Tazemetostat in advanced epithelioid sarcoma with loss of INI1/*SMARCB1*: an international, open-label, phase 2 basket study

Mrinal Gounder, Patrick Schöffski, Robin L Jones, Mark Agulnik, Gregory M Cote, Victor M Villalobos, Steven Attia, Rashmi Chugh, Tom Wei-Wu Chen, Thierry Jahan, Elizabeth T Loggers, Abha Gupta, Antoine Italiano, George D Demetri, Ravin Ratan, Lara E Davis, Olivier Mir, Palma Dileo, Brian A Van Tine, Joseph G Pressey, Trupti Lingaraj, Anand Rajarethinam, Laura Sierra, Shefali Agarwal, Silvia Stacchiotti

Summary

Background Epithelioid sarcoma is a rare and aggressive soft-tissue sarcoma subtype. Over 90% of tumours have lost INI1 expression, leading to oncogenic dependence on the transcriptional repressor EZH2. In this study, we report the clinical activity and safety of tazemetostat, an oral selective EZH2 inhibitor, in patients with epithelioid sarcoma.

Methods In this open-label, phase 2 basket study, patients were enrolled from 32 hospitals and clinics in Australia, Belgium, Canada, France, Germany, Italy, Taiwan, the USA, and the UK into seven cohorts of patients with different INI1-negative solid tumours or synovial sarcoma. Patients eligible for the epithelioid sarcoma cohort (cohort 5) were aged 16 years or older with histologically confirmed, locally advanced or metastatic epithelioid sarcoma; documented loss of INI1 expression by immunohistochemical analysis or biallelic *SMARCB1* (the gene that encodes INI1) alterations, or both; and an Eastern Cooperative Oncology Group performance status score of 0–2. Patients received 800 mg tazemetostat orally twice per day in continuous 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint was investigator-assessed objective response rate measured according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Secondary endpoints were duration of response, disease control rate at 32 weeks, progression-free survival, overall survival, and pharmacokinetic and pharmacodynamic analyses (primary results reported elsewhere). Time to response was also assessed as an exploratory endpoint. Activity and safety were assessed in the modified intention-to-treat population (ie, patients who received one or more doses of tazemetostat). This trial is registered with ClinicalTrials.gov, NCT02601950, and is ongoing.

Findings Between Dec 22, 2015, and July 7, 2017, 62 patients with epithelioid sarcoma were enrolled in the study and deemed eligible for inclusion in this cohort. All 62 patients were included in the modified intention-to-treat analysis. Nine (15% [95% CI 7–26]) of 62 patients had an objective response at data cutoff (Sept 17, 2018). At a median follow-up of 13·8 months (IQR 7·8–19·0), median duration of response was not reached (95% CI 9·2–not estimable). 16 (26% [95% CI 16–39]) patients had disease control at 32 weeks. Median time to response was 3·9 months (IQR 1·9–7·4). Median progression-free survival was 5·5 months (95% CI 3·4–5·9), and median overall survival was 19·0 months (11·0–not estimable). Grade 3 or worse treatment-related adverse events included anaemia (four [6%]) and weight loss (two [3%]). Treatment-related serious adverse events occurred in two patients (one seizure and one haemoptysis). There were no treatment-related deaths.

Interpretation Tazemetostat was well tolerated and showed clinical activity in this cohort of patients with advanced epithelioid sarcoma characterised by loss of INI1/*SMARCB1*. Tazemetostat has the potential to improve outcomes in patients with advanced epithelioid sarcoma. A phase 1b/3 trial of tazemetostat plus doxorubicin in the front-line setting is currently underway (NCT04204941).

Funding Epizyme.

Introduction

Epigenetic regulation comprises a broad and dynamic regulatory system that modulates gene expression through reversible modifications of nucleic acids and histone proteins.[1] Aberrant epigenetic modifications have been implicated in a wide range of human diseases ranging from developmental disorders to cancer. Epigenetic inhibitors (eg, DNA methyltransferase and histone deacetylase inhibitors) have shown efficacy in myeloproliferative diseases and are approved treatment options.[2]

Dysfunction of the SWI/SNF chromatin remodelling complex has been observed in approximately 20% of cancers, including childhood brain tumours, malignant rhabdoid tumours, soft-tissue sarcoma subtypes, non-small-cell lung cancer, and small-cell carcinoma of the ovary (hypercalcaemic type).[3–7] INI1, encoded by *SMARCB1*, is an important component of the SWI/SNF complex and

Lancet Oncol 2020; 21: 1423–32

Published Online October 6, 2020 https://doi.org/10.1016/S1470-2045(20)30451-4

See Comment page 1388

Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA (M Gounder MD); **Department of General Medical Oncology, and Laboratory of Experimental Oncology, University Hospitals Leuven, KU Leuven, Leuven Cancer Institute, Leuven, Belgium** (Prof P Schöffski MD); **Royal Marsden Hospital and Institute of Cancer Research, London, UK** (Prof R L Jones MD); **Robert H Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA** (Prof M Agulnik MD); **Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA** (G M Cote PhD); **Anschutz Medical Campus, University of Colorado Denver, Aurora, CO, USA** (V M Villalobos MD); **Janssen Pharmaceuticals, Spring House, PA, USA** (V M Villalobos); **Mayo Clinic, Jacksonville, FL, USA** (S Attia DO); **University of Michigan Rogel Cancer Center, Ann Arbor, MI, USA** (R Chugh MD); **National Taiwan University Hospital and Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan** (T W-W Chen MD); **University of California San Francisco, San Francisco, CA, USA** (Prof T Jahan MD); **Fred Hutchinson Cancer Research Center, Seattle, WA, USA** (E T Loggers MD); **The Hospital for Sick Children and Princess Margaret Cancer Center, Toronto, ON, Canada** (A Gupta MD); **Institut Bergonie and University of Bordeaux,**

Bordeaux, France (Prof A Italiano MD); **Dana Farber Cancer Institute and Ludwig Center at Harvard Medical School, Boston, MA, USA** (Prof G D Demetri MD); **MD Anderson Cancer Center, Houston, TX, USA** (R Ratan MD); **Oregon Health & Science University, Knight Cancer Institute, Portland, OR, USA** (L E Davis MD); **Gustave Roussy Cancer Institute, Paris, France** (O Mir MD); **University College London Hospitals NHS Foundation Trust, London, UK** (P Dileo MD); **School of Medicine, Washington University in St Louis, St Louis, MO, USA** (B A Van Tine MD); **Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA** (Prof J G Pressey MD); **Division of Oncology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA** (Prof J G Pressey); **Epizyme, Cambridge, MA, USA** (T Lingaraj BSc, A Rajarethinam MBBS, L Sierra PhD, S Agarwal MBBS); **Bristol Myers Squibb, Cambridge, MA, USA** (L Sierra); **and Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy** (S Stacchiotti MD)

Correspondence to: Dr Mrinal Gounder, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
gounderm@mskcc.org

