemotherapy, based on results of a randomized, placebo-controlled, multicenter trial of patients in China.

"Anlotinib is a new treatment option for patients with advanced STS after failure of standard chemotherapy," reported Yihebali Chi, MD, of the National Cancer Center/Cancer Hospital in Beijing.

In a study of patients with disease progression after first-line therapy, the median progression-free survival (PFS) was 6.3 months (95% confidence interval, 4.3-8.4) with anlotinib and 1.5 months (95% CI, 1.43-1.57) with placebo (hazard ratio, 0.33, *P* less than .0001). The objective response rate was 10.13% for anlotinib and 1.33% for placebo (*P* = .0145); disease control rate was 55.7% versus 22.67% (*P* less than .0001).

For 57 patients with synovial sarcomas, the median PFS was 5.73 months versus 1.43 months (HR, 0.2; *P* less than .0001). For 56 patients with alveolar soft part sarcomas, the median PFS was 18.23 months versus 3 months (HR, 0.14; *P* less than .0001). For 41 patients with leiomyosarcomas, the median PFS was 5.83 months versus 1.43 months (HR, 0.19; *P* less than .0001).

The most common grade 3 or higher adverse events were hypertension (19% with anlotinib

versus 0 with placebo), gamma-glutamyl transferase elevation (4.4% versus 1.3%), triglyceride increase (4.4% versus 0), low-density lipoprotein elevation (3.2% versus 2.7%), hyponatremia (3.2% versus 1.3%) and neutrophil count reduction (3.2% versus 0).

The study included 233 patients aged 18 years and older with angiogenesis inhibitor naive, histologically proven advanced soft tissue sarcomas, intolerance or failure to respond to anthracycline-based chemotherapy, and at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Subjects were randomly assigned (2:1) to receive anlotinib (12 mg per day, 2 weeks on and 1 week off) or to placebo. Anlotinib was given to 158 patients and placebo to 75.

› "ANLOTINIB IS A NEW TREATMENT OPTION FOR PATIENTS WITH ADVANCED STS AFTER FAILURE OF STANDARD CHEMOTHERAPY."

The authors disclosed having no relevant financial relationships. Clinical trial information: NCT02449343.

SOURCE: Chi Y et al. ASCO 2018, Abstract 11503.

DESMOPAZ: Pazopanib slows disease progression of desmoid tumors

Pazopanib elicited clinically meaningful responses in adults with progressive desmoid tumors according to RECIST 1.1 criteria based on two imaging studies within a 6-month interval in the phase 2 DESMOPAZ trial.

"Pazopanib has meaningful clinical activity in patients with progressive desmoid tumors," reported Maud Toulmonde, MD, of the Institut Bergonié, Bordeaux, France.

Patients were accrued for the study at 12 centers of the French Sarcoma Group and were randomly assigned to receive either oral pazopanib 800 mg/day or methotrexate (30 mg/m^2) plus vinblastine (5 mg/m^2) given intravenously once a week for 6 months and then every 15 days for 6 months. Treatment was administered until disease progressed (these patients were allowed to cross over to pazopanib) or patients had unacceptable toxicity. Maximum treatment time was 1 year.

Based on central pathological and radiologic review, tumors shrank in 38 of 46 assessable patients (82.6%) given pazopanib. A partial response was seen in 17 patients (37%) and stable disease was observed in 21 patients (45.7%).

In the patients given methotrexate plus vinblastine, tumors shrank in 11 of 20 assessable patients (55%), resulting in partial responses in 5 (25%) and stable disease in 6 (30%).

The 6-month nonprogressive disease rate was 86% (95% confidence interval, 72.1-94.7) in the pazopanib-treated patients (37/43) and 50% (95% CI, 27.2-72.8) in the methotrexate plus vinblastine-treated patients (10/20).

Dr. Toulmonde and most of her coauthors had no relevant financial disclosures. Some authors disclosed funding from a wide range of drug companies including Novartis, the maker of pazopanib (Votrient). Clinical trial information: NCT01876082.

SOURCE: Toulmonde M et al. ASCO 2018, Abstract 11501.

Sorafenib boosts PFS in desmoid tumor patients

Sorafenib was well tolerated with significantly improved progression-free survival in select patients with desmoid tumors, reported Mrinal M. Gounder, MD, of Memorial Sloan Kettering Cancer Center, New York.

"The study exceeded its primary endpoint for progression-free survival. ... Sorafenib may represent a new, first-line or subsequent-line standard of care in select patients with desmoid tumors," Dr. Gounder said.

