




Real-World Outcomes of Patients with Locally Advanced or Metastatic Epithelioid Sarcoma

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BACKGROUND: Limited data are available on the real-world effectiveness and safety of systemic therapies for advanced (surgically unresectable and/or metastatic) epithelioid sarcoma (ES). **METHODS:** A retrospective medical records review was conducted in patients with advanced ES who were initiating first-line or ≥ 2 lines of systemic therapy (2000-2017) at 5 US cancer centers. The real-world overall response rate (rwORR), the duration of response (rwDOR), the disease control rate (rwDCR) (defined as stable disease for ≥ 32 weeks or any duration of response), and progression-free survival (rwPFS) were assessed by radiology reports. Overall survival (OS), rwDOR, and rwPFS were estimated from the time therapy was initiated using the Kaplan-Meier method. Serious adverse events were assessed. **RESULTS:** Of 74 patients (median age at diagnosis, 33 years; range, 10.6-76.3 years), 72% were male, and 85% had metastatic disease. The median number of lines of therapy was 2 (range, 1-7 lines of therapy), and 46 patients (62%) received ≥ 2 lines of systemic therapy. First-line regimens were usually anthracycline-based (54%) or gemcitabine-based (24%). For patients receiving first-line systemic therapy, the rwORR was 15%, the rwDCR was 20%, the median rwDOR was 3.3 months (95% CI, 2.1-5.2 months), the median rwPFS was 2.5 months (95% CI, 1.7, 6.9 months), and the median OS was 15.2 months (95% CI, 11.4-21.7 months). For those who received ≥ 2 lines of systemic therapy, the rwORR was 9%, the rwDCR was 20%, the median rwDOR was 4.5 months (95% CI, 0.7-5.6 months), and the median rwPFS was 6.0 months (95% CI, 3.2-7.4 months). Over one-half of patients (51.4%) experienced an adverse event, most frequently febrile neutropenia (14%), pain (10%), anemia, dyspnea, fever, thrombocytopenia, or transaminitis (5% each). **CONCLUSIONS:** Systemic therapies demonstrate limited efficacy in patients with advanced ES and have associated toxicities. *Cancer* 2021;127:1311-1317. © 2020 Epizyme, Inc. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society This is an open access article under the terms of the Creative Commons Attribution NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: chemotherapy, epithelioid, natural history, personal medical records, review of reported cases, sarcoma, treatment efficacy.

INTRODUCTION

Epithelioid sarcoma (ES) is a rare, aggressive soft-tissue malignancy accounting for <1% of all soft-tissue sarcomas (STS) in the United States¹ and has an incidence of approximately 0.1 cases per million people.² ES can develop in any anatomic location but has a propensity to develop in the extremities and midline structures.³ ES may present as a nondescript soft-tissue mass or a nonhealing infection or ulcer, and accurate diagnosis may be delayed even after initial medical evaluation.^{1,4} Histologically, the classic type of ES appears as granuloma-like nodes of epithelioid and spindle cells, whereas the proximal subtype of ES appears as sheets of large, atypical, epithelioid cells.⁵ The loss of integrase interactor 1 (INI1) expression is a hallmark of ES and is a standard immunohistochemical test used in confirming the diagnosis.⁶ Prognosis can be unpredictable

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for patients with ES, with reported 5-year survival rates of 75% for those with localized disease; however, the 1-year survival rate is just 46% for patients with metastatic disease.⁷ Surgical resection is the initial treatment approach; however, not all ES is amenable to resection, and 33% to 77% of patients experience local recurrence even after resection.⁸⁻¹¹ Approximately 30% to 50% of patients with ES develop metastatic disease,^{8,10,11} and the median overall survival (OS) for patients with unresectable and/or metastatic (advanced) ES is 10 to 16 months.^{7,12-14}