See Online for appendix

Research in context

Evidence before this study

We searched PubMed for studies with "epithelioid sarcoma" in the title and either "prospective" OR "retrospective" in the main text. We searched for studies investigating the treatment of epithelioid sarcoma published from database inception up to Sept 4, 2020, with no language restrictions. The first search with the term "prospective" returned nine entries, and the second search with the term "retrospective" returned 38 entries. We then refined the search results to exclude review articles and publications that were not relevant to our study (eg, preclinical studies, studies in patients with early-stage disease, studies done in paediatric or adolescent patients, or studies not specifically pertaining to treatment). The remaining results were studies of cytotoxic treatments in patients with this disease, the results of which were associated with modest activity and known toxic effects. One additional retrospective study evaluated treatment with the tyrosine kinase inhibitor pazopanib, and the investigators found no meaningful improvement in efficacy when compared with anthracycline-based and gemcitabine-based therapies. Overall, the scarcity of available data suggests that cytotoxic chemotherapy or targeted therapy offer some clinical benefit. However, there remains a need for effective and well-tolerated treatment options for patients with advanced epithelioid sarcoma.

Added value of this study

To our knowledge, this is the first clinical trial to evaluate tazemetostat for the treatment of advanced epithelioid sarcoma. Tazemetostat differs from cytotoxic therapies because it inhibits an epigenetic modification caused by the loss or alteration of *SMARCB1* or INI1 expression, which is a molecular hallmark of this tumour type. The results of our study show that treatment with tazemetostat was well tolerated and resulted in durable objective responses and prolonged disease control in a subset of patients. Few patients had dose reductions or discontinuations due to adverse events, and adverse events typically associated with cytotoxic chemotherapy were not reported during our study. Genomic analysis results indicated that a notable proportion of patients with advanced epithelioid sarcoma exhibit loss of INI1 expression without any accompanying *SMARCB1* mutations.

Implications of all the available evidence

Our study showed that tazemetostat has clinical activity in a subset of patients with advanced epithelioid sarcoma characterised by loss of INI1, loss or alteration of *SMARCB1*, or both. Tazemetostat has the potential to improve outcomes in patients with advanced epithelioid sarcoma, and the tolerability data from our study support the evaluation of tazemetostat in combination with other agents in future studies. Our molecular pathology results suggest that we might be underestimating the epigenetic driver mutation frequency in epithelioid sarcomas. Therefore, future studies assessing potential predictive biomarkers in epithelioid sarcoma, and possibly other tumour types, should use both genomic and proteomic approaches.

functions as a tumour suppressor.[8,9] Various genetic and epigenetic mechanisms can result in loss of INI1 expression,[10,11] which leads to the unopposed, constitutive, oncogenic activation of EZH2, an enzyme that trimethylates lysine 27 of histone H3 (H3K27me3; appendix p 6).[9] Loss of INI1, *SMARCB1*, or both is the molecular hallmark of epithelioid sarcoma.[12,13]

Epithelioid sarcoma is a rare subtype of soft-tissue sarcoma that can originate in any anatomic location and predominantly affects young adults.[13] In selected patients with localised disease, complete surgical resection can be potentially curative.[14] Patients with surgically unresectable local recurrence or metastatic disease are treated with traditional cytotoxic chemotherapy or tyrosine kinase inhibitors, with modest clinical benefit.[15–20] Small, retrospective series[15–20] have reported a median overall survival of 11–21 months in patients with metastatic disease. Thus, novel, effective, and tolerable treatment strategies are needed, such as targeting the oncogenic dependency of epithelioid sarcoma on EZH2.

Tazemetostat, a first-in-class, oral, selective inhibitor of EZH2, was well tolerated and showed encouraging activity in a phase 1 study[21] involving patients with advanced solid tumours with loss of INI1/*SMARCB1* or that had other SWI/SNF alterations. This phase 2 basket study was designed to evaluate the activity of tazemetostat in patients with solid tumours harbouring these alterations. Herein, we report the clinical activity and safety of tazemetostat in the cohort of patients with advanced or metastatic epithelioid sarcoma.

Methods

Study design and participants

This open-label, phase 2 basket study was done at 32 hospitals and clinics in Australia, Belgium, Canada, France, Germany, Italy, Taiwan, the USA, and the UK (appendix p 2). Patients who met the eligibility requirements were enrolled into one of seven cohorts on the basis of tumour type or specified genetic alterations, with the results of other cohorts being published separately; cohort five enrolled patients with epithelioid sarcoma. Eligible patients in this cohort were aged 16 years or older with histologically confirmed, locally advanced or metastatic epithelioid sarcoma. Patients were required to have documented loss of INI1 expression by immunohistochemical analysis, biallelic *SMARCB1* alterations, or both (INI1/*SMARCB1*). Patients were enrolled on the basis of local pathology results, and INI1 immunohistochemistry results were confirmed centrally (at the Children's Hospital Los Angeles, Los Angeles, CA, USA). Additionally, patients were required to have

measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, an Eastern Cooperative Oncology Group performance status score of 0–2, a life expectancy of 3 months or more, and adequate haematological, renal, and hepatic function (appendix p 3). Data were collected regarding previous therapies, including previous systemic therapy, radiotherapy, and surgery. The minimum washout period was 14 days from previous cytotoxic or non-cytotoxic chemotherapy, or local site radiotherapy; 28 days or more from previous monoclonal antibody treatment; and 12 weeks or more from previous craniospinal radiotherapy, total body irradiation, or radiation to 50% or more of the pelvis. Key exclusion criteria were previous malignancy, other than the disease under investigation; known active CNS or leptomeningeal metastases; or grade 3 or worse thrombocytopenia, neutropenia, or anaemia. Progression (not defined by RECIST version 1.1) before study entry was determined by the treating physician and not required for study eligibility. Additional eligibility criteria are described in the study protocol (appendix).

The study was done in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and national and local policies on bioethics and human biological specimens. Each participating centre obtained approval from an institutional review board. Written informed consent was obtained from all patients. Archival tumour tissue samples, pretreatment biopsies, and radiographic scans were de-identified and sent for correlative studies and central review.

Procedures

Tazemetostat (800 mg) was administered orally twice per day in continuous 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent. Dose interruptions and reductions were permitted, as described in the protocol (appendix). Generally, no dose modifications were required for grade 1–2 adverse events. Per protocol, no more than two dose modifications were allowed. Treatment interruptions lasting more than 14 days and dose re-escalation were not permitted. Additional details are described in the protocol (appendix). At the discretion of the investigator, patients deriving clinical benefit were permitted to stay on tazemetostat beyond RECIST-defined progression (censored for the primary analysis). On-treatment visits, and haematology and blood chemistry laboratory assessments were done on days 1 and 15 of cycles 1 and 2, and on day 1 of every cycle thereafter. Disease response assessments were done every 8 weeks irrespective of treatment delays, or sooner if clinically indicated. Radiographic scans (CT, MRI, or both) were acquired at baseline and every 8 weeks thereafter, and were evaluated by investigators as per RECIST version 1.1. Confirmation of complete and partial responses was done according to RECIST version 1.1 criteria no sooner than 4 weeks since the previous disease assessment. A history of radiographic disease progression before study entry was evaluated by investigators and was not defined by RECIST version 1.1. De-identified radiographic scans were evaluated by a masked independent radiology review committee for secondary supporting evidence. Treatment-emergent adverse events were monitored throughout the study and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Patients attended a post-treatment visit within 30 days of (or within 3 days before or after) the last dose of treatment or before the start of an alternative anticancer therapy. Patients who reached 2 years of tazemetostat dosing were permitted to enrol in an open-label rollover study to provide continuing availability of tazemetostat to those benefiting from treatment. Patients who permanently discontinued the study drug were followed up for survival every 16 weeks until death, full withdrawal of consent, loss to follow-up, or until the patient had been followed up for 2 years from the start of the first dose of tazemetostat.