For this international prospective study of progression-free survival response to sorafenib, 87 patients were enrolled over 17 months at 25 sites. Patients had unresectable progressive or symptomatic desmoid tumors. Patients were stratified by pain level and disease site and randomized 2:1 to sorafenib 400 mg/day or placebo. Placebo-treated patients were crossed over to sorafenib if they reached RECIST 1.1.

After a median follow-up for 26 months, disease had progressed in 22 of 32 patients on placebo and in 7 of 43 patients on sorafenib. One sorafenib-treated patient died. Durable partial responses were seen in 14 of 43 on sorafenib and in 7 of 32 on placebo. At 1 year, progression-free survival was 43% with placebo (median PFS 9.4 months) and 87% with sorafenib (median PFS not reached [hazard ratio, 0.14; 95% confidence interval, 0.06-0.33; *P* less than .0001)].

The authors disclosed funding from a wide range of drug companies. Several authors received funding from Bayer, the maker of sorafenib (Nexavar). Clinical trial information: NCT02066181.

SOURCE: Gounder MM et al. ASCO 2018, Abstract 11500.

Trabectedin bests supportive care in advanced soft-tissue sarcomas

Trabectedin (Yondelis) was superior to best supportive care at prolonging progression-free survival (PFS) in patients with heavily pretreated advanced leiomyosarcomas and liposarcomas, investigators in the randomized phase 3 T-SAR trial reported.

Among 103 patients with soft-tissue sarcomas that had progressed after two to four lines of standard chemotherapy, median PFS for patients randomized to trabectedin was 3.12 months, compared with 1.51 for patients randomized to best supportive care.

This difference translated into a hazard ratio favoring trabectedin of 0.39 (*P* less than .0001), Axel Le Cesne, MD, of Gustave Roussy Cancer Institute in Villejuif, France, reported on behalf of colleagues in the French Sarcoma Group.

All of the benefit was apparently among patients with what he termed "L-sarcomas" – leiomyosarcoma and liposarcoma – compared with other sarcoma histologies.

"The tumor control rate after six courses of trabectedin is similar to previous studies. As already reported, trabectedin is well tolerated," he said.

Trabectedin was shown to be superior to best supportive care at delaying disease progression among patients with advanced translocation-related sarcomas in a randomized phase 2 trial in Japan, but had not been studied in this setting against other sarcoma histologies, Dr. Le Cesne said.

The investigators enrolled 103 patients and randomly assigned them to receive either best supportive care or trabectedin in a 1.5 mg/m^2 infusion over 24 hours every 3 weeks. Patients in the best supportive care arm could be crossed over to the trabectedin arm at the time of progression.

Sarcoma histologies included liposarcoma, leiomyosarcoma, undifferentiated sarcomas, myxofibrosarcoma, synovial sarcoma, and others. The L-sarcomas accounted for 60.2% of the patient population.

In total, 52 patients were randomized to trabectedin and 51 to best supportive care, but 2 patients assigned to best supportive care dropped out soon after randomization, leaving 52 and 49 patients, respectively, for the as-treated analysis. All 103 patients were assessable for efficacy.

› IN ALL, 66.7% OF PATIENTS IN THE TRABECTEDIN ARM AND 61.2% OF PATIENTS IN THE BEST SUPPORTIVE CARE ARM HAD STABLE DISEASE, AND 19.6% AND 38.8%, RESPECTIVELY, HAD DISEASE PROGRESSION.

After a median follow-up of 26 months, median PFS for all patients, as noted before, was 3.12 months in the trabectedin arm and 1.51 months in the best supportive care arm.

The overall response rate in the trabectedin arm was 13.7%, composed of seven partial responses. There were no responses in the best supportive care arm. In all, 66.7% of patients in the trabectedin arm and 61.2% of patients in the best supportive care arm had stable disease, and 19.6% and 38.8%, respectively, had disease progression.

An analysis of PFS by sarcoma histology showed that all of the benefit appeared to be in patients with L-sarcomas, with a median PFS for trabectedin-treated patients of 5.13 months, compared with 1.41 months for controls (HR, 0.29; *P* less than .0001).

In contrast, there was no significant difference between the groups among patients with non–L sarcomas, with respective median PFS of 1.81 and 1.51 months (HR, 0.60; *P* = .16). There were no treatment responses among patients in either treatment arm in this subgroup.

