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the SARCOMA JOURNAL

Official Journal of the Sarcoma Foundation of America™

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the SARCOMA JOURNAL
Official Journal of the Sarcoma Foundation of America™

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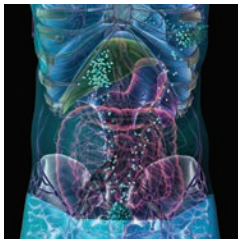
FALL 2019



COVER IMAGE: ©ELLA MARU STUDIO/ScienceSource
Illustration of cancer metastasis.

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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

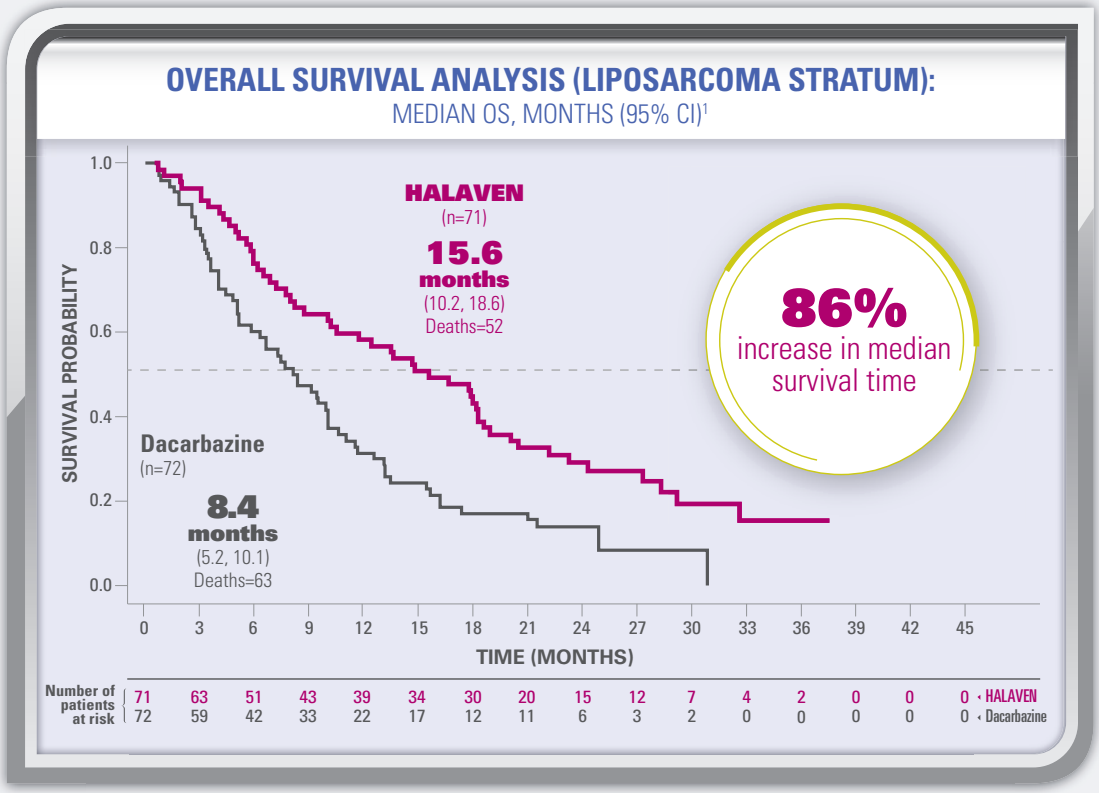
Warnings and Precautions

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]