As specified in the protocol, INI1 protein expression was assessed during screening at the local level, and then retrospectively evaluated by immunohistochemical analysis of paraffin-embedded, archival tumour tissue specimens (BAF47 clone 25 antibody; BD Biosciences, San Jose, CA, USA). These stained slides were evaluated centrally by a board-certified pathologist, and reported as either negative or positive for nuclear INI1 staining. In an exploratory post-hoc analysis, pharmacodynamic changes in H3K27me3 status were evaluated by immunohistochemistry (C36B11 antibody; Cell Signaling Technology, Danvers, MA, USA) in paired tumour biopsies taken electively at baseline and on day 1, cycle 2 of treatment. H3K27me3 status was classified as negative, low, medium, or high on the basis of staining intensity thresholds within the nuclear compartment. Optional post-hoc exploratory studies on available tumour tissues included DNA methylation array analyses, as well as whole-genome sequencing and whole-exome sequencing to identify *SMARCB1* alterations, copy number changes, bi-allelic losses, mutations, and genetic alterations (in an array of 325 cancer-specific genes). Additional details of the molecular pathology analyses are reported in the appendix (pp 3–4).

Outcomes

The primary endpoint was objective response rate defined as confirmed complete or partial response as per RECIST version 1.1. The key secondary endpoint was duration of response, defined as the time from the date of documented complete or partial response to the date of first documented disease progression or death due to any cause. Other secondary endpoints were disease control rate (defined as complete response, partial response, or stable disease at ≥32 weeks), progression-free survival (time from first study dose to first documented disease

progression or death due to any cause), overall survival (time from the date of the first dose of study drug until the date of death from any cause), safety and tolerability, population pharmacokinetic parameters of tazemetostat, and pharmacodynamic effects of tazemetostat in tumour tissues. Investigator-assessed time to response (time from the date of first dose of tazemetostat to the first confirmed complete or partial response) was also assessed as an exploratory post-hoc endpoint. Results of the entire pharmacokinetic and pharmacodynamic analyses will be reported separately because of the space required to present and discuss these results, and because phase 1 pharmacokinetic and pharmacodynamic data have been reported previously.[21] Herein we also include results from an exploratory post-hoc analysis of the pharmacodynamic inhibition of H3K27me3 in patients who underwent optional, paired tumour biopsies.

Statistical analysis

We used a two-stage Green-Dahlberg design with a stopping rule to allow for early termination at the end of stage one if there was strong evidence that there was absence of activity (appendix p 7). The stage one interim analysis was done after the first 15 patients had been enrolled, treated, and had completed at least the 24-week assessment, completed the final study visit, or terminated early from the study, whichever occurred first. An objective response rate of 5% or less was indicative of futility, and an objective response rate of 20% or higher was indicative of potential activity of tazemetostat. An additional 15 patients were planned for enrolment to stage two following confirmation of potential efficacy in stage one (appendix p 7). After stage one futility criteria were surpassed, the independent data monitoring committee endorsed continuing enrolment to stage two completion and changing the primary endpoint (on Oct 21, 2016) in patients with epithelioid sarcoma from objective response rate to disease control rate given the clinical importance of disease stabilisation in patients with sarcoma.[22] However, after additional discussions with the US Food and Drug Administration, the primary endpoint was reverted back (on Aug 7, 2017) to objective response rate, and duration of response was elevated to a key secondary endpoint. After the stage two futility criterion was surpassed, an additional 30 patients were enrolled to the expansion phase (with a planned total of 60 patients) to allow for increased precision around the point estimates for objective response rate and disease control rate and to provide an expanded safety analysis (appendix p 7).

Activity and safety analyses were assessed in the modified intent-to-treat population (ie, all patients who received at least one dose of tazemetostat). Objective response rate and disease control rate were summarised as descriptive statistics with binomial 95% CIs around the value. CIs were calculated according to the classic Clopper-Pearson estimation method. Outcomes were based on investigator assessments. Response assessments done by blinded independent review served as a sensitivity analysis. Investigator-assessed duration of response, progression-free survival, and overall survival were estimated by use of the Kaplan-Meier method and censored for progressive disease or death; 95% CIs were estimated by use of the Brookmeyer-Crowley method. Patients who continued tazemetostat after progression were censored at time of progression. In a pre-defined subgroup analysis, primary and secondary endpoints were compared between systemic treatment-naive patients and those who had received at least one line of previous systemic anticancer therapy, including adjuvant therapy, neoadjuvant therapy, or therapy for advanced disease. Exploratory post-hoc statistical comparisons of DNA methylation data with *SMARCB1* status (alterations or bialleic loss of *SMARCB1*) and clinical outcomes were done by use of Fisher's exact test (two-tailed), with a cutoff of $p<0·10$ for significance. SAS version 9.4 was used for the analyses.

An independent data and safety monitoring board composed of three members with extensive experience in oncology research and biostatistics oversaw the trial in collaboration with the trial sponsor.

This study is registered with ClinicalTrials.gov, number NCT02601950.

Role of the funding source

The funder of the study was involved in the study design, data collection, data analysis, data interpretation, and the writing of the report. All authors had access to summary data and had final responsibility for the decision to submit for publication.

Results

Between Dec 22, 2015, and July 7, 2017, 62 patients were enrolled and treated with tazemetostat (appendix p 8). All patients were included in the modified intent-to-treat population. Baseline demographics and disease characteristics are shown in (table 1). The median dose of tazemetostat administered to patients was 795·9 mg twice per day (IQR 771·4–800·0).

At data cutoff (Sept 17, 2018), nine (15% [95% CI 7–26]) of 62 patients had an objective response according to investigator assessment (nine patients with a partial response) and independent radiology review committee (one patient with a complete response and eight patients with a partial response; figure, A, and appendix p 9).

