Results of the Phase 1b Soft-Tissue Sarcoma Portion of the Global, Randomized, Double-Blind, Placebo-Controlled Study of Tazemetostat Plus Doxorubicin as Frontline Therapy for Advanced Epithelioid Sarcoma

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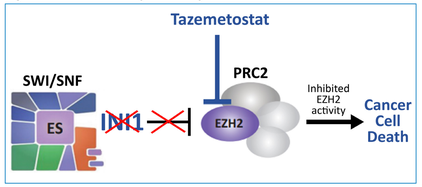
Introduction

- Epithelioid sarcoma (ES) is a rare, aggressive subtype of soft-tissue sarcoma (STS) that can originate in any anatomic location, predominantly affecting young adults (<40 years of age)[1]
- Cytotoxic chemotherapy has limited effectiveness in ES, with a median progression-free survival (PFS) of 4 months and 6 months for gemcitabine- and anthracycline-based therapies, respectively[2]
  - Patients with advanced ES are treated with palliative chemotherapy, but median overall survival (OS) is <12 months[3]
- In more than 90% of cases, ES is characterized by the loss of function of integrase interactor 1 (INI1),[4] a critical component of epigenetic regulation via the switch/sucrose nonfermentable (SWI/SNF) protein complex[5]
  - The loss of INI1 may allow enhancer of zeste homolog 2 (EZH2), a catalytic subunit of the polycomb repressive complex 2 (PRC2), to repress cell differentiation and promote tumorigenesis via increased trimethylation of histone H3 at lysine 27 (H3K27)[5]
- Tazemetostat is a selective, oral, small-molecule inhibitor of EZH2, with demonstrated clinical activity and a favorable safety profile; it is approved by the US FDA as a single agent in adults and pediatric patients aged 16 years and older with metastatic or locally advanced ES not eligible for complete resection[6,7] (**Figure 1**)

***Figure 1. Mechanism of Action of Tazemetostat*[5,7]**



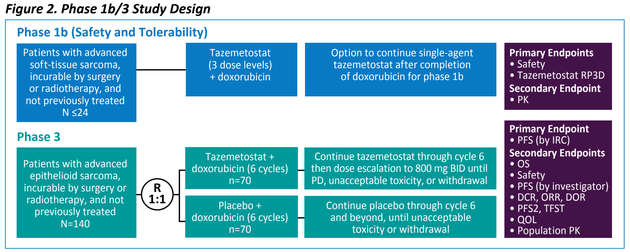
ES, epithelioid sarcoma; EZH2, enhancer of zeste homolog 2; INI1, integrase interactor 1; PRC2, polycomb repressive complex 2; SWI/SNF, switch/sucrose nonfermentable.

  - In a multicenter phase 2 study in patients with INI1-negative ES (n=62), tazemetostat was well tolerated and was associated with a 15% objective response rate and a median OS of 19 months[8]
- Combination therapy with tazemetostat and doxorubicin is supported by results from preclinical studies using, and conducted in, an ES cell line in which the combination elicited synergistic antiproliferative activity and in a mouse xenograft model of synovial sarcoma in which tazemetostat and doxorubicin demonstrated synergistic superior antitumor activity compared with what was observed for each drug alone[9-11]
- Here, we present the recommended phase 3 dose and the safety results from the phase 1b stage of a phase 1b/3 study (NCT04204941) of tazemetostat + doxorubicin in patients with advanced STS

Methods

- This phase 1b/3 multicenter, global, randomized, double-blind, placebo–controlled study (NCT04204941) is evaluating the safety and efficacy of tazemetostat in combination with doxorubicin as frontline therapy for advanced ES (**Figure 2; Table 1**)
- The phase 1b portion was designed to assess the safety of and identify the recommended phase 3 dose of tazemetostat in combination with standard-of-care doxorubicin in patients with advanced soft-tissue sarcoma

Figure 2. Phase 1b/3 Study Design



DCR, disease control rate; DOR, duration of response; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival 2; PK, pharmacokinetics; QOL, quality of life; RP3D, recommended phase 3 dose; TFST, time to first subsequent therapy.

