# Update on Phase 1 Study of Tazemetostat, an Enhancer of Zeste Homolog 2 Inhibitor, in Pediatric Patients With Relapsed or Refractory Integrase Interactor 1–Negative Tumors

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## INTRODUCTION

- A defining feature of malignant rhabdoid tumors (MRTs), epithelioid sarcoma (ES), poorly differentiated chordomas, and other tumor types is the loss of *SMARCB1 (INI1)* expression, which induces dependence on enhancer of zeste homolog 2 (EZH2)[1-3]
  - MRTs and their central nervous system (CNS) counterpart, atypical teratoid rhabdoid tumors (ATRTs), are rare but aggressive cancers associated with poor survival outcomes in pediatric populations[4,5]
  - Poorly differentiated chordoma is an emerging class of chordoma associated with a particularly aggressive course of disease among pediatric patients[2]
- Tazemetostat is a selective EZH2 inhibitor approved by the US Food and Drug Administration for treatment of patients aged ≥16 years with metastatic or locally advanced ES who are ineligible for complete resection[6]
- The EZH-102 study (NCT02601937) is a phase 1, multicenter, open-label, dose escalation (phase 1a) and dose expansion (phase 1b) study evaluating tazemetostat monotherapy in pediatric patients with relapsed or refractory (R/R) *SMARCB1 (INI1)*-negative tumors
- Data from the pediatric dose escalation study and interim efficacy and safety data from the dose expansion study were previously reported[7]
  - Objective response rates (ORRs; complete response [CR] + partial response) were 19% for patients with ATRT (4/21), 50% for those with chordoma (2/4), and 29% for patients with ES (2/7) in the dose expansion cohort

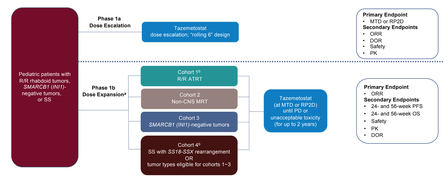
## OBJECTIVE

- To report updated efficacy, safety, subgroup analyses, and translational results from the EZH-102 dose escalation and dose expansion study

## METHODS

- The EZH-102 study is evaluating tazemetostat ≤2400 mg/m$^2$ daily as monotherapy in pediatric patients with R/R *SMARCB1 (INI1)*-negative tumors, rhabdoid tumors, and synovial sarcoma
- Phase 1b enrolled patients based on tumor type (**Figure 1**); all patients received tazemetostat in continuous 28-day cycles as an oral suspension (cohorts 1–3) or as a tablet (cohort 4)
  - Cohort 1: patients with ATRTs
  - Cohort 2: patients with non–CNS MRTs (including MRTs, rhabdoid tumors of the kidney [RTK], and selected tumors with rhabdoid features)
  - Cohort 3: patients with *SMARCB1 (INI1)*-negative tumors (including ES and poorly/de-differentiated chordoma)
  - Cohort 4: patients with synovial sarcoma with *SS18-SSX* rearrangement OR tumor types eligible for cohorts 1–3

**Figure 1.** Study Design




[a]Tazemetostat administered as an oral suspension in cohorts 1–3 and as tablets in cohort 4 in the dose expansion phase.
[b]Cohort closed to enrollment.
ATRT, atypical teratoid rhabdoid tumor; CNS, central nervous system; DOR, duration of response; MRT, malignant rhabdoid tumor; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; RP2D, recommended phase 2 dose; R/R, relapsed or refractory; SS, synovial sarcoma.

## RESULTS

- A total of 109 patients were enrolled as of October 22, 2021 (escalation, n=46; expansion, n=63; **Table 1**), with mean ages of 5.4 years in the dose escalation and 7.4 years in the dose expansion
  - Patients in the dose expansion study received tazemetostat 520 mg/m$^2$ BID, 800 mg/m$^2$ three times daily (TID), or 1200 mg/m$^2$ BID (**Table 2**)

**Table 1. Baseline Demographics and Disease Characteristics**

| Characteristic | Dose Escalation n=46 | Dose Expansion n=63 |
|---|---|---|
| Median age (range), years | 3.0 (0.8–15.0) | 4.0 (0.9–21.0) |
| Sex, n (%) | | |
| Male | 20 (43.5) | 30 (47.6) |
| Female | 26 (56.5) | 33 (52.4) |
| Prior lines of therapy, n (%) | | |
| 0 | 0 | 5 (7.9) |
| 1–2 | 29 (63.0) | 43 (68.3) |
| ≥3 | 17 (37.0) | 15 (23.8) |
| Median (range), n | 2 (1–6) | 2 (0–9) |
| Prior radiotherapy, n (%) | 32 (69.6) | 48 (76.2) |
| Tumor type, n (%) | | |
| ATRT | 20 (43.5) | 21 (33.3) |
| MRT | 9 (19.6) | 14 (22.2) |
| RTK | 1 (2.2) | 5 (7.9) |
| Selected tumors with rhabdoid features | 0 | 2 (3.2) |
| ES | 2 (4.3) | 9 (14.3) |
| Myoepithelial carcinoma | 1 (2.2) | 2 (3.2) |
| Renal medullary carcinoma | 2 (4.3) | 1 (1.6) |
| Chordoma (poorly differentiated or de-differentiated) | 1 (2.2) | 6 (9.5) |
| Other *SMARCB1*-negative malignant tumors | 8 (17.4) | 2 (3.2) |
| *SS* with *SS18-SSX* rearrangement | 2 (4.3) | 1 (1.6) |