Based on investigator assessments, median time to response was 3·9 months (IQR 1·9–7·4). At a median follow-up of 13·8 months (7·8–19·0), median duration of response was not reached (95% CI 9·2–not estimable; figure, B). The duration of response in the one patient who had a complete response, as assessed by the independent radiology review committee, was 24·4 months, and this patient had an ongoing complete response at data cutoff. 16 (26% [95% CI 16–39]) of 62 patients had disease control at 32 weeks. The median duration of exposure to

tazemetostat was 5·5 months (IQR 2·9–11·3), and 15 (24%) of 62 patients received tazemetostat treatment for more than 12 months (figure, C). 17 (27%) patients were given tazemetostat for 4 weeks or more after radiographic progression. Notably, 59 (95%) patients had radiographic progression (not defined by RECIST version 1.1) within a median of 1·4 months (IQR 0·7–2·5) before study entry.

47 (76%) of 62 patients had a progression event, and median progression-free survival was 5·5 months (95% CI 3·4–5·9; figure, D). 13 (21% [12–33]) patients had progression-free survival at 12 months. At data cutoff, 31 (50%) patients had died; median overall survival was 19·0 months (11·0–not estimable; figure, E).

In a prespecified exploratory analysis of investigator-assessed response, progression-free survival, and overall survival by whether or not patients had received previous anticancer therapy (appendix pp 10–11), six (25% [95% CI 10–47) of 24 patients who received tazemetostat as a first-line treatment and three (8% [2–21]) of 38 patients who received tazemetostat as a subsequent line of treatment had an objective response. Median duration of response was 9·5 months (IQR 7·9–not estimable) in treatment-naive patients, and was not reached (9·2–not estimable) in previously treated patients. Ten (42% [95% CI 22–63]) treatment-naive patients compared with six (16% [6–31]) previously treated patients had disease control at 32 weeks. Progression events occurred in 12 (50%) treatment-naive patients and in 35 (92%) previously treated patients. Median progression-free survival was 9·7 months (95% CI 5·5–not estimable) in treatment-naive patients and 3·4 months (1·9–5·5) in previously treated patients. Five (21%) treatment-naive patients and 26 (68%) previously treated patients died; median overall survival was not reached (95% CI not estimable–not estimable) in treatment-naive patients versus 11·0 months (6·7–15·7) in previously treated patients.

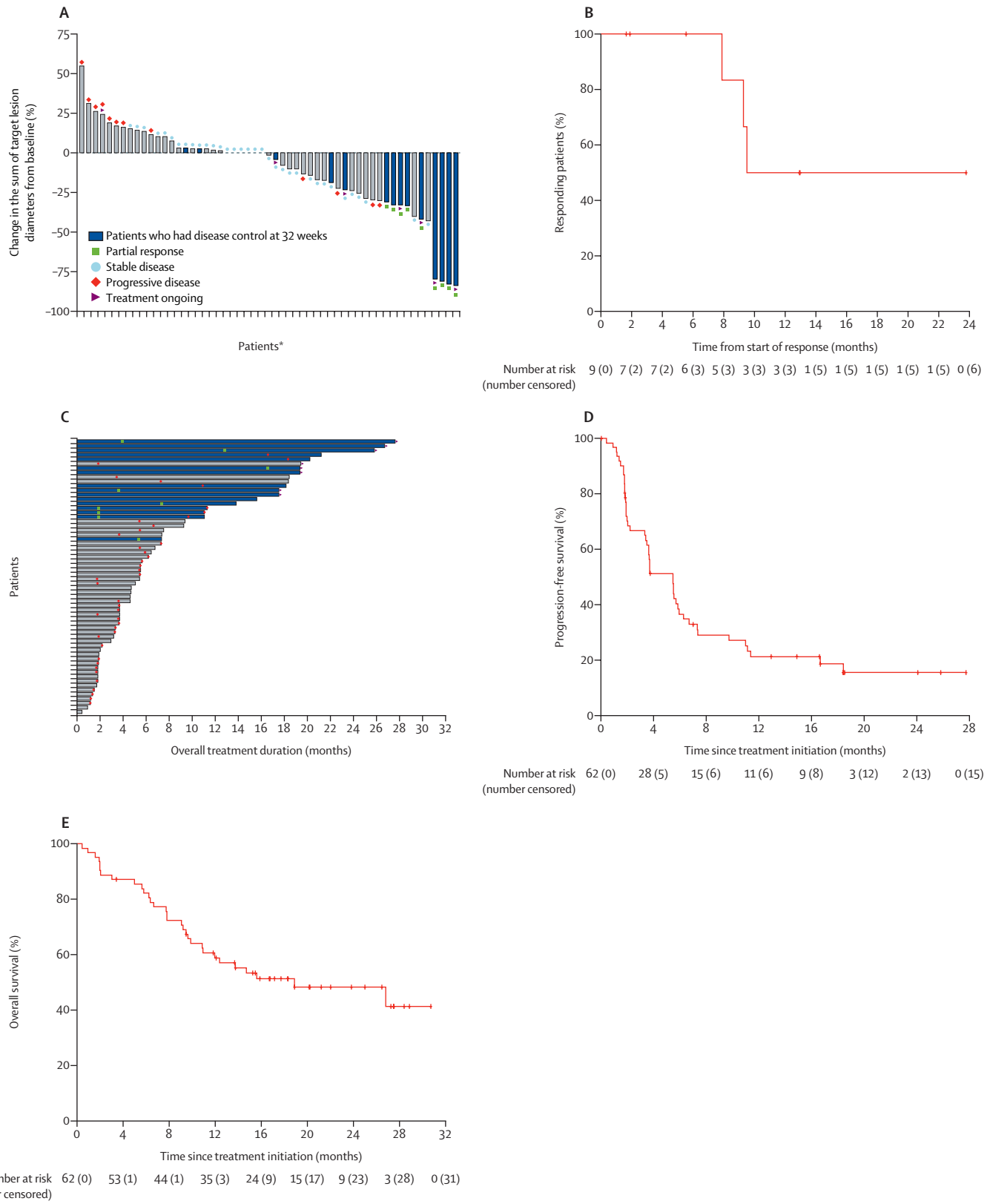
At data cutoff, eight (13%) of 62 patients remained on tazemetostat. 45 (73%) of 62 patients discontinued tazemetostat due to disease progression. Additional reasons for discontinuation included death (n=4), patient refusal of further treatment (n=2), unacceptable toxicity (n=1 [grade 2 mood disorder]), investigator discretion (n=1), and other (n=1). Overall, 17 (27%) of 62 patients continued study treatment beyond RECIST-defined progression.