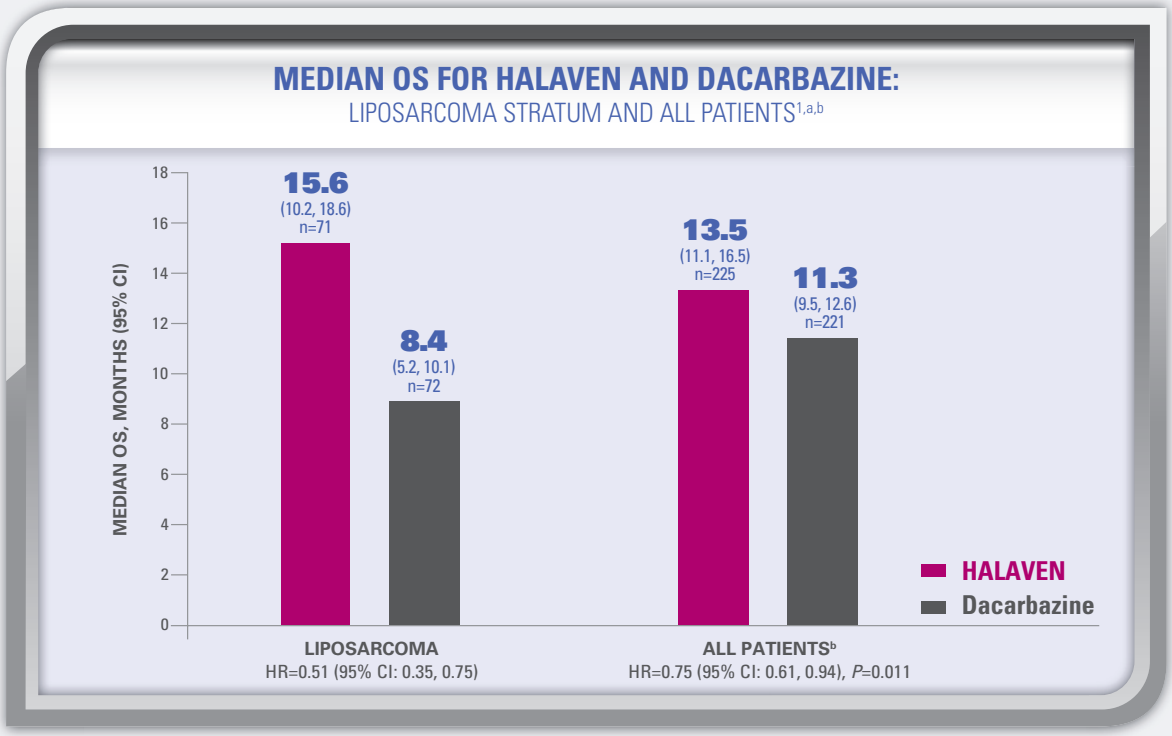
OS=overall survival; CI=confidence interval.

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.

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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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BY WILLIAM D. TAP, MD | Editor-In-Chief

Clinical trials in sarcoma bring hope and promise

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

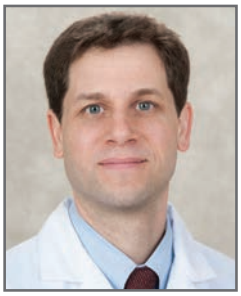
In the past 5 years, there has been a resurgence of phase 3 clinical trials in sarcoma, including several large first-line studies comparing combination therapies to doxorubicin—the gold standard since the mid-1970s. None have shown superiority. Despite this, there has been a gradual improvement in overall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

In the United States, we have seen the approval of several agents in sarcoma: pazopanib, with a 3-month improvement in progression-free survival (PFS) over placebo; trabectedin in liposarcoma and leiomyosarcoma, with a 2.7-month improvement in PFS over dacarbazine; and eribulin, based on a liposarcoma subgroup analysis that showed a 7-month improvement in overall survival over dacarbazine. None of these therapies are approved in the US in the front-line setting; rather, all after a patient generally receives a doxorubicin-based therapy.

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

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

From Dr. Tap's plenary presentation at ASCO 2019



THERE IS TREMENDOUS HOPE AND PROMISE IN SARCOMA DUE TO SIGNIFICANT ADVANCEMENTS IN OUR UNDERSTANDING — William D. Tap, MD

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ANA-ALICIA BELTRAN-BLESS, MD,* NATHANIEL BOUGANIM, MD, FRCPC*

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

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DISCLOSURES
The authors report no conflicts of interest concerning the materials or methods used in this case report or the findings specified in this paper.

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

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

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

ly, to the importance of genomic testing in these cases.

CASE PRESENTATION AND SUMMARY

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

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

A routine computerized tomography (CT) scan of the thorax-abdomen and pelvis in August 2016 revealed recurrence of disease, with multiple lung nodules as well as metastases in the retroperitoneum. She received 6 cycles of gemcitabine and docetaxel with stability of disease. The patient was then started on a PI3K inhibitor as part of a clinical trial, as genotypic analysis of the tumor revealed an activating mutation of the *PI3K* gene. The patient's course was complicated by acute obstructive renal failure requiring a double J stent for right-sided hydronephrosis.