Not surprisingly, there were more grade 3 or 4 adverse events among patients in the trabectedin arm. Neutropenia was seen in 23 patients given trabectedin and 1 given best supportive care; leukopenia in 18 patients vs. 0, thrombocytopenia in 13 vs. 0, and elevated liver transaminases in 17 vs. 1, respectively.

A total of 45 of the 49 patients who were treated in the best supportive care arm were crossed over to trabectedin.

Median overall survival was 13.6 months in the trabectedin arm and 10.8 months in the best supportive care arm. This difference was not statistically significant.

Dr. Le Cesne noted that the tumor control rate of 30% with trabectedin was similar to that seen in an earlier French trial (Lancet Oncol. 2015 Mar 1;16[3]:312-19).

PharmaMar supplied trabectedin for the study. Dr. Le Cesne disclosed honoraria from the company and from Amgen, Bayer, Lilly, Novartis, and Pfizer.

SOURCE: Le Cesne A et al. ASCO 2018, Abstract 11508.

Novel TKI PLX9486 showed efficacy against KIT mutations in GIST

A combination of the investigational agent PLX9486 with another novel tyrosine kinase inhibitor (TKI) showed some efficacy against a range of primary and secondary KIT mutations in patients with gastrointestinal stromal tumor (GIST), the results of a phase 1 dose escalation study have suggested.

Among 39 patients with GIST who had progressed on imatinib and other TKIs, the rates of clinical benefit at 16 weeks were 64% for 11 patients treated with PLX8486 monotherapy at a dose of 1,000 mg daily and 67% for 9 patients treated with PLX9486 and the investigational TKI pexidartinib.

One patient in the 1,000-mg monotherapy group had a partial response on interim analysis. The median progression-free survival in this dose group was 6 months, which was "significantly better than at lower doses," reported Andrew J. Wagner, MD, PhD, from the Dana-Farber Cancer Institute in Boston and his colleagues.

"The combination of PLX9486 with either pexidartinib or sunitinib is generally well tolerated and toxicities are typically grade 1 or 2 in nature and reversible," they wrote in a poster.

PLX9486 is an inhibitor of KIT primary mutations in exons 9 and 11 and secondary resistance mutations in exons 17 and 18. Compared with other KIT-targeted TKIs, PLX9486 has complementary selectivity for mutant forms of KIT with a greater than 150-fold selectivity for mutant versus wild-type KIT, the investigators explained.

"Combinations of PLX9486 with either pexidartinib (PLX3397) or sunitinib potentially inhibit and address all common primary and secondary KIT mutations," they wrote.

The investigators conducted a phase 1, open-label, dose-escalation study with two parts. The first part was designed to study the safety and pharmacokinetics of single-agent PLX9486 and established a maximum tolerated dose (MTD) for phase 2 studies. The second part was designed to study the drug as a single agent at the recommended phase 2 dose in GIST and other solid tumors with KIT mutations and also in combination with either pexidartinib or sunitinib in patients with GIST.

They found that single-agent PLX9486 was well tolerated at all doses tested (250, 300, 350, 500, and 1,000 mg daily) and that it selectively inhibited a spectrum of KIT mutations, "including difficult to treat exon 17/18 activation loop variants."

The combination of PLX9486 at 500 mg and pexidartinib 600 mg was associated with three partial responses and a clinical benefit rate of 67%, with a PFS on interim analysis of 6 months.

The efficacy of single agent PLX9486 was suggested by circulating tumor DNA studies, which showed reductions in circulating tumor DNA levels of exons 11 and 17/18, which reflected the selectivity profile of the TKI.

In the PLX9486 dose escalation phase, there were three cases of grade 3 or 4 toxicities, including one case each of fatigue, creatinine phosphokinase increase, and hypophosphatemia.

The combination of PLX9486 and pexidartinib was associated with grade 1 or 2 adverse events, including hair color changes in five patients; fatigue and decreased appetite in four patients each; anemia, diarrhea, nausea, alanine aminotransferase increase, and aspartate aminotransferase increase in three patients each; and weight loss, maculopapular rash, and hypertension in two patients each.

At the time of the poster presentation, the sunitinib cohort was still accruing, and interim efficacy data were not available.

"Given these interim results, it is anticipated that the selectivity profile and potency of PLX9486 + sunitinib combination will achieve broader and more durable coverage of primary and secondary KIT mutations," Dr. Wagner said.

SOURCE: Wagner AJ et al. ASCO 2018, Abstract 11509.