Most treatment-emergent adverse events that occurred among all 62 patients were grade 1–2 (table 2; appendix p 15). Grade 3–4 treatment-emergent adverse events included anaemia (eight [13%]), weight loss (four [6%]), pleural effusion (three [5%]), decreased appetite (three [5%]), and cancer pain (three [5%]). Serious treatment-emergent adverse events occurred in 25 (40%) patients; those that occurred in more than one patient included: pleural effusion (four [6%]), haemoptysis (four [6%]), death (four [6%]), dyspnoea (three [5%]), cellulitis (two [3%]), and cancer pain (two [3%]). Grade 3–4 treatment-related adverse events included anaemia (four [6%]) and weight loss (two [3%]; appendix p 15). Treatment-related serious adverse events occurred in two (3%) patients (seizure in one patient and haemoptysis in the other patient). One patient had a dose reduction due to a treatment-emergent adverse event

	All treated patients (n=62)*
Age, years	34 (25–46)
Sex	
Male	39 (63%)
Female	23 (37%)
ECOG performance status	
0 or 1	57 (92%)
2	5 (8%)
INI1 status by immunohistochemical analysis	
Negative	61 (98%)
Unknown or undetermined†	1 (2%)
Subtype‡	
Proximal	27 (44%)
Distal	31 (50%)
Unknown	4 (6%)
Stage at diagnosis	
I	2 (3%)
II	7 (11%)
III	7 (11%)
IV	37 (60%)
Unknown	9 (15%)
Progression before study entry§	59 (95%)
Time from progression to study entry, months	1·3 (0·7–2·5)
Previous anticancer therapy	
Surgery	48 (77%)
Radiotherapy	35 (56%)
Systemic anticancer therapy	38 (61%)
Therapy setting¶	
Neoadjuvant	10 (16%)
Adjuvant	8 (13%)
Advanced or metastatic disease	32 (52%)
Maintenance	1 (2%)
Unknown	1 (2%)
Number of lines of previous systemic anticancer therapy	
0	24 (39%)
≥1	38 (61%)
Median	1 (0–2)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. RECIST=Response Evaluation Criteria in Solid Tumours. *One patient did not have measurable disease at baseline and was evaluated on non-target lesions according to RECIST, version 1.1. This patient was included in the modified intent-to-treat population, which included all patients who received one or more dose of the study drug. †The INI1 status of this patient was not entered into the study database, but the absence of INI1 was specified on the local pathology report. ‡Diagnoses were confirmed by a central review of the pathology results. §Radiographic progression was not defined by RECIST, version 1.1. ¶Patients could be included in multiple categories, and some information for therapy setting was missing for some patients.

Table 1: **Baseline characteristics**


A
Change in the sum of target lesion diameters from baseline (%)
75
50
25
0
−25
−50
−75
−100
Patients who had disease control at 32 weeks
Partial response
Stable disease
Progressive disease
Treatment ongoing
Patients*
B
Responding patients (%)
100
80
60
40
20
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time from start of response (months)
Number at risk (number censored) 9 (0) 7 (2) 7 (2) 6 (3) 5 (3) 3 (3) 3 (3) 1 (5) 1 (5) 1 (5) 1 (5) 1 (5) 0 (6)
C
Patients
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32
Overall treatment duration (months)
D
Progression-free survival (%)
100
80
60
40
20
0
0 4 8 12 16 20 24 28
Time since treatment initiation (months)
Number at risk (number censored) 62 (0) 28 (5) 15 (6) 11 (6) 9 (8) 3 (12) 2 (13) 0 (15)
E
Overall survival (%)
100
80
60
40
20
0
0 4 8 12 16 20 24 28 32
Time since treatment initiation (months)
Number at risk (number censored) 62 (0) 53 (1) 44 (1) 35 (3) 24 (9) 15 (17) 9 (23) 3 (28) 0 (31)

(decreased appetite). There were eight deaths due to treatment-emergent adverse events, all of which were attributed to the disease under investigation. The remaining 23 deaths were due to disease progression. There were no treatment-related deaths.

Loss of INI1 was confirmed centrally in 56 (90%) of 62 patients. Five (8%) patients had insufficient archival tissue available for central analysis of INI1 expression, and one (2%) patient was classified as INI1-retained, and reclassified as having a poorly differentiated epithelioid rhabdoid tumour. Pharmacodynamic inhibition of H3K27me3 was confirmed in three patients who underwent optional, paired tumour biopsies with analysis of tissue (data not shown). Whole-genome sequencing (n=35) and whole-exome sequencing (n=38), done on archival tissue or tissue obtained at study screening, showed good concordance in terms of the number of alterations or genes that were altered or mutated, indicating that the majority of changes occurred on exons (data not shown). No germline alterations in *SMARCB1* were identified in the 35 samples tested using either sequencing method (data not shown). A review of 325 cancer-specific genes, including all SWI/SNF complex members, showed that *SMARCB1* was altered in 24 (63%) of 38 patient tumours (appendix p 12). No genetic alterations in *SMARCB1* were detected in 14 (37%) patients, although immunohistochemistry showed that INI1 was not expressed in any of the patients (appendix pp 5, 13). Whole-exome sequencing identified copy number losses in one or both copies of *SMARCB1* in 23 (61%) of 38 patients; other co-occurring alterations in *SMARCB1*, including somatic nucleotide variants resulting in non-sense, frameshift, or splice-site mutations, were identified in five (13%) patients. Biallelic loss of *SMARCB1* was identified in tumour samples from 12 (32%) patients. Whole-exome sequencing showed a median of 77 non-silent mutations per tumour (appendix p 13). DNA methylation array analysis of archival tissue or tissue obtained at the study screening visit was completed in 33 (53%) of 62 patients; patients without evidence of genetic alterations in *SMARCB1* were enriched in methylation cluster-1 (seven [63%] of 11 patients, p=0·0026; appendix p 14) compared with the other clusters. Patients with biallelic loss of *SMARCB1* were enriched in methylation cluster-2 (five [71%] of seven patients, p=0·03; appendix p 14) compared with the other clusters. No correlation was observed in any of the DNA methylation clusters when compared with clinical outcomes (data not shown).

Figure: **Investigator assessment of the best percentage change in the sum of target lesion diameters from baseline (A), duration of response (B), durability of disease control (C), progression-free survival (D), and overall survival (E) in the modified intention-to-treat population**

(A) n=55. (B) n=9. (C) n=62. (D) n=62. (E) n=62. RECIST=Response Evaluation Criteria in Solid Tumors. *Post-baseline sum of target lesion diameters was not calculated for seven patients in the modified intention-to-treat population because complete tumour diameter measurements could not be obtained at any post-baseline visit; these patients were excluded from the figure. One patient did not have measurable disease at baseline, and response was evaluated from their non-target lesions by use of RECIST version 1.1. This patient was included in the modified intention-to-treat population.

Discussion

Loss of INI1 expression resulting in presumably unopposed EZH2 activity is a hallmark of epithelioid sarcoma.[12,13] Given this biology, our multicohort basket study was designed to assess the activity and safety of the EZH2 inhibitor tazemetostat in patients with solid tumours, including those with epithelioid sarcoma, which is characterised by loss of INI1/*SMARCB1*, or SWI/SNF dysfunction. In patients with INI1-deficient, advanced epithelioid sarcoma, tazemetostat administration was associated with a durable objective response in nine (15%) of 62 patients, as determined by both investigator and independent radiology review committee assessments. Additionally, a notable proportion of patients had disease control for 32 weeks or more, and 13 (21%) patients remained progression-free at 1 year. The safety profile of tazemetostat showed that this drug was well tolerated, with few dose reductions or discontinuations due to adverse events. Notably, none of the grade 3 or worse adverse events commonly observed with anthracycline-based and gemcitabine-based regimens, such as nausea, neutropenia, or thrombocytopenia, were reported.[23–25] This observation highlights tazemetostat as a potential treatment option that allows patients to remain on therapy with excellent tolerability.