Table 1. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
Life expectancy of ≥3 months before enrollment	Prior systemic anticancer therapy (for both safety run-in and phase 3)
Phase 1b: 18–65 years of age Phase 3: ≥18 years of age	Prior exposure to tazemetostat or other EZH2 inhibitor
Histologically confirmed disease, incurable by surgery or radiotherapy • Phase 1b: histologically confirmed STS • Phase 3: morphology and immunophenotypic panel consistent with epithelioid sarcoma (eg, CD34, EMA, keratin, and INI1)	History of myeloid malignancies (including MDS or AML), or T-LBL/T-ALL
Measurable disease (RECIST 1.1)	Major surgery within 4 weeks before first dose of study treatment
ECOG PS 0–2	Active infection with HBV or HCV
Adequate hematologic, renal, and hepatic function	Clinically significant cardiovascular disease

AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; EZH2, enhancer of zeste homolog 2; EMA, epithelial membrane antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; INI1, integrase interactor 1; MDS, myelodysplastic syndrome; RECIST, Response Evaluation Criteria in Solid Tumors; STS, soft-tissue sarcoma; T-ALL, T-cell acute lymphoblastic leukemia; T-LBL, T-cell lymphoblastic lymphoma.

Phase 1b

- A standard 3 + 3 dose escalation design was used to assess tazemetostat 400 mg, 600 mg, and 800 mg administered orally twice daily (BID) in combination with doxorubicin (75 mg/m^2 intravenously on day 1 of each cycle, for up to 6 cycles) as frontline therapy
  - If a dose-limiting toxicity (DLT) occurred in 1 of 3 patients at a given dose level, 3 additional patients were enrolled at that dose level
  - If no DLT was observed in the first 3 patients at a given dose level or in only 1 of the 6 patients, dose escalation would proceed to the next-higher dose level
  - DLTs were predefined in the protocol
- The maximum tolerated dose (MTD) was defined as the highest dose level at which fewer than one third of patients (0/3 or 1/6 patients) experienced a DLT
- The recommended phase 3 dose of tazemetostat was determined by a safety review committee following review of the safety and pharmacokinetic (PK) data from the phase 1b trial, with a target DLT rate of <33%
- Up to 12 patients may be enrolled at the MTD to collect additional safety and PK data
- After completion of doxorubicin treatment, patients were eligible to continue receiving single-agent tazemetostat therapy at 800 mg BID until disease progression or intolerable toxicity
- A safety review committee was responsible for ongoing data review and for ensuring patient safety during dose escalation
- Tumor response (RECIST v.1.1) per investigator assessment was recorded

Results

Patients

- As of February 23, 2021, 18 patients were enrolled; 11 are still receiving tazemetostat + doxorubicin, and 7 patients discontinued (5 because of disease progression, 1 refused further treatment, 1 because of death attributed to disease progression)
  - The most common sarcoma subtype was leiomyosarcoma (n=3)
- The median age at baseline was 52.5 years (range, 29–82) and all had unresectable STS (**Table 2**)
- Median (range) time on treatment was 12.4 (0.1–54.1) weeks across all dose levels evaluated

Table 2. Baseline Demographics and Disease Characteristics

Characteristic	Tazemetostat + Doxorubicin N=18
Age	
Median (range), years	52.5 (29–82)
>65 years, n (%)	5 (27.8)
<65 years, n (%)	13 (72.2)
Sex, n (%)	
Male	6 (33.3)
Female	12 (66.7)
Race, n (%)	
White	16 (88.9)
American Indian or Alaskan native	1 (5.6)
Other	1 (5.6)
ECOG PS, n (%)	
0	3 (16.7)
1	15 (83.3)
Tumor type, n (%)	
Soft-tissue sarcoma	18 (100)
Epithelioid sarcoma	2 (11.1)
Metastatic disease, n (%)	13 (72.2)
Stage at diagnosis, n (%)	
I	0
II	0
III	4 (22.2)
IV	13 (72.2)
Not applicable	0
Unknown	1 (5.6)
Median time from last disease progression to study entry (range), months	1.38 (0.3, 29.0)
Type of sarcoma	
Leiomyosarcoma	3 (16.7)
Distal epithelioid sarcoma	2 (11.1)
Myxofibrosarcoma	2 (11.1)
Pleomorphic sarcoma	2 (11.1)
Liposarcoma	1 (5.6)
Smarca4-deficient sarcoma	1 (5.6)
Synovial sarcoma	1 (5.6)
Endometrial stromal sarcoma	1 (5.6)
Chondrosarcoma	1 (5.6)
Soft-tissue retroperitoneal sarcoma	1 (5.6)
Spindle cell sarcoma	1 (5.6)
Missing	2 (11.1)

Note: Not all percentages sum to 100% because of rounding.
ECOG PS, Eastern Cooperative Oncology Group performance status.