START WITH A BREAKTHROUGH

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

INDICATION

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

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

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

IMPORTANT SAFETY INFORMATION FOR LARTRUVO

Warnings and Precautions

Infusion-Related Reactions

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

Embryo-Fetal Toxicity

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

Most Common Adverse Reactions/Lab Abnormalities

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

Use in Specific Populations

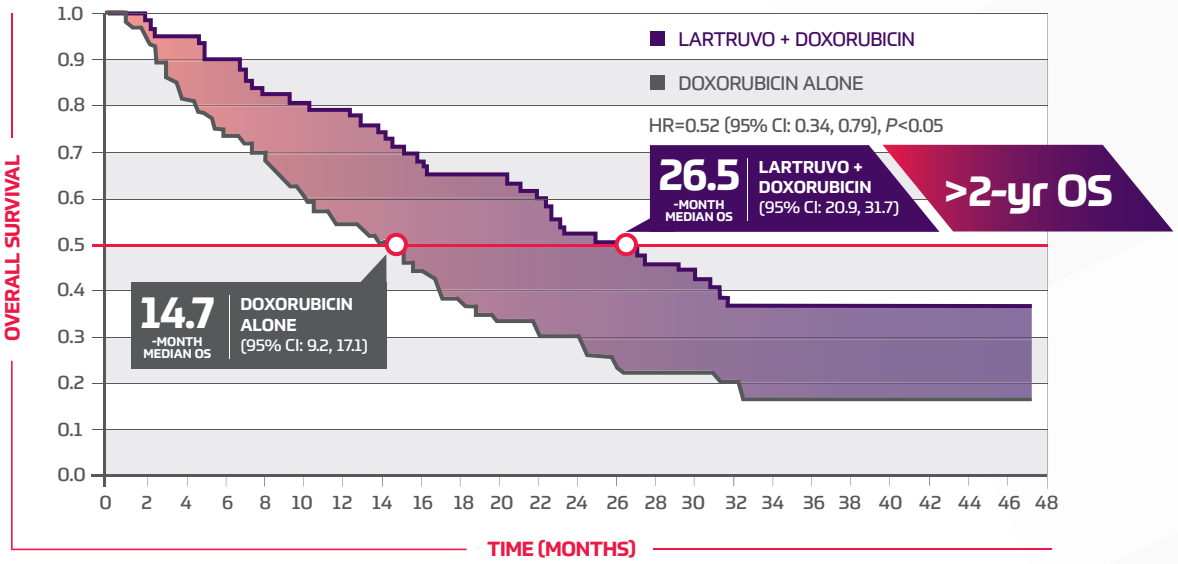
- Lactation: Because of the potential risk for serious adverse reactions in breastfeeding infants, advise women not to breastfeed during treatment with LARTRUVO and for at least 3 months following the last dose.

Please see Brief Summary of Prescribing Information on adjacent pages.

OR HCP ISI 19OCT2016

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

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



NUMBER AT RISK

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

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

CI=confidence interval; HR=hazard ratio.

OBJECTIVE RESPONSE RATE (ORR)*

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

- VS -

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

PROGRESSION-FREE SURVIVAL (PFS)†

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

- VS -

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

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

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

ORR does not include stable disease.

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

PFS based on independent review.

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

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

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

VISIT LARTRUVO.COM/HCP TO LEARN MORE

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

Lartruvo®
(OLARATUMAB)
Injection 10 mg/mL

Lilly

LARTRUVO™ (olaratumab) injection

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

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

Embryo-Fetal Toxicity

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

ADVERSE REACTIONS

Clinical Trials Experience

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

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

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

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

[b] Fatigue includes: asthenia and fatigue.

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

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

LARTRUVO™ (olaratumab) injection OR HCP BS 21OCT2016

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

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

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

[b] aPTT = activated partial thromboplastin time

Immunogenicity

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Contraception

Females

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

Infertility

Males

Based on animal models, LARTRUVO may impair male fertility.

Pediatric Use

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

Geriatric Use

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

PATIENT COUNSELING INFORMATION

Infusion-Related Reactions

Advise patients to report signs and symptoms of infusion reactions.

Embryo-Fetal Toxicity

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

Lactation

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

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

Lilly

Eli Lilly and Company, Indianapolis, IN 46285, USA

OR HCP BS 21OCT2016

Low response rate with trofosfamide for advanced STS in elderly

In elderly patients with previously untreated metastatic soft-tissue sarcomas (STSs), the oral alkylating agent trofosfamide was associated with a lower overall response rate but long-lasting remissions among patients who had complete responses, investigators reported.