In some patients, responses to tazemetostat were not observed until nearly 4 months after starting therapy—an outcome that has been observed with other epigenetic therapies—which could indicate gradual epigenetic reprogramming of tumour cells.[26,27] We found that a higher proportion of treatment-naive patients had an objective response and progression-free survival than did previously treated patients. However, it is important to note that these analyses were exploratory, and subgroups were not balanced with respect to clinical or genomic characteristics.

The published literature describing clinical outcomes in patients with epithelioid sarcoma remains scarce; outcome measures have broad CIs due to small patient populations, and most data come from retrospective reviews that lack the prospective and time-controlled requirements of clinical trials. Retrospective studies report objective response rates of up to 22% with anthracycline-based therapy and 27–58% with gemcitabine-based therapy, with median progression-free survival of 3·6 months in patients on anthracycline-based therapy and 4·8 months in those on gemcitabine-based therapy.[15,16] However, these results are not derived from prospective trials or independently reviewed radiographs. Across different therapies, objective responses in 15–22% of patients on first-line therapies and in up to 9–11% of patients on subsequent lines of therapy have been reported, with a median progression-free survival of 2·5–6·7 months in those on first-line therapies

	Grade 1–2	Grade 3	Grade 4
Non-haematological adverse events			
Fatigue	23 (37%)	1 (2%)	0
Nausea	22 (35%)	0	0
Cancer pain	17 (27%)	3 (5%)	0
Vomiting	15 (24%)	0	0
Decreased appetite	13 (21%)	3 (5%)	0
Constipation	13 (21%)	0	0
Cough	11 (18%)	0	0
Headache	11 (18%)	0	0
Diarrhoea	10 (16%)	0	0
Peripheral oedema	6 (10%)	0	0
Weight loss	6 (10%)	4 (6%)	0
Dyspnoea	5 (8%)	2 (3%)	0
Abdominal pain	5 (8%)	1 (2%)	0
Haemoptysis	4 (6%)	1 (2%)	1 (2%)
Hypertension	4 (6%)	2 (3%)	0
Weight gain	4 (6%)	1 (2%)	0
Pleural effusion	3 (5%)	3 (5%)	0
Exertional dyspnoea	2 (3%)	1 (2%)	0
Increase in blood alkaline phosphatase	2 (3%)	1 (2%)	0
Dysphagia	1 (2%)	2 (3%)	0
Increase in alanine aminotransferase	1 (2%)	2 (3%)	0
Increase in aspartate aminotransferase	1 (2%)	2 (3%)	0
Pulmonary haemorrhage	1 (2%)	1 (2%)	0
Hypercalcaemia	1 (2%)	1 (2%)	0
Flank pain	1 (2%)	1 (2%)	0
Wound infection	1 (2%)	1 (2%)	0
Pulmonary embolism	0	2 (3%)	0
Cellulitis	0	2 (3%)	0
(Continued from previous column)			
Pneumonia	0	2 (3%)	0
Brain oedema	0	0	1 (2%)
Cerebral haemorrhage	0	0	1 (2%)
Acute respiratory failure	0	0	1 (2%)
General physical health deterioration	0	1 (2%)	0
Hypercapnia	0	1 (2%)	0
Interstitial lung disease	0	1 (2%)	0
Pneumothorax	0	1 (2%)	0
Respiratory distress	0	1 (2%)	0
Respiratory failure	0	1 (2%)	0
Hypophosphataemia	0	1 (2%)	0
Aphasia	0	1 (2%)	0
Biliary tract infection	0	1 (2%)	0
Pyelonephritis	0	1 (2%)	0
Skin infection	0	1 (2%)	0
Increase in blood bilirubin	0	1 (2%)	0
Prolonged QT interval on electrocardiogram	0	1 (2%)	0
Panic attack	0	1 (2%)	0
Wound dehiscence	0	1 (2%)	0
Amenorrhoea	0	1 (2%)	0
Haematological adverse events			
Anaemia	2 (3%)	8 (13%)	0
Lymphopenia	0	0	1 (2%)

Data are n (%). All grade 1–2 events occurring in 10% or more of patients are reported. All grade 3 and grade 4 events are reported. There were eight deaths due to treatment-emergent adverse events (all due to the disease under investigation). There were no treatment-related deaths.

Table 2: **Summary of treatment-emergent adverse events (n=62)**

and 2·7–6·0 months in those on subsequent lines of therapy.[18–20] Cytotoxic chemotherapy and kinase inhibitor therapy remain a potential treatment option for this rare disease;[15–20,28] however, a need persists for more effective treatments and drugs with improved tolerability. Tolerability is particularly important when considering the young age of patients with epithelioid sarcoma, as shown by the median age of 34 years in patients recruited to this study.

Our study also explored the underlying genomic alterations that could be potential predictive biomarkers for epithelioid sarcoma. Correlative analyses between whole-genome and whole-exome sequencing data showed that 14 (37%) of 38 patients did not harbour any genomic alterations in *SMARCB1*, despite showing loss of INI1 expression. The mechanism of INI1 expression loss in the absence of *SMARCB1* mutations is currently under investigation, but it is hypothesised to result from epigenetic silencing (eg, methylation or microRNA overexpression), the effects of enhancers or super-enhancers, or post-translational modifications.[10,11,29] We analysed treatment response in patients grouped into methylation clusters; however, no correlation between methylation clusters and clinical outcomes was observed in our small sample size. Our data showed poor correlation between *SMARCB1* alterations at the DNA level and loss of INI1 by immunohistochemical staining, suggesting that genomic and proteomic approaches are needed to further understand the relationship between *SMARCB1* loss or alteration and INI1 expression. Consequently, we hypothesise that the frequency of epigenetic driver mutations across cancers could be underestimated.

Despite the rarity of epithelioid sarcoma, through international collaboration, we successfully recruited 62 patients within 18 months. This is a notable sample size; however, our findings should be interpreted with caution, because there was some variability in patient characteristics (eg, the type and number of previous anticancer treatments received). In addition, documentation of RECIST-defined radiographic progression was not required for study entry. This absence of documented progression at baseline could have resulted

in a patient cohort with more indolent disease than if objective RECIST-defined progression within a certain timeframe had been required. Another study limitation was the open-label, single-arm design, meaning that no cohort was available for direct comparison. Despite these limitations, data from this prospective trial showed that tazemetostat has meaningful clinical activity in some patients with advanced epithelioid sarcoma, and, therefore, provides another treatment option for this patient population.

In conclusion, tazemetostat treatment was associated with clinical activity in a subset of patients with advanced epithelioid sarcoma characterised by loss of INI1/*SMARCB1*. Given the favourable tolerability of this drug, there is potential for combining tazemetostat with other anticancer agents. A randomised, phase 1b/3 clinical trial of tazemetostat plus doxorubicin in the first-line setting is currently underway (NCT04204941).