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

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

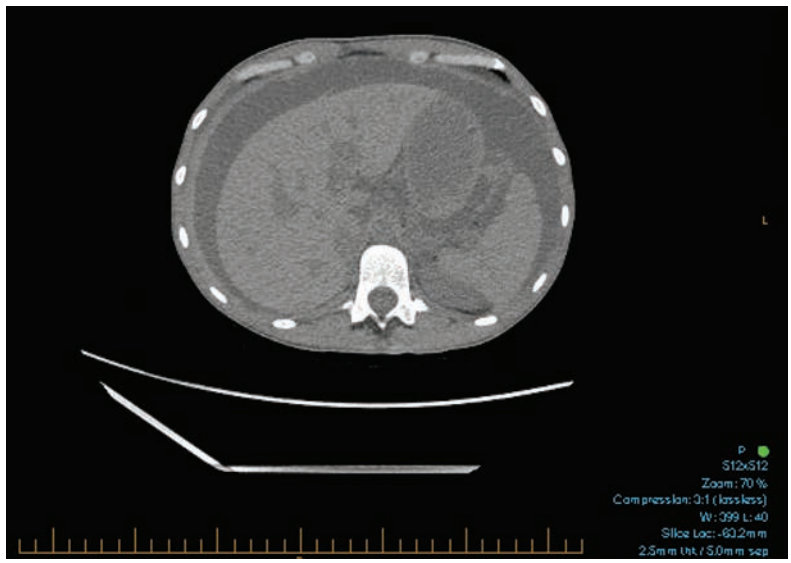

FIGURE 1. Computerized tomography of the patient's abdomen-pelvis on January 12, 10 days prior to the start of vismodegib treatment, showed progression of the patient's disease.

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

The patient's clinical status subsequently improved, with significant reduction in her chronic abdominal pain and very minimal side effects. Clinically, the patient's acute kidney injury resolved (from a creatinine of 272 µmol/L at discharge to 85 µmol/L after a week of treatment) and her liver enzymes normalized (from an alkaline phosphatase of 301 U/L to 83 U/L, and alanine transaminase of 111 U/L to 38 U/L). CT scan of her chest

› THE PATIENT CONTINUED TO HAVE A GOOD RESPONSE TO TREATMENT [WITH VISMODEGIB] FOR 6 MONTHS, WITH NO RECURRENCE OF PAIN OR ASCITES.

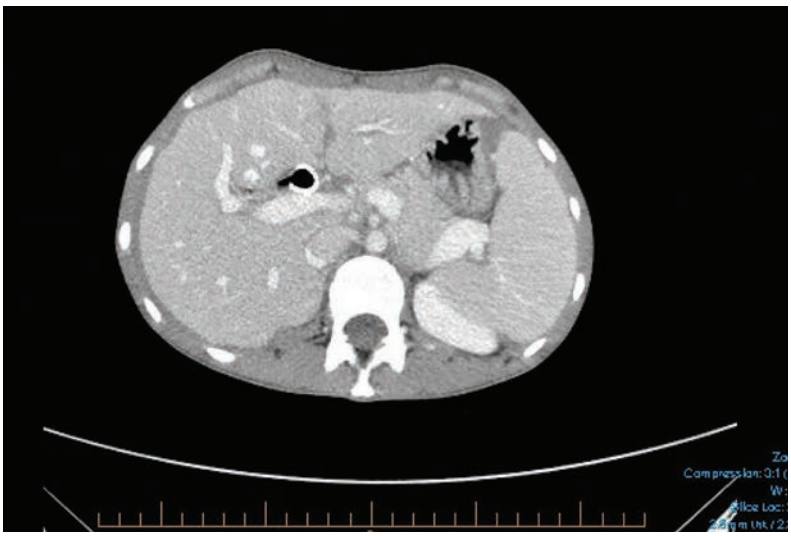

FIGURE 2. CT scan of the patient's abdomen-pelvis performed on March 14 revealed stability of disease with an absence of ascites.

and abdomen, which was performed 1 month post treatment, revealed stability of disease with absence of ascites (**FIGURE 2**). The patient continued to have a good response to treatment for 6 months, with no recurrence of pain or ascites.