To date, systemic therapies for locally advanced ES have included anthracycline-based or gemcitabine-based regimens with modest response rates.^{9,15-18} Palliative chemotherapy is associated with a median OS of 51 weeks (95% CI, 29-73 weeks), as reported by Jones et al.¹³ A retrospective study of 115 patients with advanced ES reported an overall response rate (ORR) of 22% and 27% for anthracycline-based and gemcitabine-based chemotherapy regimens, respectively, and an OS of 16 months (95% CI, 8.4-28.6 months) and 19 months (95% CI, 8.9-37.3 months), respectively.¹⁹ There were no objective responses noted with pazopanib. Recently, a phase 2 study of tazemetostat, an oral selective inhibitor of enhancer of zeste homology 2 (EZH2) in patients with ES, demonstrated an ORR of 15% (95% CI, 7%-26%) (9 of 62 patients), a disease control rate (DCR) of 26% (95% CI, 16%-39%), and a favorable toxicity profile.²⁰ This led to US Food and Drug Administration approval of tazemetostat for adults and adolescents aged ≥ 16 years with metastatic or locally advanced ES who are not eligible for complete resection.²¹

Because of the extreme rarity of ES, limited real-world data are available for this subtype of STS, and much of the sarcoma literature focuses on STS overall. This lack of data leads to a gap in knowledge for ES, specifically preventing an accurate assessment of the unmet needs of patients with ES and how their treatment might benefit from different strategies than treatments for patients with other forms of STS. Thus the objective of this retrospective medical records review was to provide real-world data on the effectiveness and safety of current standard-of-care therapies for patients with locally advanced, unresectable, and/or metastatic ES receiving systemic therapy in the United States.

MATERIALS AND METHODS

Study Design and Population

For this multicenter, noninterventional, retrospective medical records review, we evaluated the medical records of patients aged ≥ 10 years with histologically confirmed, locally advanced, unresectable or metastatic ES who initiated systemic anticancer therapy for its

treatment between January 1, 2000 and December 31, 2017 (study period). This study was conducted in line with the relevant US Food and Drug Administration guidance on best practices for conducting and reporting pharmacoepidemiologic and natural history studies for drug development.^{22,23}

Historical data from ES patients who participated in any clinical trial with tazemetostat were included only up to the date of trial enrollment. Any patients who initiated tazemetostat as first-line therapy were excluded from this retrospective medical records review because this study aimed to provide benchmarking real-world practice data on standard-of-care treatments for locally advanced unresectable and metastatic ES. If a patient initiated tazemetostat after first-line treatment, all data after the initiation of tazemetostat were excluded from analyses, but data before tazemetostat initiation were included. Patients receiving other investigational drugs were eligible for inclusion.

Medical records were collected from 5 US study sites: Memorial Sloan Kettering Cancer Center (New York, New York), Dana-Farber Cancer Institute (Boston, Massachusetts), the University of Texas MD Anderson Cancer Center (Houston, Texas), the University of Michigan Comprehensive Cancer Center (Ann Arbor, Michigan), and the University of Colorado Cancer Center (Aurora, Colorado). Study investigators and clinical research coordinators retrospectively abstracted de-identified medical record data using an electronic case report form; no protected health information was collected. The study was approved by institutional review boards for each site between February 20, 2018 and April 30, 2018.

Study Outcomes

The primary efficacy outcomes of this study were real-world ORR (rwORR) and real-world duration of response (rwDOR). rwORR was defined as the proportion of patients, among all receiving that line of therapy, with a documented radiologic scan showing a physician-assessed complete response or a less than complete response of any duration (*documented response*). rwORR was assessed by investigator retrospective review of radiology reports because Response Evaluation Criteria in Solid Tumors (RECIST) assessments were not performed as part of routine clinical practice. rwDOR was defined as the duration between the first scan showing a documented response and the first scan showing progressive disease or the end of treatment if no progression occurred. rwDOR was evaluable in patients who had ≥ 2 consecutive radiologic scans.

The secondary efficacy outcomes were the real-world DCR (rwDCR), real-world time to treatment failure

(rwTTF), real-world progression-free survival (rwPFS), and OS. rwDCR was defined as the proportion of patients who had a scan showing a documented response or stable disease lasting for ≥ 32 weeks among all patients receiving that line of therapy. rwTTF was defined as the time from initiation of therapy to discontinuation of therapy for any reason, including disease progression, treatment toxicity, or death. rwPFS was defined as the time from initiation of therapy to disease progression or death if it occurred within 30 days of the end of therapy. OS was defined as time from initiation of first-line therapy to death from any cause.