In a randomized phase 2 trial that compared trofosfamide with doxorubicin (Adriamycin), the 6-month progression-free survival (PFS) rate with trofosfamide, the primary endpoint, was 27.6% versus 35.9% in the doxorubicin arm, said Joerg Thomas Hartmann, MD, from Franziskus Hospital in Bielefeld, Germany.

"Median age was 70 years, which means that the population included [patients] 10-15 years older as compared to other trials in metastatic adult sarcoma. The trial met its predefined endpoint, demonstrating that patients treated with trofosfamide attained a 6-month progression-free rate of more than 20%," he said.

› THE STUDY DETERMINED WHETHER ORAL CONTINUOUS OR "METRONOMIC" THERAPY WITH TROFOSFAMIDE COULD PRODUCE A 6-MONTH PFS RATE OF AT LEAST 20% IN PATIENTS OLDER THAN 60 YEARS WITH PREVIOUSLY UNTREATED STSs.

Trofosfamide is an oral alkylating agent chemically related to cyclophosphamide and ifosfamide. It has been evaluated in a variety of hematologic and solid malignancies and has shown particular activity in patients with chemotherapy-naive and treatment-refractory adult STSs.

Dr. Hartmann and his colleagues conducted the phase 2 study to determine whether oral continuous or "metronomic" therapy with trofosfamide could produce a 6-month PFS rate of at least 20% in patients older than 60 years with previously untreated STSs. They selected this rate of 20% or higher based on the European Organisation for Research and Treatment of Cancer (EORTC) target criterion for doxorubicin of 25%.

They also compared grade 3 or greater toxicities of the two regimens, as well as overall response rate according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. and overall survival.

A total of 120 patients with histologically confirmed STSs with no prior first-line chemotherapy and with adequate bone marrow, renal, and liver function were enrolled. The histologies included pleomorphic sarcoma not otherwise specified, leiomyosarcoma, liposarcoma, and others not specified by Dr. Hartmann.

The patients were randomly assigned on a 1:2 basis to receive either intravenous doxorubicin 60 mg/m^2 on day 1 of each 21-day cycle for a total of six cycles (40 patients) or oral trofosfamide 300 mg/day for days 1 through 7 followed by 150 mg/day until disease progression or unacceptable toxicities (80 patients). The median patient age in each arm was 70 years.

After a median follow-up of 18.4 months, the trial met its primary endpoint of a 6-months PFS with trofosfamide exceeding 20% (27.6%).

Overall response rates were 7.7% in the doxorubicin arm and 6.6% in the trofosfamide arm.

All three responses in the doxorubicin arm were partial. In the trofosfamide arm there were five responses, including two complete responses and three PR.

The duration of responses in the patients treated with trofosfamide who achieved a complete response were 8.8 and 46.6 months (median, 27.7 months). The median duration of response for trofosfamide-treated patients with a partial response was 8.2 months (range, 1.4-14.9 months).

In contrast, the median duration of response in the patients treated with doxorubicin who

achieved a partial response was 4.3 months (range, 2.2-5.6 months).

Grade 3 or 4 adverse events occurred in significantly more patients treated with doxorubicin than they did in patients treated with trofosfamide (61.5% vs. 38.2%, respectively; P = .01). However, deaths within 30 or 60 days of starting on the assigned study drug were higher in the trofosfamide arm (zero vs. two and three vs. six, respectively).

Rates of anemia, leukocytopenia, nausea, and asthenia were similar between the groups, but trofosfamide was significantly associated with higher rates of dyspnea (P = .0148) and fatigue (P = .0264) and with lower rates of neutropenia (P less than .0001) and mucositis (P = .0008).

The trial was supported by Baxter Oncology of Germany. Dr. Hartmann reported having no conflicts of interest to disclose.

SOURCE: Hartman JT et al. ASCO 2018, Abstract 11507.

ctDNA profiles pre- and posttreatment KIT mutations in GIST

Detection of circulating tumor DNA (ctDNA), aka "liquid biopsy," may serve as a noninvasive marker for disease heterogeneity and aid in the assessment of clinical responses to therapy for patients with gastrointestinal stromal tumors (GIST), according to investigators.