Dose-Limiting Toxicities

- Two DLTs, both of febrile neutropenia, were observed, one in the tazemetostat 600 mg BID + doxorubicin cohort (n=1/6; 17%) and one in the tazemetostat 800 mg BID + doxorubicin cohort (n=1/6; 17%)
- No doses of tazemetostat above the approved dose of 800 mg BID were tested in combination in this study

Recommended Phase 3 Dose

- Following the safety and PK data review by the safety review committee, the RP3D of tazemetostat was determined to be 800 mg BID when used in combination with doxorubicin

Safety

- Treatment-emergent adverse events (TEAEs) led to study drug interruption in 14 patients and to dose reduction in 7 patients; no TEAEs led to study drug discontinuation (**Table 3**)
  - No dose response was observed regarding the nature, frequency, or severity of TEAEs

Table 3. Overview of Treatment-Emergent Adverse Events

Patient, n (%)	Tazemetostat + Doxorubicin N=18
Any TEAE	16 (88.9)
Any TEAE grade 3 or 4	15 (83.3)
Any TEAE leading to dose reduction	7 (38.9)
Any TEAE leading to study drug interruption	14 (77.8)
Any TEAE leading to study discontinuation	0
Any TEAE leading to withdrawal from study	0
Any TESAE	13 (72.2)
Any treatment-related TESAE	10 (55.6)
Any protocol-defined AE of special interest	0

AE, adverse event; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

- Treatment-related TEAEs of any grade occurred in 16 patients; grade 3 or 4 treatment-related TEAEs occurred in 14 patients
  - Treatment-related TEAEs were defined as attributable to either study agent
- The most common treatment-related TEAEs were neutropenia, anemia, and fatigue (**Table 4**)

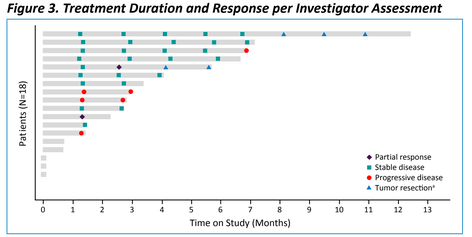
Table 4. Most Common All-Grade Treatment-Related TEAEs (Occurring in ≥20% of Patients)

Preferred Term, n (%)	Tazemetostat + Doxorubicin N=18
Neutropenia	12 (66.7)
Anemia	10 (55.6)
Fatigue	10 (55.6)
Nausea	10 (55.6)
Stomatitis	9 (50.0)
Febrile neutropenia	7 (38.9)
Vomiting	7 (38.9)
Constipation	6 (33.3)
Decreased appetite	5 (27.8)

Exposure Response Analysis

- Two patients (1 in each of the 600-mg and 800-mg dose cohorts) achieved a partial response, and 8 (44%) patients achieved a best response of stable disease (**Figure 3**)
- Two patients, one with myxofibrosarcoma and one with myxoid liposarcoma (1 each in the 400-mg and 600-mg dose cohorts), achieved tumor changes that enabled surgical resection, even though the tumors did not meet RECIST criteria for a partial response
  - Both patients remain without evidence of disease

Figure 3. Treatment Duration and Response per Investigator Assessment



*Pathology of two fully resected masses showed evidence of clinical activity, even though the tumors did not meet RECIST criteria for a partial response.

Conclusions

- Tazemetostat 800 mg BID + doxorubicin is the recommend dose to be tested in the phase 3 portion of the trial
- The safety profile of this combination was consistent with the respective safety information for tazemetostat and for doxorubicin; treatment-related TEAEs include known toxicities of the individual agents[8,12]
- The global, double-blind, randomized, phase 3 confirmatory trial will assess the efficacy and safety of tazemetostat 800 mg BID + doxorubicin compared with placebo + doxorubicin in patients with ES who have unresectable disease and have not received prior systemic therapy

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