ATRT, atypical teratoid rhabdoid tumor; ES, epithelioid sarcoma; MRT, malignant rhabdoid tumor; RTK, rhabdoid tumor of the kidney; SS, synovial sarcoma.

**Table 2. Escalation and Expansion Phase Dosing**

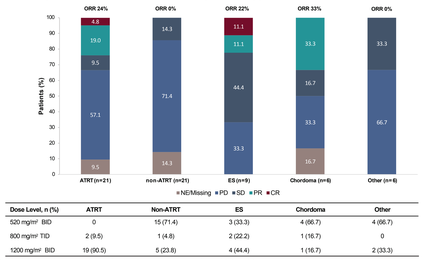
| Dosing Phase, n | 240 mg/m$^2$ n=8 | 300 mg/m$^2$ n=6 | 400 mg/m$^2$ n=6 | 520 mg/m$^2$ n=33 | 700 mg/m$^2$ n=6 | 800 mg/m$^2$[a] n=6 | 900 mg/m$^2$ n=6 | 1200 mg/m$^2$ n=38 | Total N=109 |
|---|---|---|---|---|---|---|---|---|---|
| Escalation | 8 | 6 | 6 | 7 | 6 | 0 | 6 | 7 | 46 |
| Expansion | 0 | 0 | 0 | 26 | 0 | 6 | 0 | 31 | 63 |

Dosed (mg/m$^2$) twice daily unless otherwise noted.
[a]Three times daily.

### Efficacy

- ORRs were 7% (3/46; CR, 4%) in the dose escalation study and 14% (9/63; CR, 3%) in the dose expansion study
  - Per tumor category in the dose expansion study, ORRs were 24% (5/21) in ATRT, 22% (2/9) in ES, 33% (2/6) chordoma, 0% in non–CNS MRTs (0/21), and 0% in other tumors (0/6) (**Figure 2**)
- ORR for patients with prior radiotherapy was 14% (11/80) vs 3% (1/29) without prior radiotherapy across both cohorts

**Figure 2. Response Rates in Dose Escalation, by Tumor Type and Dose Level[a,b]**

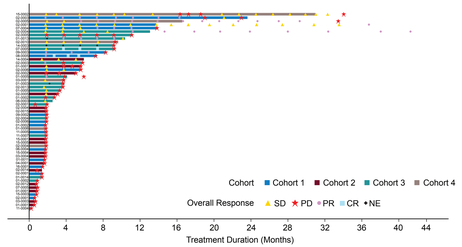



| Dose Level, n (%) | ATRT | Non-ATRT | ES | Chordoma | Other |
|---|---|---|---|---|---|
| 520 mg/m$^2$ BID | 0 | 15 (71.4) | 3 (33.3) | 4 (66.7) | 4 (66.7) |
| 800 mg/m$^2$ TID | 2 (9.5) | 1 (4.8) | 2 (22.2) | 1 (16.7) | 0 |
| 1200 mg/m$^2$ BID | 19 (90.5) | 5 (23.8) | 4 (44.4) | 1 (16.7) | 2 (33.3) |

[a]ORR calculated as the percentage of patients achieving a confirmed CR or PR using disease-appropriate standardized response criteria from the start of tazemetostat treatment until disease progression or the start of subsequent anticancer therapy.
[b]Efficacy in solid tumors was evaluated using RECIST 1.1 criteria; CNS tumors were evaluated using RANO criteria.
ATRT, atypical rhabdoid tumors; BID, twice daily; CR, complete response, ES, epithelioid sarcoma; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TID, three times daily.