In a phase 1 trial of the investigational agent DCC-2618, a pan-KIT/platelet-derived growth factor receptor alpha (PDGFRA) switch control inhibitor, identification of ctDNA by next-generation sequencing (NGS) was accomplished in the majority of patients, with findings that support the need for a broad-spectrum KIT inhibitor for patients with GIST resistant to imatinib (Gleevec), reported Suzanne George, MD, of Dana-Farber Cancer Institute in Boston, and her colleagues.

"This data demonstrates for the first time that the distribution of resistance mutations in KIT across exons 13, 14, 17, and 18 or a combination thereof is similar in 2nd-, 3rd-, and 4th-line patients," they wrote in a poster.

The dose-finding and escalation trial included baseline evaluations of KIT/PDGFRA mutations with both ctDNA and fresh tumor biopsy, and ctDNA measurements during treatment.

Biopsy detected 68 KIT mutations at baseline in 81 patients, and ctDNA detected 75 mutations in 95 patients. Some patients had multiple mutations within one exon.

An analysis of mutations by response showed that of 73 patients with detectable KIT mutations by ctDNA at baseline, 35 became KIT ctDNA negative during at least one treatment time point. Of this group, 8 had a partial response (PR) and 27 had stable disease (SD). In all, 57 of the 73 patients had a more than 50% reduction in KIT mutation allele frequency (MAF).

> **"THE MUTATIONAL PROFILE OF KIT IN TUMORS AND PLASMA AT BASELINE IN GIST PATIENTS SUPPORTS THE NEED FOR A BROAD-SPECTRUM KIT INHIBITOR IN ALL POST-IMATINIB LINES OF THERAPY."**

Some patients with stable disease remained KIT negative out to 60 weeks following the first DCC-2618 dose.

The investigators also looked at ctDNA at baseline (21 patients) and post treatment (20 patients) in those who had a PR as their best response. Ten of these patients had KIT mutations detected at baseline, and of this group, eight became KIT negative after treatment; one had no detectable mutations in one exon and one exon with an MAF less than 0.1%. No post-

treatment samples were available for the remaining patient.

There were preliminary data suggesting that DCC-2618 in the second line could be more efficacious than sunitinib (Sutent) in the same setting, and that, in KIT-driven GIST, DCC-2618 may provide more benefit in the second line, compared with the fourth or subsequent lines of therapy, the authors stated.

"The mutational profile of KIT in tumors and plasma at baseline in GIST patients supports the need for a broad-spectrum KIT inhibitor in all post-imatinib lines of therapy," they wrote.

The trial is supported by Deciphera Pharmaceuticals. Dr. George disclosed stock or other ownership in Abbott Laboratories and AbbVie, consulting/advising for AstraZeneca, Blueprint Medicines, and Deciphera, and institutional research funding from Ariad, Bayer, Blueprint Medicine, Deciphera, Novartis, and Pfizer.

SOURCE: George S et al. ASCO 2018, Abstract 11511.

Rapid drug alteration a bust in metastatic GIST

For patients with gastrointestinal stromal tumor (GIST) with KIT mutations conferring resistance to imatinib, a strategy of rapid alteration of drugs with complementary activity against KIT mutations is feasible but has thus far failed to yield significant clinical benefits, investigators said.

There were no objective responses among 12 patients treated continuously with 3 days of sunitinib (Sutent) followed by 4 days of regorafenib (Stivarga), and although 4 patients had stable disease in the short term, in each case the disease progressed within 16 weeks, reported Cesar Serrano-Garcia, MD, from the Dana-Farber Cancer Institute and Brigham and Women's Hospital in Boston, and his colleagues.

"Drug exposure is critical to effectively target specific resistant subpopulations and low exposure may have contributed to the lack of efficacy in this cohort," they wrote in a poster.

The investigators noted that the main mechanism of resistance to imatinib (Gleevec) in GIST is polyclonal emergence of KIT secondary mutations. They then theorized that rapid alteration of sunitinib with regorafenib, which both have complementary activity against different KIT resistance mutations, could be a novel therapeutic strategy for controlling imatinib-resistant disease.

Both agents are active against KIT and platelet-derived growth factor receptor alpha (PDGFR-alpha). Sunitinib has stronger activity against ATP-binding pocket mutations, and regorafenib is more effective against activation loop oncoproteins, the investigators explained.

They conducted a phase Ib trial to evaluate the safety and preliminary efficacy of the strategy in patients with metastatic GIST that had advanced on therapy with all established protocols. The trial had a standard 3+3 design to determine the recommended phase 2 dose; a total of 14 patients were enrolled, but only 12 received one or more complete cycles.