Contributors

MG wrote the manuscript; MG, PS, RLJ, GMC, VMV, RC, GDD, BAVT, TL, AR, LS, SAg, and SS contributed to the study design; MG, PS, RLJ, MA, GMC, VMV, SAt, RC, TW-WC, TJ, ETL, AG, AI, GDD, RR, LED, OM, PD, BAVT, JGP, and SS collected and interpreted the data; TL, AR, LS, and SAg analysed and interpreted the data; and all authors contributed to the revision of the manuscript.

Declaration of interests

MG reports personal fees and a travel grant from Epizyme; personal fees from Springworks, Karyopharm, Daiichi, Bayer, Amgen, Tracon, Flatiron, Medscape, Physicians Education Resource, and UpToDate; and grants from the National Cancer Institute, National Institutes of Health (P30CA008748). PS reports personal fees from Deciphera; and his institution received financial support from Exelixis, Plexxikon, Eisai, Loxo, Eli Lilly, Blueprint Medicines, Ellipses Pharma, Deciphera, Merck, Servier, Genmab, Adaptimmune, Intellisphere, and Transgene. RLJ reports research grants from Merck Sharp & Dohme; and personal fees from Adaptimmune, Blueprint, Clinigen, Eisai, Epizyme, Daiichi, Deciphera, Immunedesign, Lilly, Merck, Pharmamar, Tracon, and UptoDate. MA reports personal fees from Novartis, Eli Lilly, Immune Design, Bayer, Janssen, Eisai, and Bristol Myers Squibb. GMC reports personal fees from Epizyme, PharmaMar, and Agios; non-financial support (pharmaceutical drugs for an investigator-sponsored clinical trial) from PharmaMar, Eisai, and the EMD Serono Research and Development Institute; financial support to his institution for the conduct of clinical trials from Epizyme, PharmaMar, Agios, Otsuka, Amgen, Eisai, Macrogenics, Boston Biomedical, Plexxicon, EMD Serono Research and Development Institute, CBA Pharma, SpringWorks Therapeutics, Bavarian-Nordic, Aileron Therapeutics, and Bayer. VMV reports personal fees from Epizyme, Lilly, Nanocarrier, Agios, Daiichi, Novartis, Janssen, Springworks, AbbVie, and Blueprint. SAt reports research grants from the Desmoid Tumour Research Foundation; personal fees from Immune Design; and research grants to his institution from AB Science, TRACON Pharma, CytRx Corporation, Bayer, Novartis, Daiichi Sankyo, Eli Lilly, Immune Design, Karyopharm Therapeutics, Epizyme, Blueprint Medicines, Genmab, CBA Pharma, Merck, Philogen, Gradalis, Deciphera, Takeda, Incyte, Springworks, Adaptimmune, Advenchen Laboratories, Bavarian Nordic, BTG, PTC Therapeutics, GlaxoSmithKline, and FORMA Therapeutics. RC reports grants from Epizyme, Aadi Bioscience, Novartis, Springworks, Plexxikon, Advenchen, Mundipharma, Pfizer; personal fees from Epizyme, Janssen, and Immune Design; and non-financial support from Janssen, Springworks, and GlaxoSmithKline. TW-WC reports grants from Eisai; personal fees from Eisai, Novartis, Eli Lilly, Roche, Bayer, and Pfizer; non-financial support from Epizyme, Eisai and Novartis; travel sponsorship from Eisai, Roche, and Pfizer; and manuscript preparation support from Epizyme. TJ reports grants from Aduro Pharma, AstraZeneca, Bristol Myers Squib, Eli Lilly, Epizyme, Polaris Pharma, and Trizell; and non-financial support from Atara Pharmaceuticals. AI reports personal fees from Epizyme. GDD reports grants from Epizyme, Novartis, Bayer, Pfizer, Loxo Oncology, AbbVie, Daiichi-Sankyo, Adaptimmune, GlaxoSmithKline, Janssen, PharmaMar, Roche-Genentech, and Ignyta; personal fees from Epizyme, Novartis, Bayer, Pfizer, EMD-Serono, Sanofi, Loxo Oncology, AbbVie, Mirati Therapeutics, Daiichi-Sankyo, WIRB Copernicus Group, ZioPharm, Polaris Pharmaceuticals, MJ Hennessey-OncLive, Adaptimmune, Blueprint Medicines, Merrimack Pharmaceuticals, G1 Therapeutics, CARIS Life Sciences, CHAMPIONS Oncology, Janssen, PharmaMar, Translate BIO, Roche-Genentech, and Ignyta; non-financial support from Epizyme, Novartis, AbbVie, Daiichi-Sankyo, PharmaMar, and Roche-Genentech; travel support from Epizyme, Novartis, Bayer, Pfizer, EMD-Serono, Loxo Oncology, Daiichi-Sankyo, WIRB Copernicus Group, MJ Hennessey-OncLive, Adaptimmune, Blueprint Medicines, Merrimack Pharmaceuticals, CARIS Life Sciences, PharmaMar, and Roche-Genentech; equity or equity options from Blueprint Medicines, Merrimack Pharmaceuticals, G1 Therapeutics, CARIS Life Sciences, Bessor Pharmaceuticals, ERASCA Pharmaceuticals, CHAMPIONS Oncology, and Translate BIO; and a use patent on imatinib for gastrointestinal stromal tumours through Novartis, with royalties paid to Dana-Farber. RR reports personal fees from Epizyme. LED reports personal fees and support for the conduct of clinical trials from Epizyme. OM reports personal fees from Amgen, Bristol Myers Squibb, Eli Lilly, Ipsen, Janssen, Lundbeck, Merck Sharp & Dohme, Pfizer, Roche, Servier, and Vifor Pharma; and non-financial support from Blueprint Medicines. BAVT reports research grants from Pfizer, Merck, and Tracon; and personal fees from Epizyme, Pfizer, Eli Lilly, CytRx, Janssen, CARIS Life Sciences, Bayer, Immune Design, Daiichi-Sankyo, Adaptimmune, GlaxoSmithKline, and Plexxicon. JGP reports personal fees from General Dynamics and Cellectar; and financial support to his institution for the conduct of clinical trials from Epizyme. TL, AR, LS, and SAg are employees of and own stock in Epizyme. SS reports personal fees from Epizyme and Eli Lilly; and research funding to his institution from Epizyme, Novartis, and Eli Lilly. ETL, AG, and PD declare no competing interests.

Data sharing

Individual deidentified participant data that underlie the results reported in this Article will be made available on a case-by-case basis, including the study protocol and statistical analysis plan. Data availability will begin 9 months after publication and end 36 months after publication. To gain access, data requestors should submit a proposal to istgrants@epizyme.com. Proposals will be reviewed by an independent review committee.