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

DISCUSSION

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

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

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

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SFA awards grants to 15 researchers

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

Investigator	Affiliation	Research title
Claudio Brancolini, PhD[1]	University of Udine, Italy	Resetting the epigenetic addiction in leiomyosarcomas: a therapeutic perspective
Eleanor Chen, MD, PhD[2]	University of Washington, USA	Identify and characterize therapeutic targets against cancer stemness and chemotherapy resistance in rhabdomyosarcoma
Enrique De Alava, MD, PhD[3]	Instituto de Biomedicina de Sevilla, Spain	Translational assessment of predictive factors of response of Ewing sarcoma to genotoxic therapy
Annette Duensing, MD[4]	University of Pittsburgh Cancer Institute, USA	Dissecting DNA damage and repair pathways in leiomyosarcomas: Improving therapy by understanding biology
Andrew Futreal, PhD[3]	MD Anderson Cancer Center, USA	Immune profiling of pleomorphic rhabdomyosarcoma
Jlenia Guarnerio, PhD[1]	Cedars-Sinai Medical Center, USA	Switching the tumor immune microenvironment from "cold" to "hot" in UPS
Philip Hinds, PhD[5]	Tufts University, USA	Enabling anti-tumor immunity in osteosarcoma through manipulation of the pRb pathway
Roberto Perris, PhD[6]	Universita degli Studi di Parma, Italy	Immunotargeting of the prognostic NG2/CSPG4 cell surface proteoglycan in soft-tissue histotypes
Seth Pollack, MD[7]	Fred Hutchinson Cancer Research Center, USA	Modulation of cold sarcoma microenvironments to enable T cells in experimental systems
David Scadden, MD[8]	Massachusetts General Hospital, USA	Identification of molecular targets promoting differentiation and loss of self renewal in osteosarcoma
Juan Manuel Schvartzman, MD, PhD[8]	Memorial Sloan Kettering Cancer Center, USA	Deciphering the effects of IDH mutations on chromatin and differentiation in chondrosarcoma
Jacob Scott, MD[7]	Cleveland Clinic, USA	Uncovering polygenic signatures of Ewings sarcoma drug sensitivity during the evolution of resistance
David Shultz, MD, PhD[3]	Princess Margaret Cancer Centre, Canada	Characterizing the genetic landscape of radiation associated cutaneous angiosarcomas
Joshua Waterfall, PhD[9]	Institut Curie, France	Intratumoral heterogeneity in dedifferentiated liposarcoma
Lai Man Natalie Wu, PhD[7]	Cincinnati Children's Hospital Medical Center, USA	Single-cell transcriptomics and epigenomics to identify tumor-microenvironment interactions for targeted treatment of MPNST

Awards received:

1. Spring for Sarcoma York, PA, Research Award
2. STL Cure Sarcoma Research Award
3. Race to Cure Sarcoma Research Award
4. Dr. Richard and Valerie Aronsohn Memorial Research Award
5. Sarcoma Foundation of America Research Award
6. Christopher Langbein Research Award
7. Zach Cohen Memorial Research Award
8. Pittsburgh Cure Sarcoma Research Award
9. Jay Vernon Jackson Memorial Research Award

This issue of The Sarcoma Journal *features reports from the annual meeting of the American Society of Clinical Oncology (ASCO), held in Chicago, May 31 – June 4, 2019.*

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

PHOTO CREDIT: BY © ASCO/LUKE FRANKE 2019

› ACCELERATED APPROVAL ALLOWED PATIENTS TO HAVE ACCESS TO A POTENTIALLY LIFE-PROLONGING DRUG WITH LITTLE ADDED TOXICITY.

BEHIND OLARATUMAB'S PHASE 3 DISAPPOINTMENT

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

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

Results

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

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

A large and concerted effort is underway, Dr. Tap said, to understand the re-

sults of the ANNOUNCE study alone and in context with the phase 1b/2 study. "There are no noted discrepancies in study conduct or data integrity which could explain these findings or the differences between the two studies."

Possible explanations

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

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

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

Discussion

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

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

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

The study was sponsored by Eli Lilly and Company.

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

ADDITION OF TEMOZOLOMIDE MAY IMPROVE OUTCOMES IN RMS

Investigators from the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) found that the addition of temozolomide (T) to vincristine and irinotecan (VI) may improve outcomes in adults and children with relapsed or refractory rhabdomyosarcoma (RMS). Principal investigator of the study, Anne Sophie Defachelles, MD, pediatric oncologist at the

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

PHOTO CREDIT: BY © ASCO/SCOTT MORGAN 2019

› THE ADDITION OF TEMOZOLOMIDE TO TREATMENT WITH VINCRISTINE AND IRINOTECAN ACHIEVED A "LARGE AND SIGNIFICANT REDUCTION IN RISK OF DEATH."

