A Phase 2, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adults (Epithelioid Sarcoma Cohort) (NCT02601950)

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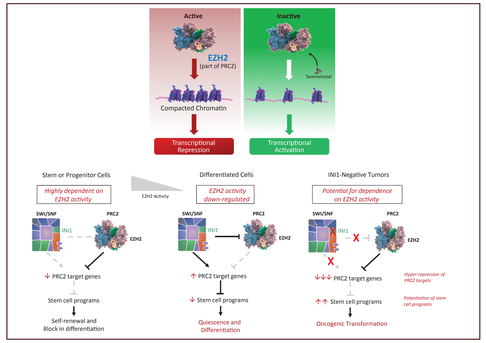
BACKGROUND

- Epithelioid sarcoma (ES) is a rare soft tissue sarcoma (STS); currently available treatments for metastatic STS have been shown to have limited activity in terms of durable clinical benefit and significant toxicities[1-3]
- Loss of integrase interactor 1 (INI1), a subunit of the SWItch/Sucrose Non-Fermentable (SWI/SWF) complex and a negative regulator of enhancer of zeste homolog 2 (EZH2), occurs in over 90% of ES tumors and is a characteristic diagnostic feature of ES[4-7]
  - EZH2, a histone methyltransferase in polycomb repressive complex 2 (PRC2), is a known oncogenic driver[5-7]
- In INI1-deficient preclinical models, EZH2 inhibition reprograms pathways related to abnormal cell growth, leading to cell death or differentiation and subsequent tumor control and regression[8]
- Tazemetostat, a potent, selective, orally available inhibitor of EZH2, has shown clinical activity in malignant rhabdoid tumors and in patients with ES[9,10] (Figure 1)
- Here we report interim phase 2 safety and activity of tazemetostat in patients with ES

Figure 1. Tazemetostat inhibits EZH2-mediated repression of transcription



EZH2, enhancer of zeste homolog 2; INI1, integrase interactor 1; PRC2, polycomb repressive complex 2; SWI/SNF, SWItch/Sucrose Non-Fermentable.

METHODS

- Study EZH-202 (NCT02601937) is a phase 2, open-label, multi-center study of tazemetostat that enrolled patients aged ≥16 years into 7 cohorts. The current study reflects patients with ES (Cohort 5)
- Tazemetostat 800 mg was administered orally twice daily in continuous 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent
- All patients were required to have tumor INI1 loss confirmed by histology
  - Key inclusion and exclusion criteria are presented in Table 1
- In cohort 5, tazemetostat was studied in adults (≥16 years of age) with ES in a 2-stage Green-Dahlberg design (Figure 2)
- Primary endpoint is RECIST 1.1 overall response rate (ORR)
- Secondary endpoints included disease control rate (DCR; confirmed RECIST 1.1 complete response [CR] or partial response [PR] of any duration, or stable disease [SD] lasting ≥32 weeks), safety/tolerability, and duration of response
- Response assessment was evaluated after 8 weeks of treatment and then every 8 weeks thereafter while on study

Statistical considerations

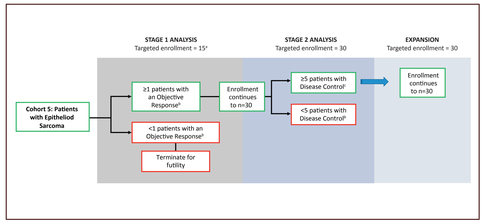
- Stage 1 futility was performed after the first 15 patients enrolled completed at least the 24-week assessment, the final study visit, or terminated early and required ≥1 patient achieving an objective response (CR or PR)
- Stage 2 success required disease control in ≥5/30 treated patients
- Stage 2 futility criterion was passed in October, 2016 (final N=32); the Expansion Stage opened in December, 2016 (final N=32)

Table 1. Key inclusion and exclusion criteria for cohort 5

Inclusion
Advanced measurable disease
ECOG performance status of 0 or 1
Life expectancy >3 months
Morphology and immunophenotypic panel consistent with INI1-negative tumors and loss of INI1 confirmed by IHC
Molecular confirmation of tumor bi-allelic INI1 loss or mutation when INI1 IHC is equivocal or unavailable
Expansion Stage inclusion criteria required that the patient's disease had progressed within 6 months prior to study enrollment. Stages 1 and 2 did not include this as a criteria[a]
Exclusion
Prior exposure to tazemetostat or other inhibitor(s) of EZH2
Prior malignancy other than the malignancies under study **EXCEPTION:** disease-free for 5 years, or with a history of a completely resected non-melanoma skin cancer or successfully treated in situ carcinoma is eligible
Major surgery within 3 weeks prior to enrollment
Cardiovascular impairment

[a]77% of patients in Stages 1 and 2 had documented progression within 6 months prior to study enrollment.
CLIA/CAP, Clinical Laboratory Improvement Amendments/College of American Pathologists; ECOG, Eastern Cooperative Oncology Group; EZH2, enhancer of zeste homolog 2; IHC, immunohistochemistry; INI1, integrase interactor 1; NYHA, New York Heart Association.

