TPS255

A Phase 1b/2 Open-Label Study Evaluating Tazemetostat in Combination with Enzalutamide or Abiraterone/Prednisone in Chemotherapy-Naive Patients With Metastatic Castration-Resistant Prostate Cancer

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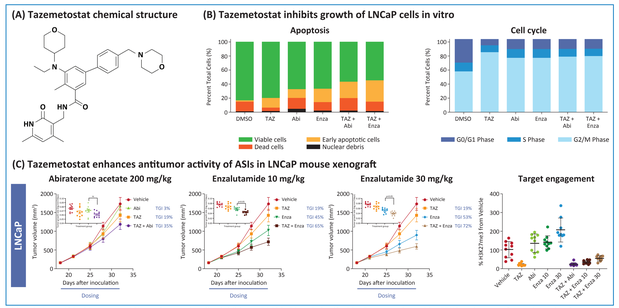
BACKGROUND

- Enhancer of zeste homolog 2 (EZH2) is a histone methyltransferase involved in cell cycle arrest and terminal differentiation.[1] EZH2 overexpression and/or mutation can result in aberrant trimethylation of histone H3 at lysine 27 (H3K27), leading to oncogenic transformation of cells[2]
  - Overexpression of EZH2 and decreased expression of target genes are associated with poor prognosis in patients with metastatic castration-resistant prostate cancer (mCRPC)[3,4]
- EZH2 is hypothesized to play an oncogenic role in androgen-driven prostate cancer in 2 different ways:[5,6]
  - As a transcriptional repressor, dependent on methyltransferase activity
  - As a transcriptional activator, targeting the androgen receptor in a polycomb repressive complex 2- and catalytic activity-independent manner
- Patients with mCRPC may initially respond to treatment with second-generation androgen signaling inhibitors (ASIs), such as enzalutamide (E) and abiraterone (A), but eventually develop resistance. Therapies with novel mechanisms of action that may delay or reverse drug resistance to ASIs are needed to improve long-term outcomes for such patients
- A combination treatment approach comprising existing ASIs plus an agent that modulates the EZH2 oncogenic signaling pathway may be able to overcome resistance to ASI therapy
- Tazemetostat (TAZ) is a selective, orally bioavailable, small molecule inhibitor of EZH2[7] approved by the FDA for the treatment of patients aged ≥16 years with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection **(Figure 1)**

Figure 1. Structure and Preclinical Activity of Tazemetostat[8]



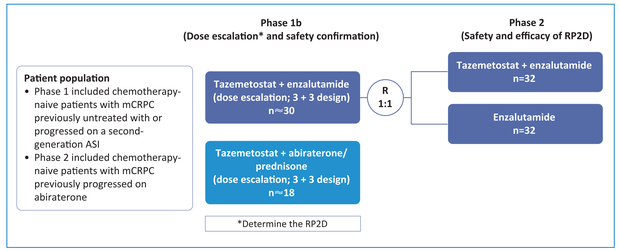
Abbreviations: Abi, abiraterone; ASIs, androgen signaling inhibitors; DMSO, Dimethyl sulfoxide; Enza, enzalutamide; EZH2, enhancer of zeste homolog 2; TAZ, tazemetostat; TGI, tumor growth inhibition.

- In phase 1 and 2 studies, TAZ has demonstrated clinically meaningful responses in B-cell lymphomas and molecularly defined solid tumors, and has a favorable safety profile[9,10]
- In preclinical models of prostate cancer, combination treatment of TAZ + E or TAZ + A/prednisone (P) resulted in a greater reduction in tumor growth than that observed with either drug alone[11]
- Based on these preclinical data, we designed a phase 1b/2 study (study name: EZH-1101; clinicaltrials.gov identifier: NCT04179864) to evaluate the safety and efficacy of TAZ + E or A/P (phase 1b), and TAZ + E versus E alone (phase 2) in chemotherapy-naive patients with metastatic castration-resistant prostate cancer

STUDY DESIGN

- This is a 2-part, global, multicenter, open-label, randomized, phase 1b/2 study. The study design is presented in **Figure 2**
- Total study enrollment will be approximately 112 patients, and the total study duration will be approximately 28 months

Figure 2. Study Design of EZH-1101 (NCT04179864)



Abbreviations: ASI, androgen signaling inhibitor; mCRPC, metastatic castration-resistant prostate cancer; R, randomization; RP2D, recommended phase 2 dose.