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

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

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

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

Results

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

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

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

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

SOURCE: Defachelles AS, et al. J Clin Oncol 37, 2019 (suppl; abstr 10000)

The study was sponsored by Centre Oscar Lambret and SFCE (Société Française de Lutte contre les Cancers et Lucémies de l'Enfant et de l'Adolescent) served as collaborator.

Drs. Defachelles and Wagner had no relationships to disclose. A few coauthors had advisory/consulting or speaker roles for various commercial interests, including two for Merck (temozolomide).

PAZOPANIB INCREASES PATHOLOGIC NECROSIS RATES IN STS

Pazopanib added to a regimen of preoperative chemoradiation in non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) significantly increased the rate of near-complete pathologic response in both children and adults with intermediate or high-risk disease. Pazopanib, a multitargeted receptor tyrosine kinase inhibitor, works in multiple signaling pathways involved in tumorigenesis—VEGFR-1, -2, -3, PDGFRα/β, and c-kit. A phase 3 study demonstrated significant improvement in progression-free survival (PFS) in advanced STS patients and was the basis for its approval in the US

and elsewhere for treatment of this patient population. Preclinical data suggest synergy between pazopanib and cytotoxic chemotherapy, forming the rationale for the current trial with neoadjuvant pazopanib added to chemoradiation.

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

Patients with metastatic or non-metastatic NRSTS were eligible to enroll if they had initially unresectable extremity or trunk tumors with the expectation that they would be resectable after therapy. Patients had to be 2 years or older—there was no upper age limit—and had to be able to swallow a tablet whole. The dose-finding phase of the study determined the pediatric dose to be 350 mg/m^2 and the adult dose to be 600 mg/m^2, both taken orally and once daily. Patients in the chemotherapy cohort were then randomized to receive chemotherapy—ifosfamide and doxorubicin—with or without pazopanib. At 4 weeks, patients in both arms received preoperative radiotherapy (45 Gy in 25 fractions), and at week 13, surgery of the primary site if they did not have progressive disease. After surgery, patients received continuation therapy with or without pazopanib according to their randomization arm. Upon completion and recovery from the continuation therapy, patients could receive surgery/radiotherapy of their metastatic sites.

Results

As of the June 30, 2018, cutoff, 81 patients were enrolled on the chemotherapy arms: 42 in the pazopanib plus chemoradiation arm and 39 in the chemoradiation-only arm. Sixty-one percent of all patients were 18 years or older, and the median age was 20.3 years. Most patients (73%) did not have metastatic disease, and the major histologies represented were synovial sarcoma (49%) and undifferentiated pleomorphic sarcoma (25%).

At week 13, patients in the pazopanib arm showed significant improvement, with 14 (58%) of those evaluated having pathologic necrosis of at least 90%, compared with 4 (22%) in the chemoradiation-only arm (P=.02). The study was closed to further accrual.

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

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

In the post-presentation discussion, Dr. Raphael E. Pollock, MD, PhD, of The Ohio State University, called it a tremendous challenge to interdigitate primary local therapies in systemic approaches, particularly in the neoadjuvant context. He pointed out that in an earlier study, a 95% to 100% necrosis level was needed to achieve a significant positive impact on outcomes and perhaps a subsequent prospective trial could determine the best level. He questioned whether the availability of only 60% of patient responses could affect the conclusions and whether the high number of toxicities

PHOTO CREDIT: BY © ASCO/SCOTT MORGAN 2019

› ACCORDING TO THE INVESTIGATORS, THIS TRIAL OF PAZOPANIB IS THE FIRST EVER COLLABORATIVE STUDY CODEVELOPED, WRITTEN, AND CONDUCTED BY PEDIATRIC AND ADULT CANCER COOPERATIVE GROUPS.

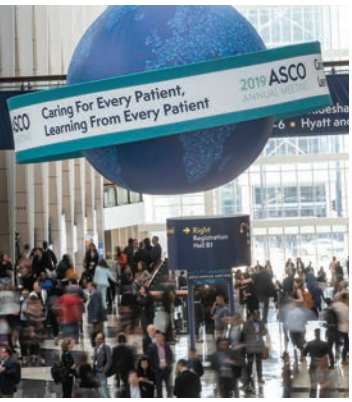

PHOTO CREDIT: BY © ASCO/NICK AGRO 2019

› THE COMBINATION OF GEMCITABINE PLUS PAZOPANIB ACHIEVED A HIGHER RESPONSE RATE THAN SINGLE-AGENT GEMCITABINE OR PAZOPANIB, BUT NOT HIGHER THAN THE GEMCITABINE-DOCETAXEL COMBINATION.