Figure 2. Study design



[a]All patients will have completed at least the week 24 assessment, completed the final study visit, or terminated early from the study, whichever is sooner. [b]Objective response: RECIST 1.1 – confirmed complete response or partial response at week 24. [c]Disease control: RECIST 1.1 - confirmed response [CR + PR or (SD for at least 32 weeks)]. RECIST, Response Evaluation Criteria in Solid Tumors.

RESULTS

- Datacut of 21 August 2018

Patient characteristics

- Of 62 patients enrolled, mean age was 37 years, 63% were male, and the median number of prior systemic therapies was one (Table 2)

Patient disposition

- Overall, 51 (82%) patients discontinued from the study
  - The majority of patients discontinued due to disease progression (n=43; 69%)
  - Four patients discontinued due to death not related to study drug, 2 patients discontinued after refusing further treatment of study drug, and one patient each for investigator discretion and other
  - No patients discontinued due to a treatment-emergent adverse event (TEAE)

Clinical Activity

- PRs were confirmed in 8 patients with an ORR of 13% and a DCR [CR+PR+(SD ≥32 weeks)] of 24%
- Patients who were naïve to treatment demonstrated a greater ORR, DCR, and PFS

Table 2. Patient demographics and disease characteristics

Clinical Characteristics	Total Number of Patients N=62
Age (years), mean (SD)	37 (15)
Male/female, n (%)	39 (63) / 23 (37)
Subtype (%)	
Proximal	20 (32)
Distal	29 (47)
Unknown[a]	13 (21)
Stage at diagnosis	
I	2 (3)
II	7 (11)
III	7 (11)
IV	37 (60)
Not applicable/unknown	9 (15)
Median time (months) from last PD to study entry, median (range); n=59	1.4 (0.3 to 12.8)
Number of lines of prior anticancer therapy	
0	24 (39)
1	12 (19)
2	12 (19)
≥3	14 (23)
Median (range)	1 (0–9)

[a]Unknown reflects data not included by investigator; PD, progressive disease; SD, standard deviation.

Table 3. Best response to tazemetostat treatment

Endpoint Category, n (%)	No Prior Anticancer Therapy N=24	Prior Anticancer Therapy N=38	Total N=62
DCR [CR + PR + (SD≥32 weeks)] 90% CI	9 (38) (21.2, 56.3)	6 (16) (7.1, 28.8)	15 (24) (15.5, 34.8)
ORR (CR + PR) 90% CI	5 (21) (8.6, 38.9)	3 (8) (2.2, 19.2)	8 (13) (6.6, 22.1)
Best Response			
CR	0	0	0
PR	5 (21)	3 (8)	8 (13)
SD	16 (67)	20 (53)	36 (58)
PD	2 (8)	11 (29)	13 (21)
Non-evaluable, missing, or unknown	1 (4)	4 (11)	5 (8)
Median duration of response, weeks Range	41 (7.1+, 48.1+)	48+ (40.1, 95.0+)	48+ (7.1+, 95.0+)
Median progression-free survival, weeks 90% CI	25.7 (23.7, NE)	14.7 (8.3, 16.0)	16.1 (15.1, 25.3)
Median overall survival, weeks 90% CI	NE	47.4 (33.7, 64.1)	82.4 (47.7, NE)

CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate, PD, progressive disease; PR, partial response; SD, stable disease; +, responses ongoing/medians not reached

Figure 3. Durability of disease control in patients without prior anticancer therapy

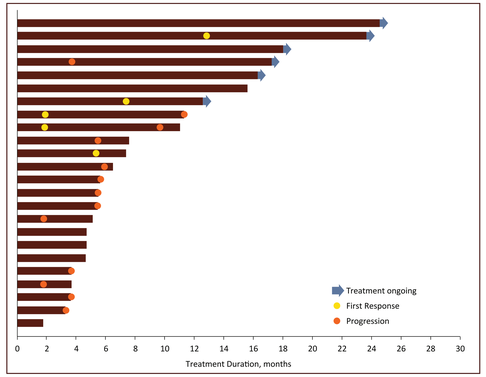


Figure 4. Durability of disease control in patients with prior anticancer therapy