The safety outcome was the proportion of patients documented in medical records to have experienced clinically significant adverse events (AEs) (ie, resulting in treatment modification or discontinuation, patient hospitalization, death, or permanent sequelae).

A subgroup analysis of OS after first-line therapy by ES subtype (classic and proximal ES) was performed among patients with known ES subtype. Histologically confirmed ES subtype was not available for over one-quarter of patients, thus a secondary stratification was added in which the classification of distal versus proximal ES was based on the location of the primary tumor at diagnosis, as an approximation of ES subtype, as categorized by Frezza et al.¹⁹

Statistical Analyses

Data from all centers were pooled for the analyses. Summary statistics included the number and percentage of patients in each category for discrete variables, and the mean, standard deviation, and median for continuous variables. rwORR and rwDCR were described in percentages with 95% CIs. rwDOR, rwTTF, OS, and rwPFS were estimated from the start of therapy using the Kaplan-Meier method, and medians and 95% CIs were reported. Second-line and subsequent lines of therapy were assumed to be independent from each other and, as such, were analyzed together for all efficacy outcomes except OS; OS was only estimated from the initiation of first-line therapy. Descriptive statistics were used to calculate the percentage of patients experiencing clinically significant AEs. The results of the ES subgroup analysis were compared between groups using a log-rank test. A *P* value $\leq .05$ was used to determine statistical significance. All analyses were conducted using SAS version 9.4 (SAS Institute Inc).

RESULTS

Patient Demographic and Clinical Characteristics

Seventy-four eligible patients were identified during the medical records abstraction (June 4, 2018 to November

TABLE 1. Summary of Patient Demographic and Clinical Characteristics, N = 74

| Characteristic | No. of Patients (%) |
|---|---------------------|
| Age: Median [range], y | 33.1 [10.6-76.3] |
| Male sex | 53 (71.6) |
| Race | |
| White | 54 (73.0) |
| Black or African American | 5 (6.8) |
| Asian | 5 (6.8) |
| Native Hawaiian or other Pacific Islander | 1 (1.4) |
| Unknown/not sure | 9 (12.2) |
| Disease stage | |
| Locally advanced unresectable | 11 (14.9) |
| Metastatic | 63 (85.1) |
| Location of primary tumor at diagnosis ^a | |
| Proximal | 54 (73.0) |
| Distal | 19 (25.7) |
| Unknown | 1 (1.4) |
| ES subtype | |
| Proximal | 46 (62.2) |
| Classic | 8 (10.8) |
| Other ^b | 1 (1.4) |
| Unknown/not sure | 19 (25.7) |
| INI1/BAF47 status ^c | |
| Negative | 37 (90.2) |
| Positive | 3 (7.3) |
| Unknown/not sure | 1 (2.4) |

Abbreviations: BAF47, barrier-to-autointegration factor 47; ES, epithelioid sarcoma; INI1, integrase interactor 1.

^aProximal primary sites include head, neck, trunk, pelvis, groin, perineal region, buttock, proximal upper limb, and proximal lower limb. Distal primary sites include hand, foot, distal upper limb, and distal lower limb.

^bOther subtypes of ES include hybrid features of proximal and conventional types.

^cPercentages for INI1/BAF47 test results were based on n = 41 tested cases. For 3 patients with conflicting INI1 and BAF47 results, the INI1 result was selected for this variable.

30, 2018). The median age at diagnosis was 33.1 years (range, 10.6-76.3 years) (Table 1). The majority of patients were male (71.6%), white (73.0%), and had metastatic ES (85.1%) and proximal-type ES (83.6%; 46 of 55 of patients with known subtype), with loss of INI1/barrier-to-autointegration factor 47 (INI1/BAF47) expression by immunohistochemistry (37 of 41 tested tumors; 90.2%).

Therapy Lines and Treatments

All patients received at least 1 line of systemic anticancer therapy (median, 2 lines; range, 1-7 lines), and 46 patients received ≥ 2 lines (2L+) of therapy. Anthracycline-based (54.1%) and gemcitabine-based (24.3%) regimens were the most common first-line therapies. Gemcitabine-based regimens were favored over anthracycline-based regimens in patients who received 2L+ therapy (47.8% vs 15.2% of patients, respectively), whereas pazopanib was used by 5.4% of patients as first-line therapy and by 6.5% of those who received 2L+ therapy.