Acknowledgments

This study was funded by Epizyme. We thank all of the patients, caregivers, and families who have contributed to the study. We acknowledge Neil Michaud and Scott Daigle for their contributions to the molecular pathology analysis, and Jay Yang for providing statistical assistance. The results published here on tumour mutational burden are, in part, based on data generated by The Cancer Genome Atlas Research Network. Support for third party editorial assistance was provided by Meredith Kalish of Ashfield Healthcare Communications (Lyndhurst, NJ, USA), and funded by Epizyme. A medical writer, funded by Epizyme, did the literature search. VMV was affiliated to the University of Colorado Denver (Aurora, CO, USA) at the time the study was done, but is now affiliated to Janssen Pharmaceuticals (Spring House, PA, USA). LS was affiliated to Epizyme (Cambridge, MA, USA) at the time the study was done, but is now affiliated to Bristol Myers Squibb (Cambridge, MA, USA).

For more on **The Cancer Genome Atlas Research Network** see https://www.cancer.gov/tcga

References

1 Allis CD, Jenuwein T. The molecular hallmarks of epigenetic control. *Nat Rev Genet* 2016; **17:** 487–500.

2 Fratta E, Montico B, Rizzo A, Colizzi F, Sigalotti L, Dolcetti R. Epimutational profile of hematologic malignancies as attractive target for new epigenetic therapies. *Oncotarget* 2016; **7:** 57327–50.

3 Kadoch C, Hargreaves DC, Hodges C, et al. Proteomic and bioinformatics analysis or mammalian SWI/SNF complexes identifies extensive roles in human malignancy. *Nat Genet* 2013; **45:** 592–601.

4 Schwartzentruber J, Korshunov A, Liu XY, et al. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. *Nature* 2012; **482:** 226–31.

5 Nacev BA, Feng L, Bagert JD, et al. The expanding landscape of 'oncohistone' mutations in human cancers. *Nature* 2019; **567:** 473–78.

6 Arnaud O, Le Loarer F, Tirode F. BAFfling pathologies: alterations of BAF complexes in cancer. *Cancer Lett* 2018; **419**: 266–79.

7 Ramos P, Karnezis AN, Craig DW. Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in SMARCA4. *Nat Gen* 2014; **46:** 427–29.

8 Phelan ML, Sif S, Narlikar GJ, Kingston RE. Reconstitution of a core chromatin remodeling complex from SWI/SNF subunits. *Mol Cell* 1999; **3:** 247–53.

9 Wilson BG, Wang X, Shen X, et al. Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. *Cancer Cell* 2010; **18:** 316–28.

10 Papp G, Krausz T, Stricker TP, Szendrői M, Sápi Z. SMARCB1 expression in epithelioid sarcoma is regulated by miR-206, miR-381, and miR-671–5p on both mRNA and protein levels. *Genes Chromosomes Cancer* 2014; **53:** 168–76.

11 Sápi Z, Papp G, Szendrői M, et al. Epigenetic regulation of SMARCB1 by miR-206, -381 and -671–5p is evident in a variety of SMARCB1 immunonegative soft tissue sarcomas, while miR-765 appears specific for epithelioid sarcoma. A miRNA study of 223 soft tissue sarcomas. *Genes Chromosomes Cancer* 2016; **55:** 786–802.

12 Modena P, Lualdi E, Facchinetti F, et al. SMARCB1/INI1 tumor suppressor gene is frequently inactivated in epithelioid sarcomas. *Cancer Res* 2005; **65:** 4012–19.

13 Chbani L, Guillou L, Terrier P, et al. Epithelioid sarcoma: a clinicopathologic and immunohistochemical analysis of 106 cases from the French sarcoma group. *Am J Clin Pathol* 2009; **131:** 222–27.

14 de Visscher SA, van Ginkel RJ, Wobbes T, et al. Epithelioid sarcoma: still an only surgically curable disease. *Cancer* 2006; **107:** 606–12.

15 Frezza AM, Jones RL, Lo Vullo S, et al. Anthracycline, gemcitabine, and pazopanib in epithelioid sarcoma: a multi-institutional case series. *JAMA Oncol* 2018; **4:** e180219.

16 Pink D, Richter S, Gerdes S, et al. Gemcitabine and docetaxel for epithelioid sarcoma: results from a retrospective, multi-institutional analysis. *Oncology* 2014; **87:** 95–103.

17 Spillane AJ, Thomas JM, Fisher C. Epithelioid sarcoma: the clinicopathological complexities of this rare soft tissue sarcoma. *Ann Surg Oncol* 2000; **7:** 218–25.

18 Gounder MM, Merriam P, Ratan R, et al. Real-world outcomes of patients with locally advanced or metastatic epithelioid sarcoma. *Ann Oncol* 2019; **30** (suppl 5)**:** 1687P (abstr).

19 Touati N, Schöffski P, Litiere S, et al. European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group experience with advanced/metastatic epithelioid sarcoma patients treated in prospective trials: clinical profile and response to systemic therapy. *Clin Oncol (R Coll Radiol)* 2018; **30:** 448–54.

20 Jones RL, Constantinidou A, Olmos D, et al. Role of palliative chemotherapy in advanced epithelioid sarcoma. *Am J Clin Oncol* 2012; **35:** 351–57.

21 Italiano A, Soria JC, Toulmonde M, et al. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. *Lancet Oncol* 2018; **19:** 649–59.

22 Grunwald V, Litière S, Young R, et al. Absence of progression, not extent of tumour shrinkage, defines prognosis in soft-tissue sarcoma - an analysis of the EORTC 62012 study of the EORTC STBSG. *Eur J Cancer* 2016; **64:** 44–51.

23 Eli Lilly and Company. Highlights of prescribing information: GEMZAR (gemcitabine for injection). 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020509s082lbl.pdf (accessed Sept 8, 2020).

24 Janssen Products. Highlights of prescribing information: DOXIL (doxorubicin hydrochloride liposome injection). 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/050718s055lbl.pdf (accessed Sept 8, 2020).

25 Pfizer. Highlights of prescribing information: ELLENCE (epirubicin hydrochloride injection). 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/050778s024s025lbl.pdf (accessed Sept 8, 2020).

26 Silverman LR, Fenaux P, Mufti GJ, et al. Continued azacitidine therapy beyond time of first response improves quality of response in patients with higher-risk myelodysplastic syndromes. *Cancer* 2011; **117:** 2697–702.

27 Shen L, Kantarjian H, Guo Y, et al. DNA methylation predicts survival and response to therapy in patients with myelodysplastic syndromes. *J Clin Oncol* 2010; **28:** 605–13.

28 In GK, Hu JS, Tseng WW. Treatment of advanced, metastatic soft tissue sarcoma: latest evidence and clinical considerations. *Ther Adv Med Oncol* 2017; **9:** 533–50.

29 Papp G, Changchien YC, Péterfia B, et al. SMARCB1 protein and mRNA loss is not caused by promoter and histone hypermethylation in epithelioid sarcoma. *Mod Pathol* 2013; **26:** 393–403.