A Phase I Study of the EZH2 Inhibitor Tazemetostat in Pediatric Subjects with Relapsed or Refractory INI1-Negative Tumors or Synovial Sarcoma

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Dose Escalation: * To determine the MTD or the RP2D of tazemetostat when administered as an oral suspension BID in pediatric subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors or synovial sarcoma.* To evaluate the preliminary…

Ethical review	Approved WMO
Status	Completed
Health condition type	Soft tissue neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50516

Source
ToetsingOnline

Brief title
EZH-102

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
rhabdoid tumors, Soft Tissue sarcoma

Research involving
Human

Sponsors and support

Primary sponsor: Epizyme, Inc.

Source(s) of monetary or material Support: Epizyme Inc.

Intervention

Keyword: Pediatric Subjects, Rhabdoid Tumors, Tazemetostat, Various Soft Tissue Sarcoma

Outcome measures

Primary outcome

Dose Escalation:

* Incidence and severity of treatment-emergent adverse events (AEs) qualifying as protocol-defined DLTs in Cycle 1

* Establishment of the protocol defined RP2D and/or MTD

Dose Expansion:

Overall response rate (CR + PR) to tazemetostat for each cohort in pediatric subjects with relapsed or refractory atypical teratoid rhabdoid tumor (ATRT) (Cohort 1), non-ATRT rhabdoid tumors (Cohort 2), INI-1 negative tumors (Cohort 3), and tumor types eligible for Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (Cohort 4),using disease-appropriate standardized response criteria

Secondary outcome

Dose Escalation:

* Overall response rate (CR+PR) to tazemetostat in pediatric subjects with relapsed or refractory CNS and solid tumors, using disease-appropriate standardized response criteria

Dose expansion:

* Progression-free survival (PFS) and overall survival (OS) at 24 and 56 weeks and overall following receipt of tazemetostat for subjects with relapsed/refractory atypical teratoid rhabdoid tumor (ATRT) (Cohort 1 - closed to enrollment), non-ATRT rhabdoid tumors (Cohort 2), INI1-negative tumors (Cohort 3) and tumor types eligible for Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (Cohort 4 - closed to enrollment) using disease-appropriate standardized response criteria

All Parts and Cohorts:

* Safety and tolerability parameters including treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, and other safety measures
* PK parameters including Cmax, Tmax, t1/2, AUC(0-t), AUC(0-12hr), CL/F, Vd/F, Ka (if data permits)
* Response duration, for the subset of subjects with a confirmed CR or PR, defined as the time from the first documented evidence of CR or PR to time of first documented disease progression or death due to any cause, using disease-appropriate standardized response criteria

Exploratory Endpoints:

- To assess the PK and pharmacodynamic (PD) relationship for tazemetostat in pediatric subjects
- Tumor target gene expression and phenotypic markers including those for differentiation, apoptosis, inflammation and cell proliferation and their correlation with activity
- H3K27 methylation in PBMC population

- Somatic mutation analysis of tumor tissue and blood derived circulating DNA

Study description

Background summary

Tazemetostat (EPZ-6438) is a selective small molecule inhibitor of the histone-lysine methyltransferase EZH2 gene [Knutson, 2013]. Tazemetostat inhibits both wild-type EZH2 and mutated EZH2 residues Y641, A677G and A687 with half maximal inhibitory concentrations (IC50) ranging from 2-38 nmol/L. The compound shows a 35-fold selectivity over the most closely related HMT, EZH1 and greater than a 4500-fold selectivity over other HMTs. It selectively inhibits intracellular H3K27 methylation in a concentration- and time-dependent manner, leading to selective cell killing of cell lines. Tazemetostat specifically inhibits human lymphoma cell lines bearing EZH2 point mutations and INI1 unit deficient (also known as SNF5, SMARCB1, or BAFT47) MRT cell lines with IC50 in the nanomolar range. Additionally, tazemetostat administered orally has demonstrated antitumor activity in vivo against several EZH2 mutant human lymphoma xenograft murine models.

Study objective

Dose Escalation:
* To determine the MTD or the RP2D of tazemetostat when administered as an oral suspension BID in pediatric subjects with relapsed/refractory rhabdoid tumors, INI1-negative tumors or synovial sarcoma.
* To evaluate the preliminary anti-tumor activity of tazemetostat as assessed by ORR, using a disease appropriate standardized response criteria

Dose Expansion:
* To evaluate the anti-tumor activity of tazemetostat as assessed by overall response rate (ORR) in selected pediatric subjects with relapsed/refractory atypical teratoid rhabdoid tumor (ATRT) (Cohort 1 - closed to enrollment), non-ATRT rhabdoid tumors (Cohort 2), INI1-negative tumors (Cohort 3) and tumor types eligible for Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (Cohort 4 - closed to enrollment) using disease appropriate standardized response criteria.
* To determine the progression-free survival (PFS) and overall survival (OS) at 24 and 56 weeks and overall in selected pediatric subjects with relapsed/refractory atypical teratoid rhabdoid tumor (ATRT) (Cohort 1), non-ATRT rhabdoid tumors (Cohort 2), INI1-negative tumors (Cohort 3), and tumor types eligible for Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (Cohort 4) using disease-appropriate standardized response criteria