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

SOURCE: Weiss AR, et al. J Clin Oncol 37, 2019 (suppl; abstr 11002)

The study was sponsored by the National Cancer Institute.

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

GEMCITABINE PLUS PAZOPANIB A POTENTIAL ALTERNATIVE IN STS

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

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

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

Adverse events (AEs) of grade 3 or higher occurred in 19.9% of patients on G+D and 20.6% on G+P. Serious AEs occurred in 33% (G+D) and 22% (G+P). Dose reductions were necessary in 80% of patients on G+P and doses were held in 93%. Dr. Somaiah explained that this may have been because the starting dose of gemcitabine and pazopanib (1000 mg/m^2 of gemcitabine on days 1 and 8 and 800 mg of pazopanib) was "probably higher than what we should have started at." The rate of doses held was also higher in the pazopanib arm (93%) compared with the docetaxel arm (58%). This was likely because pazopanib was a daily dosing, so if there was a toxicity it was more likely to be held than docetaxel, she observed. Grade 3 or higher toxicities occurring in 5% or more of patients in either arm consisted generally of cytopenias and fatigue. The G+P arm experienced a high amount of neutropenia, most likely because this arm did not receive granulocyte-colony stimulating factor (GCSF) support, as opposed to the G+D arm.

Dr. Somaiah pointed out that the 12% response rate for the G+P combination is similar to what has been previously presented and higher than single-agent gemcitabine or pazopanib, but not higher than the G+D combination. The PFS of 4.1 months was less than anticipated, she added, but it was similar on both arms.

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

SOURCE: Somaiah N, et al. J Clin Oncol 37, 2019 (suppl; abstr 11008)

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

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

rEECur TRIAL FINDING OPTIMAL CHEMOTHERAPY REGIMEN FOR EWING SARCOMA

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

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

Results

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

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

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

Median progression-free survival (PFS) for all patients was approximately 5 months. Bayesian analysis suggested there was a low probability that GD was more effective than the other 3 arms: a 22% chance that GD was better than Arm A, a 3% chance that it was better than

PHOTO CREDIT: BY © ASCO/PHIL MCCARTEN 2019

› THE "DROP-A-LOSER" TRIAL IS DESIGNED TO FIND THE STANDARD OF CARE FOR EWING SARCOMA.

Arm B, and a 7% chance that it was better than Arm C. Bayesian analysis also suggested there was a probability that OS favored GD. Because the trial directs only the first 4 or 6 cycles of treatment and the patients receive more treatment after trial-directed therapy, investigators were not fully able to interpret this.

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

› rEECur IS A POTENTIALLY PRACTICE-CHANGING TRIAL AT THIS EARLY STAGE.

SOURCE: McCabe MG, et al. J Clin Oncol 37, 2019 (suppl; abstr 11007)

The rEECur trial is sponsored by the University of Birmingham (UK) and received funding from the European Union's Seventh Framework Programme under a grant agreement.

Dr. McCabe disclosed no conflicts of interest. Other authors disclosed consulting, advisory roles, or research funding from numerous pharmaceutical companies, including Lilly (gemcitabine) and Pfizer (irinotecan). Dr. Desai disclosed a consulting/advisory role and institutional research funding from Lilly.

ABEMACICLIB MEETS PRIMARY ENDPOINT IN PHASE 2 TRIAL OF DDLS

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

Of three agents in the clinic with the potential to target *CDK4* and *CDK6*—palbociclib, ribociclib, and abemaciclib—abemaciclib is more selective for *CDK4* than *CDK6*. *CDK4* amplification occurs in more than 90% of well-differentiated and dedifferentiated liposarcomas. Abemaciclib also has a different side effect profile, with less hematologic toxicity than the other 2 agents. The current study was considered positive if 15 patients or more of a 30-patient sample size were progression-free at 12 weeks.

Results

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

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

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

an unconfirmed PR. At data cutoff, 11 patients remained on study with stable disease or PR. The investigators conducted correlative studies that indicated all patients had *CDK4* and *MDM2* amplification with no loss of retinoblastoma tumor suppressor. They observed an inverse correlation between *CDK4* amplification and PFS—the higher the level of *CDK4* amplification, the shorter the PFS. They also found additional genomic alterations, including *JUN*, *GLI1*, *ARID1A*, *TERT*, and *ATRX*. *TERT* amplification was also associated with shorter PFS. Based on these findings, the investigators believe a phase 3 study of abemaciclib in DDLS is warranted.