Phase 1b

- Using a modified 3+3 design, TAZ dosing will start at 400 mg twice daily, escalating to 600 mg twice daily, and to 800 mg twice daily in both the TAZ + A/P and TAZ + E groups, and further to 1200 mg twice daily and to 1600 mg twice daily in the TAZ + E group, if no dose-limiting toxicities are observed
- In the TAZ + E group, 160 mg of E will be given once daily. In the TAZ + A/P group, 1000 mg of A will be given once daily in combination with 5 mg of P twice daily
  - Patients previously treated with E and/or apalutamide will receive TAZ + A/P; conversely, patients previously treated with A/P will receive TAZ + E. Previously untreated patients will be distributed equally between both treatment arms
- A single dose of TAZ will be administered on day 1 of cycle 1 (28-day cycles). TAZ twice daily in combination with E or A/P will be administered from day 2 up to day 20, and from day 22 up to day 28. On day 21, a single dose of TAZ in combination with E or A/P will be administered
- Pharmacokinetic samples will be collected on days 1, 2, and 21 of cycle 1, and day 1 of cycle 2
- All study drugs will be administered orally

Phase 2

- Phase 2 will be an open-label study in which patients with chemotherapy-naive mCRPC previously treated with A/P will be randomized 1:1 to either TAZ + E or E alone
- TAZ will be administered at the recommended phase 2 dose (RP2D) twice daily in continuous 28-day cycles for as long as patients tolerate treatment and continue ASI therapy, or until radiographic or unequivocal clinical progression
  - E and TAZ will be administered on day 1 of each cycle
- Tumor assessments will be performed every 9 weeks for 6 months and every 12 weeks thereafter

PATIENT SELECTION

- Key patient eligibility criteria are presented in **Table 1**

Table 1. Key Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
Males ≥18 years of age, with a life expectancy of >3 months	Known symptomatic brain metastases
Histologically or cytologically confirmed prostate adenocarcinoma	Untreated/impending spinal cord compression
Metastatic or progressive disease; progression defined by rising PSA or soft tissue progression per RECIST 1.1, or 2 new bone lesions since last therapy	Prior treatment with any of the following within the indicated timeframe prior to day 1 of starting treatment: • First generation AR antagonists or radionuclide therapy within 4 weeks • 5 alpha reductase inhibitors, ketoconazole, estrogens or progesterones within 2 weeks • Chemotherapy within 3 weeks • Enzalutamide within 28 days of first planned dose of TAZ
Surgically or medically castrated with screening serum testosterone ≤50 ng/dL	Prior exposure to tazemetostat or other EZH2 inhibitor
Previously untreated with/progressed on a second-generation ASI* (phase 1b)	Presence of hypersensitivity to the study drugs
ECOG performance status score of 0–1	Major surgery within 4 weeks of randomization
Adequate hematologic, renal, and hepatic function	Presence of severe concurrent disease, infection, comorbidity, clinically significant cardiovascular disease, GI disorder, history of seizure or T-LBL/T-ALL or another invasive cancer within 3 years of randomization

*abiraterone, enzalutamide, or apalutamide.
Abbreviations: AR, androgen receptor; ASI, androgen signaling inhibitor; ECOG, Eastern Cooperative Oncology Group; EZH2, enhancer of zeste homolog 2; GI, gastrointestinal; PSA, prostate specific antigen; T-ALL, T-cell acute lymphoblastic leukemia; T-LBL, T-cell lymphoblastic lymphoma; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