All:
* To assess the safety, tolerability and pharmacokinetic (PK) parameters of tazemetostat administered as an oral suspension BID and/or tablets three times daily (TID), in pediatric subjects
* To evaluate the duration of response in subjects achieving a PR or CR according to a disease appropriate standardized response criteria
* To assess the PK-pharmacodynamic (PD) relationship for tazemetostat in pediatric subjects
* To assess the effects of tazemetostat on H3K27 methylation in peripheral blood mononuclear cell (PBMC) subsets
* To assess tumor tissue and/or blood for somatic mutations, messenger ribonucleic acid (mRNA) and proteins as candidate markers of clinical response to tazemetostat

Study design

This is a Phase 1, open-label, dose escalation and dose expansion study with BID (suspension) and TID (tablet) oral doses of tazemetostat. Subjects will be screened for eligibility within 14 days of the planned first dose of tazemetostat. Response assessment will be evaluated after 8 weeks of treatment and subsequently every 8 weeks for the first 12 cycles. Starting with Cycle 13, response will be assessed every 12 weeks.
Tazemetostat will be given continuously, assuming subject (and/or parent/guardian) and Investigator consent/assent, until disease progression or unacceptable toxicity.

Subjects will be dosed in continuous 28-day cycles for the first 12 cycles. Starting with Cycle 13, subjects will be dosed in continuous 21-day cycles. Subjects may receive tazemetostat for approximately 2 years. (Note: If treatment with study drug is discontinued prior to completing 2 years, subjects will be followed for a maximum duration of 2 years from start of study drug dosing.)

The study has two parts: Dose Escalation and Dose Expansion

Intervention

Subjects will receive tazemetostat as an oral agent BID. Treatment may continue, assuming subject and/or parent/guardian and Investigator consent, until disease progression or unacceptable toxicity.

Study burden and risks

Based on the pre-clinical toxicology of tazemetostat, the potential risks associated with treatment include: GI AEs (nausea, vomiting, and diarrhea), lymphoid AEs (lymphoid depletion, lymphoma), liver AEs, renal AEs, bone AEs,

and photosensitivity.
Given the available safety and initial activity data of tazemetostat in adult subjects, non-clinical safety profile, non-clinical efficacy data in xenograft models, and unmet need in pediatric patients, there is an appropriate potential benefit to risk consideration to study tazemetostat in pediatric subjects with INI1-negative tumors.

Contacts

Public
Epizyme, Inc.

Technology Square 400
Cambridge, MA 02139
US
Scientific
Epizyme, Inc.

Technology Square 400
Cambridge, MA 02139
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Age (at time of consent/assent): *6 months to *18 years

Cohort 4 only: *10 years to *18 years
2. Performance Status:
If <12 years of age: Lansky Performance Status >50%
If *12 years of age: Karnofsky Performance Status >50%
3. Has provided signed written informed consent/assent
4. Has a life expectancy of >3 months
5. Has relapsed or refractory disease and no standard treatment options
6. Is ineligible or inappropriate for other treatment regimens known to have effective potential
7. Has a documented local diagnostic pathology of original biopsy
8. Has all prior treatment related clinically significant toxicities resolve to * Grade 1 per CTCAE, version 4.03 or are clinically stable and not clinically significant, at time of enrollment
9. Prior therapy(ies), must be completed according to the protocol
10. Has adequate hematologic BM & coagulation factors), renal & hepatic function as defined by criteria in the protocol
11. Specific requirements for subjects with CNS involvement eg: stable deficits within certain timeframe, stable seizure, treated brain metastases without evidence of progression.
12. Has a LV fractional shortening of >27% or an LV ejection fraction of *50% by ECHO or MUGA scan & NYHA *2
13. Has a QT interval corrected by Fridericia's formula (QTcF) *450 msec
14. Is able to swallow and retain orally administered medication and does not have any uncontrolled GI condition that may alter absorption
15. Has sufficient tumor tissue available for central confirmatory testing of IHC and/or cytogenetics/FISH and/or DNA mutation analysis
16. Is willing and able to comply with all aspects of the protocol as judged by Investigator
17. 18. For female subjects of childbearing potential and for male subjects with a female partner of childbearing potential Subject must adhere to contraception methods described in the protocol
For Dose Escalation Only:
All criteria above and the following:
1. Has evaluable disease as defined as lesions that can be accurately measured at least in one dimension by radiographic examination or physical examination or/and other lesions such as bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis or hepatosplenomegaly from disease.
2. Has one of the following histologically confirmed tumors: Rhabdoid tumor: ATRT, MRT, RTK, selected tumors with rhabdoid features, INI1-negative tumor (Epithelioid sarcoma, Epithelioid malignant peripheral nerve sheath tumor, EMC, Myoepithelial carcinoma, Renal medullary carcinoma), other INI1-negative malignant tumors, Synovial sarcoma with SS18-SSX rearrangement.
3. For subjects with ATRT, MRT, or RTK, or tumors with rhabdoid features only: the following test results must be available:
*Morphology and immunophenotypic panel consistent with rhabdoid tumor, and
*Loss of INI1 or SMARCA4 confirmed by IHC, or