› THE AUTHORS ACKNOWLEDGED THAT LOW DRUG EXPOSURE LEVELS MAY EXPLAIN THE LACK OF ANY RESPONSES IN THIS COHORT.

The median patient age was 63.5%. Nine patients had Eastern Cooperative Oncology Group performance status of 0, and five had an ECOG status of 1. The patients had received a median of four prior lines of therapy, and all had received at least three lines.

The primary mutations were at KIT exon 11 in eight patients, exon 9 in five patients, and a KIT/PDGFR-alpha wild type in one patient.

Of the 12 patients who received one or more complete cycles, 7 were treated with sunitinib 37.5 mg daily for 3 days, followed by regorafenib 120 mg daily for 4 days. There were no dose-limiting toxicities in this group. The median number of cycles delivered was 2 (range 1-4).

The other five patients were treated with sunitinib at the same 37.5-mg daily dose for 3 days, followed immediately by regorafenib 160 mg daily for 4 days. There were two dose-limiting toxicities in this group, both grade 3 hypophosphatemia, one of which was refractory to phosphorous replacement.

Antitumor activity according to Response Evaluation Criteria in Solid Tumors version 1.1 included four cases of stable disease at the time of the efficacy analysis, and eight cases of disease progression. The median progression-free survival was 1.9 months. As noted before, there were no complete or partial responses among the 12 patients.

A pharmacokinetic profile at cycle 1 showed that neither drug reached its reported active blood drug levels.

The patients appeared to tolerate the treatment well, with grade 1 or 2 fatigue in all patients being the most common adverse events. Grade 3 or 4 events included hand-foot syndrome, hypertension, and hypophosphatemia in two patients each.

As noted, the authors acknowledged that low drug exposure levels may explain the lack of any responses in this cohort.

"Therapeutic strategies based on KIT inhibition remain crucial in GIST patients progressing to multiple lines," they wrote.

The study was supported by an ASCO Young Investigator Award, Pfizer, and Bayer. Dr. Serrano-Garcia disclosed honoraria from Bayer, a consulting or advisory role for Deciphera, research funding from Bayer and Deciphera, and travel accommodations and expenses from Pfizer.

SOURCE: Serrano-Garcia C et al. ASCO 2018, Abstract 11510.

Adjuvant chemotherapy benefits high-risk sarcoma patients

Patients with high-risk soft-tissue sarcomas identified by patient data and a risk calculator had significantly better overall and disease-free survival when they were treated with adjuvant doxorubicin and ifosfamide, a retrospective analysis from a randomized clinical trial showed.

The findings suggest that future clinical trials for sarcoma therapies may need to focus on specific risk categories, investigators said.

Among 290 patients with soft-tissue sarcomas (STS) of the trunk wall or extremities, adjuvant chemotherapy with doxorubicin, ifosfamide, mesna, and lenograstim more than halved the risk of death for patients determined by the nomogram to have a low probability of 10-year overall survival, reported Sandro Pasquali, MD, from the Fondazione IRCCS Istituto Nazionale dei Tumori in Milan, and his colleagues.

"These findings interpret conflicting results of randomized controlled trials on perioperative chemotherapy in STS showing that inclusion of low-risk tumors has diluted the effect of chemotherapy leading to negative results and small study effect in meta-analysis," they wrote in a poster presented at the annual meeting of the American Society of Clinical Oncology.

The clinical trial in question, EORTC-STBSG 62931, results of which were published in 2012 in the Lancet Oncology, was technically a failure, because it did not show a significant benefit of adjuvant chemotherapy vs. observation in patients with STS.

To see whether adjuvant chemotherapy may have benefited select patients, the investigators calculated 10-year probabilities of overall survival (P-OS) for 290 patients with STS of the trunk wall or extremities out of the total trial cohort of 351 patients. The P-OS for each of three categories – low (51% or less), intermediate (52%-66%), and high (67% or greater) – was calculated using individual patient data and the freely available

smartphone-based nomogram Sarculator (available in the Apple App Store and Google Play).

They calculated disease-free survival at the study median follow-up of 8 years.

The tumor histologies included malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor, and others.

A total of 52 patients were in the low P-OS group, including 24 treated with observation, and 28 with adjuvant chemotherapy. Respective numbers for the intermediate and high P-OS categories were 34/34, and 90/80.