STUDY OBJECTIVES AND END POINTS

- In phase 1b, the primary objectives are to select the RP2Ds of TAZ for each combination and to determine their safety and tolerability in chemotherapy-naive patients and patients previously treated with a second-generation ASIs
- In phase 2, the primary objective is to determine the benefit of combining TAZ with E as assessed by radiographic progression-free survival (rPFS) in chemotherapy-naive patients
- Primary and secondary end points are presented in **Table 2**

Table 2. Primary and Secondary Study End Points

Primary End Points	Secondary End Points (Both Study Phases)	
Phase 1b • Safety and tolerability • TAZ RP2D (both combinations) **Phase 2** • Radiographic progression-free survival	• Response rate for patients with ≥50% reductions in PSA • Time to PSA progression • Time to first skeletal-related event • Objective response rate per PCWG3 and RECIST 1.1 • Best overall response per RECIST 1.1	• Disease control rate • Time to initiation of new systemic treatment • PK of TAZ • CTC conversion rate* • CTC response rate† • Safety

*CTC conversion rate defined as the proportion of subjects who entered the study with a detectable number of CTCs converted to an undetectable number of CTCs.
†CTC response rate defined as the proportion of patients with ≥30% reduction in CTCs from baseline.
Abbreviations: CTC, circulating tumor cells; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PK, pharmacokinetics; PSA, prostate-specific antigen; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; RP2D, recommended phase 2 dose; TAZ, tazemetostat.

- Additional exploratory study objectives include evaluating the rate of pain progression at baseline and at 6 months from baseline, measurement of H3K27me3 levels in paired pre- and on-treatment biopsies, assessing genetic and molecular characteristics of responders and non-responders, and assessing immune cell profiles in tumor biopsy samples

STATISTICAL CONSIDERATIONS

- In phase 2, the efficacy analyses will use the intent-to-treat population, which is defined as all randomized patients
- To compare TAZ + E versus E alone, 53 rPFS events from a total of 64 subjects (32 per treatment arm) will provide approximately 80% power for the analysis of rPFS, with a 2-sided total type I error of 0.10 to reject the null hypothesis that there is no difference in rPFS between the combination versus single-agent treatment arms
  - The sample size assumes 10% of patients lost to follow-up over an 8-month enrollment period and a total study duration of 28 months

CURRENT STATUS

- The study started on September 26, 2019 and is due to complete on March 06, 2023
- In total, 20 study centers have been planned globally; 4 patients have been recruited at 3 of these centers
- For more information, please refer to ClinicalTrials.gov identifier: NCT04179864

REFERENCES

1. Mu W, et al. *Epigenetics Chromatin*. 2018;11(1):71.
2. Chase A, Cross NC. *Clin Cancer Res*. 2011;17(9):2613–2618.
3. Varambally S, et al. *Nature*. 2002;419(6907):624–629.
4. Yu J, et al. *Cancer Res*. 2007;67(22):10657–10663.
5. Xu K, et al. *Science*. 2012;338(6113):1465–1469.
6. Kim J, et al. *Cell Reports*. 2018;25(10):2808–2820.
7. Knutson SK, et al. *PNAS*. 2013;110(19):7922–7927.
8. Motwani V, et al. Poster presented at the 2019 American Association for Cancer Research, the National Cancer Institute, and the European Organization for Research and Treatment of Cancer (AACR-NCI-EORTC) International Conference on Molecular Targets and Cancer Therapeutics; October 26–30, 2019; Boston, MA. Poster #B011.
9. Morschhauser F, et al. Oral presentation at the Annual Meeting of the American Society of Hematology (ASH); December 7–10, 2019; Orlando, FL. Presentation #123.
10. Ribrag V, et al. Poster presented at the 2018 Annual Meeting of the American Society of Hematology (ASH); December 1–4, 2018; San Diego, CA. Poster #4196.
11. Ku SY, et al. *Science*. 2017;355(6320):78–83.

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