*Molecular confirmation of tumor bi-allelic INI1 or SMARCA4 loss or mutation when INI1 or SMARCA4 IHC is equivocal or unavailable
4. For subjects with INI1 negative tumor only:
the following test results must be available:
*Morphology and immunophenotypic panel consistent with INI1-negative tumors, and
*Loss of INI1 confirmed by IHC, or
*Molecular confirmation of tumor bi-allelic INI1 loss or mutation when INI1 IHC is equivocal or unavailable
5. For subjects with synovial sarcoma only:
the following test results must be available:
*Morphology consistent with synovial sarcoma, and
*Cytogenetics or FISH and/or molecular confirmation (e.g.DNA sequencing) of SS18 rearrangement t(X;18)(p11;q11)
For Dose Expansion Only:
All listed above and in addition:
1. Has measurable disease
2. Has one of the following tumors: Cohort 1: ATRT, Cohort 2: MRT, RTK, selected tumors with rhabdoid features, Cohort 3: INI1-negative tumors or synovial sarcoma: ES,Epithelioid malignant peripheral nerve sheath tumor, EMC, Myoepithelial carcinoma, Renal medullary carcinoma, Chordoma (poorly differentiated or de-differentiated), other INI1-negative malignant tumors, Cohort 4: one of the tumor types defined in Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement.
3. For subjects with ATRT/MRT/RTK only-have test results available:
*Morphology and immunophenotypic panel consistent with rhabdoid tumor, and,
*Loss of INI1 or SMARCA4 confirmed by IHC, or *Molecular confirmation of tumor bi-allelic INI1 or SMARCA4 loss/mutation
4. For subjects with INI1-negative tumors only: - Have test results available:
*Morphology and immunophenotypic panel consistent with INI1-negative tumors, and *Loss of INI1 confirmed by IHC, or *Molecular confirmation of tumor bi-allelic INI1 loss/mutation
5. For subjects with synovial sarcoma with SS18-SSX rearrangement (In Cohort 4 only): morphology consistent with synovial sarcoma & Cytogenetics or FISH &/or molecular confirmation of SS18 rearrangement t (X;18)(p11;q11)
6. For subjects Cohort 4: Able to swallow and retain orally administered tablets

Exclusion criteria

1. Has had prior exposure to tazemetostat or other inhibitor(s) of enhancer of zeste homolog2 (EZH2)
2. Is being actively treated for another concurrent malignancy or is less than five years from completion of treatment for another malignancy
3. Has participated in another interventional clinical study and received investigational drug within 30 days or five half-lives, whichever is longer,

prior to the planned first dose of tazemetostat
4. Has had major surgery within 2 weeks prior to enrollment
5. Has clinically active heart disease including prolonged QTcF (>450 msec)
6. Is currently taking any prohibited medication(s) as described in section 7.3
7. Is unwilling to exclude grapefruit juice, Seville oranges and grapefruit from the diet and all foods that contain those fruits from time of enrollment to while on study
8. Has an active infection requiring systemic treatment
9. Is immunocompromised (ie congenital immunodeficiency), including subjects with known history of infection with human immunodeficiency virus (HIV)
10. Has known history of chronic infection with hepatitis B virus (hepatitis B surface antigen positive) or hepatitis C virus (detectable HCV RNA)
11. Has had a symptomatic venous thrombosis within 14 days prior to study enrollment
12. For subjects with CNS involvement (primary tumor or metastatic disease): Have any active bleeding, or new intratumoral hemorrhage of more than punctate size on Screening MRI obtained within 14 days of starting study drug,or known bleeding diathesis or treatment with anti-platelet or anti-thrombotic agents
13. Has known hypersensitivity to any of the components of tazemetostat or other inhibitor(s) of EZH2, or hypersensitivity to Ora-sweet or methylparaben
14. Has an uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, or psychiatric illness/social situations that would limit compliance with study requirements
15. For female subjects of childbearing potential: Is pregnant or nursing
16. For male subjects: Is unwilling to adhere to contraception criteria from time of enrollment in study to at least 3 months after last dose of tazemetostat.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Completed

Start date (anticipated):	10-10-2017
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tazemetostat
Generic name:	Tazemetostat

Ethics review

Approved WMO Date:	11-10-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-02-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	05-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	22-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-002468-18-NL
CCMO	NL57333.078.16

Study results

Date completed:	26-04-2021
Results posted:	11-07-2022
Actual enrolment:	2

First publication
14-06-2022