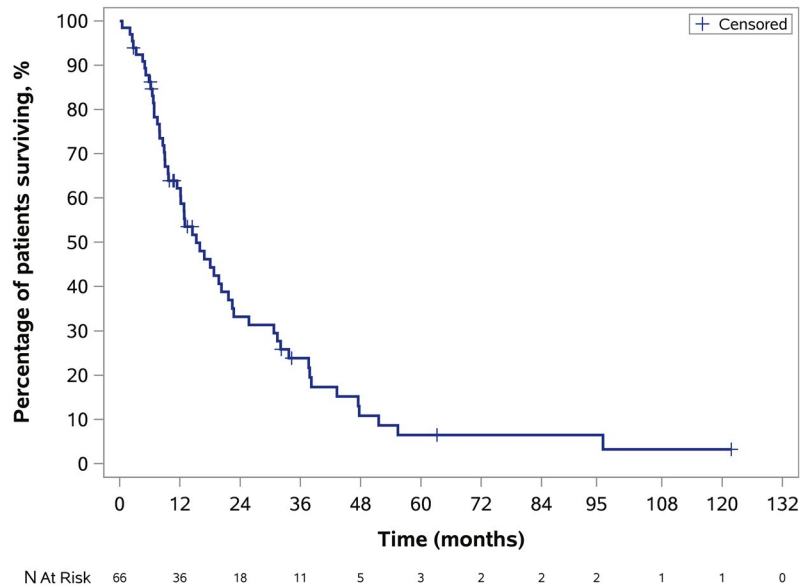


Figure 1. This Kaplan-Meier curve illustrates overall survival according to first-line therapy in patients with locally advanced or metastatic epithelioid sarcoma

Real-World Tumor Response Outcomes by Line of Therapy

The rwORR was 14.9% (95% CI, 7.7%-25.0%; 11 of 74 lines of therapy) patients who received first-line therapy and 9.4% (95% CI, 4.4%-17.1%; 9 of 96 lines) among those who received 2L+ therapy; and the rwDCR was 20.3% (95% CI, 11.8%-31.2%; 15 of 74 lines) and 19.8% (95% CI, 12.4%-29.2%; 19 of 96 lines), respectively. After first-line therapy, 3 of 74 patients (4.1%) had a complete response; no patients had a complete response in subsequent lines. Six of 11 patients who had a complete response or less than a complete response to first-line therapy had evaluable data for DOR, with a median rwDOR of 3.3 months (95% CI, 2.1-5.2 months). Eight of 9 patients who received 2L+ therapy and had a complete or less than complete response were evaluable for DOR, with a median rwDOR of 4.5 months (95% CI, 0.7-5.6 months). rwTTF data were evaluable for 64 patients after first-line therapy and for 85 patients after 2L+ therapy, and the median rwTTF was 2.9 months (95% CI, 1.7-3.5 months) and 2.4 months (95% CI, 1.6-3.6 months), respectively. The most common reason for treatment discontinuation was disease progression (first-line therapy, 54.0%; 2L+ therapy, 50.6%).

Real-World Survival Outcomes

The median follow-up for the total population (N = 74) was 16.8 months (range, 0.1-162.7 months). Of 54 patients who had evaluable data after first-line therapy, the median rwPFS was 2.5 months (95% CI, 1.7-6.9 months). Among the

patients who received 2L+ therapy, the median rwPFS was 6.0 months (95% CI, 3.2-7.4 months) in 58 who were evaluable further lines of therapy. Among the 66 patients who had known treatment and death dates in the first-line, the median OS was 15.2 months (95% CI, 11.4-21.7 months) (Fig. 1). Sixty-eight patients (91.9%) died (2 did not have recorded dates of death); of these, 33 deaths (48.5%) were attributable to tumor progression, and the cause of death was not provided for the remaining 35 patients (51.5%).