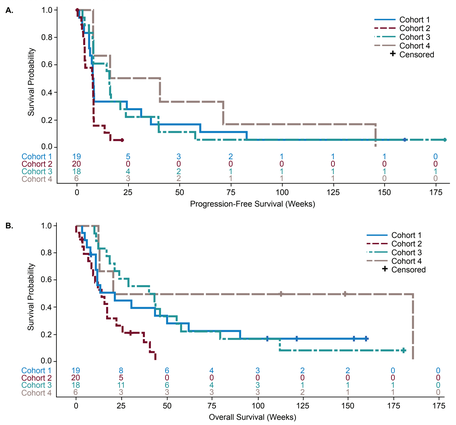
- In the dose expansion study, median duration of exposure was 8.0 weeks (2 months) (range: 0.3–134.7 weeks [0.1–33.7 months]) (**Figure 3**)
- Median PFS and OS were greater in cohort 4 than in the other cohorts, although the ranges were similar across all cohorts
  - Median PFS was 8 weeks (95% confidence interval [CI]: 8–13) (**Figure 4A**)
  - Median OS was 21 weeks (95% CI: 13–38) (**Figure 4B**)

**Figure 3. Time on Treatment in Dose Expansion Cohorts[a]**




[a]Upon disease progression, patients may have been rechallenged with tazemetostat at a dose of 520 mg/m$^2$ BID (for patients without an ATRT) or 1200 mg/m$^2$ BID (for ATRT or any *SMARCB1*-negative tumors with CNS involvement), at the investigator's discretion.
ATRT, atypical teratoid rhabdoid tumor; BID, twice daily; CNS, central nervous system; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

**Figure 4. Kaplan-Meier Curves in Dose Expansion Cohorts for (A) Progression-Free Survival and (B) Overall Survival**




### Safety

- Rates of any-grade treatment-emergent adverse events (TEAEs) were 96% in the dose escalation study and 98% in the dose expansion study (**Table 3**)
  - Grade 3/4 TEAE rates were 54% in the dose escalation study and 64% in the dose expansion study
  - The most common TEAEs of any grade were vomiting, pyrexia, fatigue, headache, and nausea
- In the dose escalation and expansion studies, any-grade TEAEs led to the following:
  - Dose reductions in 13% and 11% of patients, respectively
  - Study drug discontinuations in 9% and 2% of patients, respectively

**Table 3. Most Common Treatment-Emergent Adverse Events (≥10% Incidence)**

| TEAE, n (%) | Dose Escalation Study n=46 | | Dose Expansion Study n=63 | |
|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Any TEAE | 44 (95.7) | 25 (54.3) | 62 (98.4) | 40 (63.5) |
| Vomiting | 19 (41.3) | 0 | 36 (57.1) | 2 (3.2) |
| Pyrexia | 13 (28.3) | 2 (4.3) | 18 (28.6) | 1 (1.6) |
| Fatigue | 12 (26.1) | 0 | 13 (20.6) | 0 |
| Headache | 12 (26.1) | 0 | 15 (23.8) | 0 |
| Nausea | 12 (26.1) | 0 | 25 (39.7) | 0 |
| Cough | 11 (23.9) | 0 | 19 (30.2) | 0 |
| Constipation | 10 (21.7) | 0 | 11 (17.5) | 0 |
| Diarrhea | 10 (21.7) | 2 (4.3) | 19 (30.2) | 2 (3.2) |
| Anemia | 8 (17.4) | 4 (8.7) | 17 (27.0) | 7 (11.1) |
| Decreased appetite | 8 (17.4) | 1 (2.2) | 16 (25.4) | 2 (3.2) |
| Nasal congestion | 7 (15.2) | 0 | 5 (7.9) | 0 |
| Abdominal pain | 6 (13.0) | 1 (2.2) | 9 (14.3) | 0 |
| Otitis media | 5 (10.9) | 1 (2.2) | 4 (6.3) | 1 (1.6) |
| Platelet count decreased | 5 (10.9) | 3 (6.5) | 3 (4.8) | 1 (1.6) |
| Pneumonia | 5 (10.9) | 2 (4.3) | 2 (3.2) | 1 (1.6) |
| Upper respiratory tract infection | 5 (10.9) | 0 | 6 (9.5) | 0 |
| Lymphocyte count decreased | 4 (8.7) | 2 (4.3) | 7 (11.1) | 3 (4.8) |
| Tumor pain | 3 (6.5) | 1 (2.2) | 9 (14.3) | 6 (9.5) |
| Hypertension | 3 (6.5) | 0 | 7 (11.1) | 2 (3.2) |
| Edema, peripheral | 1 (2.2) | 0 | 8 (12.7) | 1 (1.6) |
| Asthenia | 0 | 0 | 7 (11.1) | 1 (1.6) |

TEAE, treatment-emergent adverse event.