The investigators found that, for patients in the low P-OS group, adjuvant chemotherapy cut the risk of death by slightly more than half, with a hazard ratio of 0.46 ($P = .033$). In contrast, there were no significant differences in the risk of death for patients at either intermediate or high probability of 10-year OS (HR, 1.00 and 1.08, respectively; P values not significant).

Similarly, adjuvant chemotherapy cut the risk of disease progression by the same amount, with an HR of 0.46 ($P = .021$), whereas there was no additional benefit among patients at either intermediate or high probability of 10-year OS (HR, 0.74 and 0.90; P values were not significant).

The absolute risk reduction for adjuvant chemotherapy was 21% (8-yr disease-free survival of 34% for adjuvant chemotherapy vs. 13% for observation), with a number needed to treated of 4.76.

The study was supported by the European Organization for Research and Treatment of Cancer. Dr. Pasquali reported having no conflicts of interest.

SOURCE: Pasquali S et al. ASCO 2018, Abstract 115118.

Lurbinectedin shows activity against relapsed Ewing

Single-agent lurbinectedin (PM1183, Zepsyre) showed "encouraging" activity against advanced Ewing sarcoma in previously treated adults, results of a phase 2 study indicated.

Among 28 adults with Ewing sarcoma (ES) that had relapsed after up to two prior lines of therapy, treatment with lurbinectedin was associated with five partial responses and six cases of stable disease, reported Vivek Subbiah, MD, from the University of Texas MD Anderson Cancer Center in Houston and his colleagues.

"Treatment in combination with other agents is warranted in this patient population," they wrote in a poster.

Lurbinectedin's mechanism of action is through blocking DNA transcription and inducing DNA double-strand breaks, which leads to programmed cell death.

"Moreover, in sarcomas associated with translocations, such as ES, in which the translocation produces a fusion protein that acts as a deregulated transcription factor, lurbinectedin might interfere with the binding of this protein to specific DNA promoters and thus with the synthesis of downstream proteins," the investigators wrote.

This agent is being investigated against ES as part of a phase 2 basket trial, which is testing the drug against a variety of malignancies. The ES cohort in this study included 15 adults who had received up to two prior chemotherapy regimens. The trial rules called for recruitment of a minimum of 10 more patients if at least one of the first 15 had a confirmed response. There were two responses among the 15 patients, leading to an expansion cohort with 13 patients, for a total of 28 in the current analysis.

The median patient age was 33 years (range, 18-74 years). The majority of patients had good performance status, with Eastern Cooperative Oncology Group scores of 0 (11 patients) or 1 (15 patients); one patient had an ECOG PS score of 2, and one had unknown status.

All but one patient had received a minimum of two prior lines of therapy.

The patients were treated with lurbinectedin 3.2 mg/m^2 in a 1-hour infusion on day 1 of every 21-day cycle,

with the longest duration of therapy out to 14 cycles.

Among 25 evaluable patients, eight had tumor shrinkage, ranging from less than 5% (two patients) to more than 45% (four patients).

Median progression-free survival (PFS) was 2.7 months. The 4-month PFS rate was 42.9%, and the 6-month rate was 21.4%.

A total of 11 patients had some clinical benefit, including five partial responses and six cases of stable disease.

Grade 3 or 4 treatment-related adverse events included febrile neutropenia (two events grade 3, and two grade 4), anemia (five events, all grade 3), neutropenia (five grade 3, and 10 grade 4), thrombocytopenia (four grade 3 events), and elevated alanine aminotransferase levels (two grade 3 events).

Myelosuppression was transient and manageable with granulocyte colony-stimulating factor, the investigators said.

The study was supported by PharmaMar. Dr. Subbiah disclosed travel, accommodations, and/or expenses from the company and from Bayer; a consulting or advisory role with MedImmune; and institutional research funding from PharmaMar and multiple other companies.

› **"IN SARCOMAS ASSOCIATED WITH TRANSLOCATIONS, SUCH AS ES, IN WHICH THE TRANSLOCATION PRODUCES A FUSION PROTEIN THAT ACTS AS A DEREGULATED TRANSCRIPTION FACTOR, LURBINECTEDIN MIGHT INTERFERE WITH THE BINDING OF THIS PROTEIN TO SPECIFIC DNA PROMOTERS AND THUS WITH THE SYNTHESIS OF DOWNSTREAM PROTEINS."**

SOURCE: Subbiah V et al. ASCO 2018, Abstract 11519.

These reports were written by Neil Osterweil, Mary Jo Dales, and Susan London.

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