Among the 49 patients who had known histologically confirmed ES subtype, first-line treatment date, and date of death (classic ES, n = 7; proximal ES, n = 42), the median OS was 21.7 months (95% CI, 3.3-55.4 months) for those with classic ES and 12.8 months (95% CI, 9.6-22.4 months) for those with proximal ES. The difference in OS was not statistically significant ($P = .303$). Among the 65 patients who had known primary tumor location, first-line treatment date, and date of death (distal ES, n = 16; proximal ES, n = 49), the median OS was 19.7 months (95% CI, 6.9-55.4 months) for those with distal ES and 13.0 months (95% CI, 9.0-20.3 months) for those with proximal ES. Similar to the previous subgroup comparison, the difference in OS was not statistically significant between groups ($P = .365$).

Safety Outcomes

Among all patients, 51.4% experienced a clinically significant AE across all treatment lines. The most common AEs were febrile neutropenia (13.5%), pain (9.5%), and

anemia, dyspnea, fever, thrombocytopenia, and transaminitis (5.4% each).

DISCUSSION

Cytotoxic chemotherapies and the tyrosine kinase inhibitor pazopanib are indicated for the treatment of many forms of STS, including advanced ES. However, because of the rarity of ES, limited real-world data are available on the outcomes of patients who have advanced ES treated with traditional systemic therapy regimens. To address this gap in the literature, the current multicenter, retrospective medical record review generated real-world evidence on the efficacy of systemic therapies used to treat patients with locally advanced, unresectable or metastatic ES. In contrast with most of the existing retrospective real world studies in patients with ES, which either reported results for patients with early stage disease or had very small sample sizes with advanced ES,^{5,13,24} our study consisted entirely of patients who were diagnosed with metastatic ES (85.1%) or locally advanced unresectable ES (14.9%). The current cohort of 74 patients is substantial given the extreme rarity of the disease. Our study demonstrates the feasibility of evaluating the natural history of rare cancers by collaborating across institutions in accordance with US Food and Drug Administration guidance to collect real-world data.

The current results demonstrate that outcomes for patients who are treated with conventional systemic therapies for advanced ES in standard practice remain modest, with rwORRs of 15% after first-line treatment and 9% after 2L+ treatment among all therapies. The median rwDOR among the small numbers of patients noted by physicians as having an objective response (first-line therapy, 15%; 2L+ therapy, 9%) was short (first-line therapy, 3 months; 2L+ therapy, 5 months). This is underscored by a median OS of approximately 15 months with first-line therapy and 92% of patients dying during the study period, with disease progression noted as the primary cause of death in all known cases.

Jones et al, in a single-center retrospective study of a prospectively maintained ES database in the United Kingdom, reported an ORR of 15% among 20 patients who received first-line chemotherapy for locally advanced or metastatic ES (ie, doxorubicin and ifosfamide, single-agent anthracycline, or trabectedin), similar to the current results.¹³ In that study, the ORR was 0% after second-line and third-line treatment (including phase 1 investigational agents, ifosfamide, and trabectedin),

although the study is difficult to interpret because of the small sample size.

Other real-world studies in patients with ES have reported outcomes for patients treated with gemcitabine-based versus anthracycline-based regimens. Frezza et al, in an international, multicenter, retrospective study of 117 patients with locally advanced or metastatic ES, reported ORRs of 27% and 22% in patients receiving gemcitabine-based and anthracycline-based regimens, respectively.¹⁹ Pink et al, in a German multicenter, retrospective study of 17 patients with ES who received chemotherapy, reported response rates of 58% and 0% in patients receiving gemcitabine-based and anthracycline-based regimens, respectively.¹²

The median OS observed in our study (15 months for first-line therapy) falls within previously reported estimates. Among patients who were treated in the first-line, the extrapolated median OS reportedly ranged from 4 to 7 months^{5,7,9} and to 23 months.²⁵ Three other real world studies have reported a median OS of 12 to 21 months among patients treated with gemcitabine-based regimens and 16 months among those treated with anthracycline-based regimens.^{12,13,19} In the subgroup analyses comparing OS between patients with histologically confirmed ES subtype or by primary tumor location, there was a numerical trend of longer OS among patients who had distal/classic ES versus proximal ES, although the differences in OS were not statistically significant. Because these findings are based on a small number of patients, we advise caution when interpreting them. However, these observations are consistent with the results of prior studies reporting more favorable clinical outcomes, including longer OS and less aggressive disease course, among patients with distal/classic ES versus proximal ES.^{5,24,26-28}