- Any-grade treatment-related TEAE (TR-TEAE) rates were 72% in the dose escalation study and 78% in the dose expansion study (**Table 4**)
  - Grade 3/4 TR-TEAE rates were 15% in the dose escalation study and 22% in the dose expansion study
- Serious TR-TEAE rates were 9% in the dose escalation and 10% in the dose expansion studies

**Table 4. Most Common Treatment-Related Treatment-Emergent Adverse Events (≥10% Incidence)**

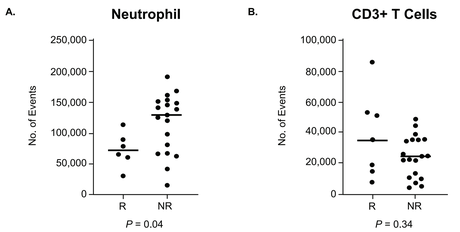
| TR-TEAE, n (%) | Dose Escalation Study n=46 | | Dose Expansion Study n=63 | |
|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Any TR-TEAE | 33 (71.7) | 7 (15.2) | 49 (77.8) | 14 (22.2) |
| Vomiting | 12 (26.1) | 0 | 28 (44.4) | 0 |
| Fatigue | 10 (21.7) | 0 | 8 (12.7) | 0 |
| Nausea | 7 (15.2) | 0 | 21 (33.3) | 0 |
| Platelet count decreased | 5 (10.9) | 3 (6.5) | 2 (3.2) | 1 (1.6) |
| Diarrhea | 5 (10.9) | 0 | 9 (14.3) | 2 (3.2) |
| Constipation | 5 (10.9) | 0 | 4 (6.3) | 0 |
| Decreased appetite | 3 (6.5) | 0 | 8 (12.7) | 1 (1.6) |
| Anemia | 2 (4.3) | 1 (2.2) | 11 (17.5) | 4 (6.3) |

TR-TEAE, treatment-related treatment-emergent adverse event.

### Translational Results

- There were significant differences between responders (R) and nonresponders (NR) at cycle 1, day 1 (C1D1) for neutrophil counts ($P$<0.05) (**Figure 5**)
  - All responders (6/6) had <125,000 total neutrophils at C1D1 vs 42% (8/19) of nonresponders
  - 50% (3/6) of responders had >50,000 total cluster of differentiation 3 (CD3) T cells vs 0% (0/19) of nonresponders

**Figure 5. Differences at Cycle 1, Day 1 Between Responders and Nonresponders in (A) Neutrophil Count and (B) CD3 T-Cell Count**




C1D1, cycle 1 day 1; NR, nonresponder; R, responder.

## METHODS, cont'd

- Dose expansion study endpoints
  - Primary endpoint: ORR
  - Secondary endpoints: progression-free survival (PFS), overall survival (OS), safety/tolerability, pharmacokinetic measures, and duration of response (DOR)
  - Exploratory endpoint: selected flow analysis using 250,000 cells from peripheral blood for up to 25 patients
- Key inclusion criteria
  - Patients ≥6 months to <18 years of age
    - Patients in cohort 4 only: >10 years to <18 years of age
  - R/R disease, with no standard treatment options and ineligible/inappropriate for other treatment options
  - Evaluable disease (dose escalation only)
- Key exclusion criteria
  - Prior exposure to tazemetostat or other EZH2 inhibitors
  - History of chronic hepatitis B virus or hepatitis C virus infection, human immunodeficiency virus infection, T-cell acute lymphoblastic leukemia/T-cell lymphoblastic lymphoma, or myelodysplastic syndrome
  - Major surgery within 2 weeks prior to enrollment
  - Symptomatic venous thrombosis within 14 days prior to enrollment
  - For patients with CNS involvement, active bleeding or new intratumoral hemorrhage, known bleeding diathesis, or treatment with antiplatelet or antithrombic agents

## CONCLUSIONS

- Tazemetostat showed promising antitumor activity in pediatric patients with R/R *SMARCB1 (INI1)*-negative tumors, including ATRT, ES, and chordoma
  - ORRs were 24% in ATRT, 22% in ES, and 33% in chordoma
  - Patients in every major tumor type category exhibited moderate rates (33%–71%) of stable disease
  - The potential link between prior radiotherapy and response to tazemetostat requires further exploration to determine if it is attributable to tumor type
- Tazemetostat was generally well tolerated in pediatric patients, with a safety profile similar to that in adults
- The biological and clinical significance of differences in peripheral blood cell counts between responders and nonresponders at C1D1 requires additional investigation

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## Author Disclosures

**S. Chi** has served as a consultant for Blueprint Medicines and Epizyme. **F. Bourdeaut** has served as a consultant for Bristol Myers Squibb. **M. Casanova** has served as an advisor for Astra-Zeneca, Bayer, Bristol Myers Squibb, Pfizer, and Servier. **L. Kilburn** has served as a consultant for Blueprint Medicines. **D. Hargave, G. McCowage,** and **N. Pinto** have no relevant disclosures to declare. **R. Chadha, B. Kahali,** and **C. Tapia** are or were employees of Epizyme, Inc., and may own stock/options in the company. **K. Nysom** has served on an advisory board and as a consultant and teacher for Y-mAbs; has served on an advisory board for EUSA Pharma; and has served as a teacher and on an advisory board for Bayer.

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