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

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

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

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

nab-SIROLIMUS PROVIDES BENEFIT IN ADVANCED MALIGNANT PECOMA

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

Investigators enrolled 34 patients 18 years or older with histologically confirmed malignant PEComa. Patients could not have had prior mTOR inhibitors. They received infusions of 100 mg/m^2 *nab*-sirolimus on days 1 and 8 every 21 days until progression or unacceptable toxicity. Patients were a median age of 60 years and 44% were 65 or older; 82% were women, which is typical of the disease. Most patients (88%) had no prior systemic therapy for advanced PEComa.

Results

The drug was well tolerated, with toxicities similar to those of oral mTOR inhibitors. Treatment-related adverse events (TRAEs) occurring in 25% or more of patients were mostly grade 1 or 2 toxicities. Hematologic TRAEs included anemia (47%) and thrombocytopenia (32%) of any grade. Nonhematologic events of any grade included stomatitis/mucositis (74%), dermatitis/rash (65%), fatigue (59%), nausea (47%), and diarrhea (38%), among others. A few grade 3 events occurred on study, most notably stomatitis/mucositis (18%). Severe adverse events (SAEs) were also uncommon, occurring in 7 of 34 patients (21%). Pneumonitis is common in orally administered mTOR inhibitors; 6 patients (18%) treated with *nab*-sirolimus

› STRIKINGLY, 9 OF 9 PATIENTS WITH *TSC2* MUTATIONS DEVELOPED A PARTIAL RESPONSE WITH *nab*-SIROLIMUS IN MALIGNANT PECOMA.

had grade 1 or 2 pneumonitis.

Of the 31 evaluable patients, 13 (42%) had an objective response, all of which were partial responses (PR). Eleven (35%) had stable disease and 7 (23%) had progressive disease. The disease control rate, consisting of PR and stable disease, was 77%. The median duration of response had not been reached as of the data cutoff on May 10, 2019. At that time, it was 6.2 months (range, 1.5 to 27.7+). The median time to response was 1.4 months and the median progression-free survival (PFS) was 8.4 months. The PFS rate at 6 months was 61%. Three patients had received treatment for over a year and another 3 patients for more than 2 years.

Correlation with biomarkers

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

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

› TWENTY-FOUR PATIENTS WERE PROGRESSION-FREE AT WEEK 12, SATISFYING THE STUDY DECISION RULE FOR CLINICAL BENEFIT OF CABOZANTINIB IN GIST.

SOURCE: Wagner AJ, et al. J Clin Oncol 37, 2019 (suppl; abstr 11005).

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

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

CABOZANTINIB ACHIEVES DISEASE CONTROL IN GIST

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

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

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

ued cabozantinib treatment as of the database cutoff in January 2019.

Results

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

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

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

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

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

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

Presenting author, Patrick Schöffski, MD, of KU Leuven and Leuven Cancer Institute in Belgium, disclosed institutional relationships with multiple pharmaceutical companies for consulting and research funding, including research funding from Exelixis, the developer of cabozantinib. No other abstract coauthor disclosed a relationship with Exelixis.

LAROTRECTINIB EFFECTIVE IN TRK FUSION CANCERS

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

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

› TRK FUSION CANCER IS A RARE MALIGNANCY SEEN IN A WIDE VARIETY OF ADULT AND CHILDHOOD TUMOR TYPES.

sions. Cornelis Martinus van Tilburg, MD, of the Hopp Children's Cancer Center, Heidelberg University Hospital, and German Cancer Research Center in Heidelberg, Germany, presented the findings.

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

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

› AS OF THE DATA CUTOFF, 84% OF PATIENTS WHO RESPONDED TO LAROTRECTINIB WERE ESTIMATED TO HAVE A RESPONSE DURATION OF A YEAR OR MORE.

Efficacy

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

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

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

SOURCE: van Tilburg CM, et al. J Clin Oncol 37, 2019 (suppl; abstr 10010).