Our current study is subject to several limitations. First, in real-world observational studies, especially those performed retrospectively, it is not possible to implement consistent monitoring and application of homogeneous evaluation criteria (eg, RECIST) that are inherent to clinical trial design. A review of radiology scans was used to determine clinical response, which could have led to an overestimation of the rwORR compared with the ORR assessed in clinical trials.²⁹ Second, the differential diagnosis of ES is broad, and previous studies have indicated that $\geq 90\%$ of ES tumors may have a loss of expression of INI1,^{6,28} consistent with the current results (90%). However, loss of expression of INI1 has also been observed in other epithelioid malignant neoplasms that

may mimic ES.^{6,28} Because the objective of this study was to assess the efficacy and safety of systemic therapies for the treatment of locally advanced, unresectable or metastatic ES, it was required that eligible patients received at least 1 line of systemic therapy. However, this may have resulted in a higher proportion of eligible patients with proximal-type ES because patients with distally located tumors of the foot or hand, which are more common among patients with distal-type ES, tend to have a better surgical prognosis, making them less likely to require systemic therapy.^{10,30} Thus the patients assessed in this study may not be representative of the overall population of patients with ES. Finally, because safety outcomes were abstracted from medical records, these outcomes may be underreported.

Conclusions

This US-based real-world observational study characterized the efficacy of standard-of-care treatments for patients with locally advanced unresectable or metastatic ES that were available to patients during the study period. The results of this study demonstrate a modest response to current chemotherapies. The short duration of responses and OS in this aggressive disease highlights the need for more effective and well tolerated therapies.

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CONFLICT OF INTEREST DISCLOSURES

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Rajarethinam are employees of Epizyme, Inc, and own stock and stock options in the company. Mei Sheng Duh, Priyanka J. Bobbili, Lynn Huynh, Todor I. Totev, and Angela K. Lax are employees of Analysis Group, Inc, which received research funding and consulting fees for this study.

AUTHOR CONTRIBUTIONS

Mrinal M. Gounder: Conceptualization, data curation, investigation, methodology, resources, supervision, and writing—initial draft. **Priscilla Merriam:** Conceptualization, data curation, investigation, methodology, resources, supervision, and writing—initial draft. **Ravin Ratan:** Conceptualization, data curation, investigation, methodology, resources, and supervision. **Shreyaskumar R. Patel:** Conceptualization, data curation, investigation, methodology, resources, and supervision. **Rashmi Chugh:** Conceptualization, data curation, investigation, methodology, resources, and supervision. **Victor M. Villalobos:** Conceptualization, data curation, investigation, methodology, resources, and supervision. **Mark Thornton:** Conceptualization, methodology, supervision. **Brian A. Van Tine:** Conceptualization, methodology, supervision. **Amr H. Abdelhamid:** Data curation, and investigation. **Jennifer Whalen:** Funding acquisition, methodology, and supervision. **Jay Yang:** Methodology, data validation, and data visualization. **Anand Rajarethinam:** Conceptualization, funding acquisition, methodology, resources, supervision, data validation, and data visualization. **Mei Sheng Duh:** Conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, and writing—initial draft. **Priyanka J. Bobbili:** Conception, data curation, formal analysis, funding acquisition, methodology, project administration, software, and supervision. **Lynn Huynh:** Conceptualization, data curation, formal analysis, methodology, project administration, software, supervision, and writing—initial draft. **Todor I. Totev:** Conceptualization, data curation, formal analysis, methodology, project administration, software, supervision, and writing—initial draft. **Angela K. Lax:** Data curation, formal analysis, project administration, software, and supervision. **Shefali Agarwal:** Conceptualization, funding acquisition, investigation, methodology, resources, and supervision. **George D. Demetri:** Conceptualization, data curation, investigation, methodology, resources, and supervision. All authors participated in the final editing and review of the article and approved the final version for potential publication.

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