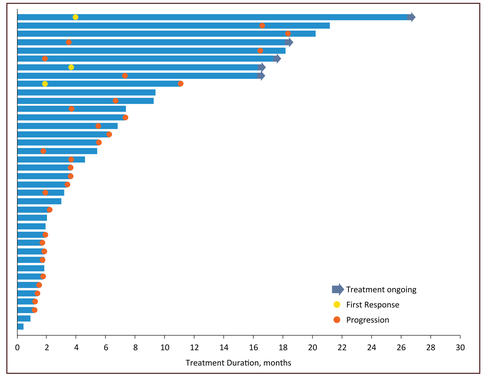
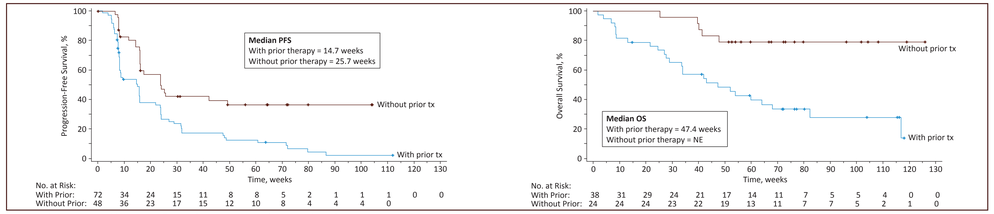


Figure 5. Progression-free survival and overall survival based on prior treatment status



+, censored; NE, not estimable; OS, overall survival; PFS, progression-free survival; TX, therapy.

Safety

- The most common TEAEs included fatigue (37%), nausea (35%), and cancer pain (32%) (Table 4)
  - Treatment-related TEAEs grade ≥3 reported in ≥2 patients were anemia (6%) and decreased weight (3%)

Table 4. TEAEs occurring in ≥10% of patients

	Patients (N=62)			
	All TEAEs		Treatment-related TEAEs	
Adverse event, n (%)	All grades	Grade ≥3	All grades	Grade ≥3
Fatigue	23 (37)	1 (2)	16 (26)	1 (2)
Nausea	22 (35)	0	16 (26)	0
Cancer pain	20 (32)	3 (5)	3 (5)	0
Decreased appetite	16 (26)	3 (5)	10 (16)	1 (2)
Constipation	13 (21)	0	5 (8)	0
Vomiting	15 (24)	0	10 (16)	0
Diarrhea	10 (16)	0	8 (13)	0
Cough	11(18)	0	0	0
Anemia	10 (16)	8 (13)	6 (10)	4 (6)
Dyspnea	8 (13)	4 (6)	0	0
Headache	11 (18)	0	4 (6)	0
Weight decreased	10 (16)	4 (6)	8 (13)	2 (3)
Pleural effusion	7 (11)	4 (6)	0	0

[a]Ten patients experienced TEAEs that were uncoded at the time of the datacut.
TEAE, treatment-emergent adverse event.

CONCLUSION

- This was the largest prospective clinical trial of ES to date
- Tazemetostat showed promising single agent activity, resulting in durable confirmed responses (13%) and a DCR of 24%
- Tazemetostat demonstrated favorable safety with no patients discontinuing due to an adverse event and very few patients experiencing grade ≥3 TEAEs related to treatment
- As ES is an aggressive sarcoma subtype, and currently available treatments for metastatic STS have been shown to have limited activity, tazemetostat represents a promising potential therapeutic option

REFERENCES

1. Jacobs AJ, et al. *Sarcoma*. 2015:279601.
2. Armah HB, Parwani AV. *Arch Pathol Lab Med*. 2009;133:814–819.
3. Jawad MU, et al. *Clin Orthop Relat Res*. 2009;467:2939–2948.
4. Hollman TJ, Hornick JL. *Am J Surg Pathol*. 2011;35:e47–e63.
5. Wilson BG, et al. *Cancer Cell*. 2010;18:316–328.
6. Shain AH, et al. *Proc Natl Acad Sci USA*. 2012;109:E252–E259.
7. Wang X, et al. *Nat Genet*. 2017;49:289–295.
8. Knutson SK, et al. *Proc Natl Acad Sci USA*. 2013;110:7922–7927.
9. Italiano A et al. *The Lancet Oncology*. 2018;19:649–659.
10. Jones RL, et al. Presented at ESMO 2018.

ACKNOWLEDGMENTS

- We thank all of the physicians, study coordinators, site staff and most of all, the patients, caregivers, and families who have contributed to this study
- Third-party writing assistance was provided by Ashfield Healthcare and funded by Epizyme, Inc.

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Presented at the 2018 Annual Meeting of the European Society of Medical Oncology (ESMO); 19–23 October 2018; Munich, Germany