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

Adolescent and young adult (AYA) survival trends

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

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

Risk of death

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

No characteristic conferred a lower risk of death for bone/STS patients

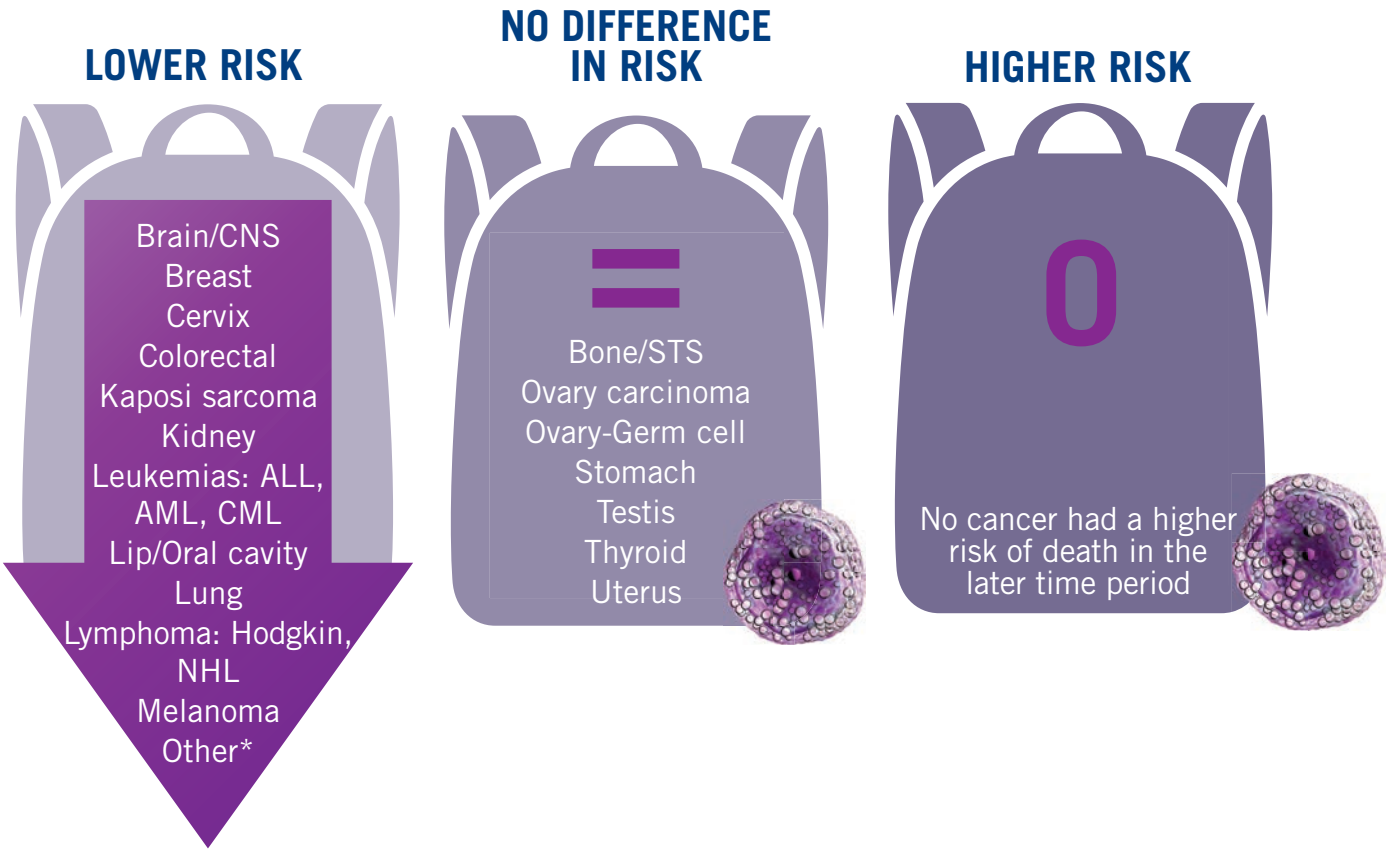
- All tumor stages
- Sex – both
- All age groups, except 25-29
- Asian-Pacific Islanders
- Latino whites
- Non-Latino whites
- High socioeconomic status
- Mid-high socioeconomic status
- Mid-low socioeconomic status
- Low socioeconomic status

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

Data from Moke DJ, et al. Emerging cancer survival trends, disparities, and priorities in adolescents and young adults: a California Cancer Registry-based study. *JNCI Cancer Spectr.* 2019;3(2):pkz031.

Risk of death

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



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

Data from Moke DJ, et al. Emerging cancer survival trends, disparities, and priorities in adolescents and young adults: a California Cancer Registry-based study. *JNCI Cancer Spectr.* 2019;3(2):pkz031.

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