SUMMARY OF CHANGES

For Protocol Amendment #6 to: NRG-GY014

NCI Protocol #: NRG-GY014
Local Protocol #: NRG-GY014

NCI Version Date: January 11, 2023

This amendment is in response to an RRA from Dr. Richard Piekarz (rpiekarz@nih.gov)

Section	Comments
Title Page	The NCI Version Date is now January 11, 2023

7.3	The Tazemetostat CAEPR has been updated to Version 2.5, November 16, 2022:
	
	• Added New Risk:
	  • Less Likely: Alkaline phosphatase increased; Bronchial infection; Creatinine increased
	  • Also Reported on Tazemetostat Trials But With Insufficient Evidence for Attribution: Activated partial thromboplastin time prolonged; Death NOS; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Skin and subcutaneous tissue disorders - Other (HSV oral infection); Thrush
	
	• Increase in Risk Attribution:
	  • Changed to Likely from Less Likely: Anemia; Fatigue; Nausea; Vomiting
	  • Changed to Less Likely from Also Reported on Tazemetostat Trials But With Insufficient Evidence for Attribution: Abdominal pain; Alanine aminotransferase increased; Aspartate aminotransferase increased; Edema limbs; Fever; Headache; Hyperglycemia; Hypertriglyceridemia; Hyponatremia; Hypophosphatemia; Lymphocyte count decreased; Tumor pain; Upper respiratory infection; White blood cell decreased
	
	• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:

Section	Comments
	• Added: Anemia; Abdominal pain; Anorexia; Constipation; Cough; Diarrhea; Dyspnea; Fever; Headache; Lymphocyte count decreased; White blood cell decreased
ICD	Please see the ICD for additional changes.

NRG ONCOLOGY

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NRG ONCOLOGY
NRG-GY014
(ClinicalTrials.gov NCT # 03348631)

A PHASE II STUDY OF TAZEMETOSTAT (EPZ-6438) IN RECURRENT OR PERSISTENT ENDOMETRIOID OR CLEAR CELL CARCINOMA OF THE OVARY, AND RECURRENT OR PERSISTENT ENDOMETRIOID ENDOMETRIAL ADENOCARCINOMA

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Group; and SWOG.

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Protocol Agent

Agent	Supply	NSC #	IND #	IND Sponsor
Tazemetostat	CTEP	791066		DCTD

Participating Sites

☒ U.S.
☐ Canada
☐ Approved International Member Sites

Document History

	Version Date
Amendment 6	**January 11, 2023**
Amendment 5	April 06, 2022
Amendment 4	December 9, 2021
Amendment 3	October 20, 2021
Amendment 2	July 7, 2020
Amendment 1	08/13/2019
Initial	01/25/2019

<table>
<tr><th colspan="3">CONTACT INFORMATION (08/13/2019) (07-JUL-2020) (20-OCT-2021) (06-APR-2022)</th></tr>
<tr><th>For regulatory requirements:</th><th>For patient enrollments:</th><th>For data submission</th></tr>
<tr><td>Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select Regulatory > Regulatory Submission.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.</td><td>Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.</td><td>Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password.

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).</td></tr>
<tr><td colspan="3"><u>For clinical questions (i.e. patient eligibility or treatment-related)</u> Contact the Study PI of the Lead Protocol Organization</td></tr>
<tr><td colspan="3"><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> Contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
</table>

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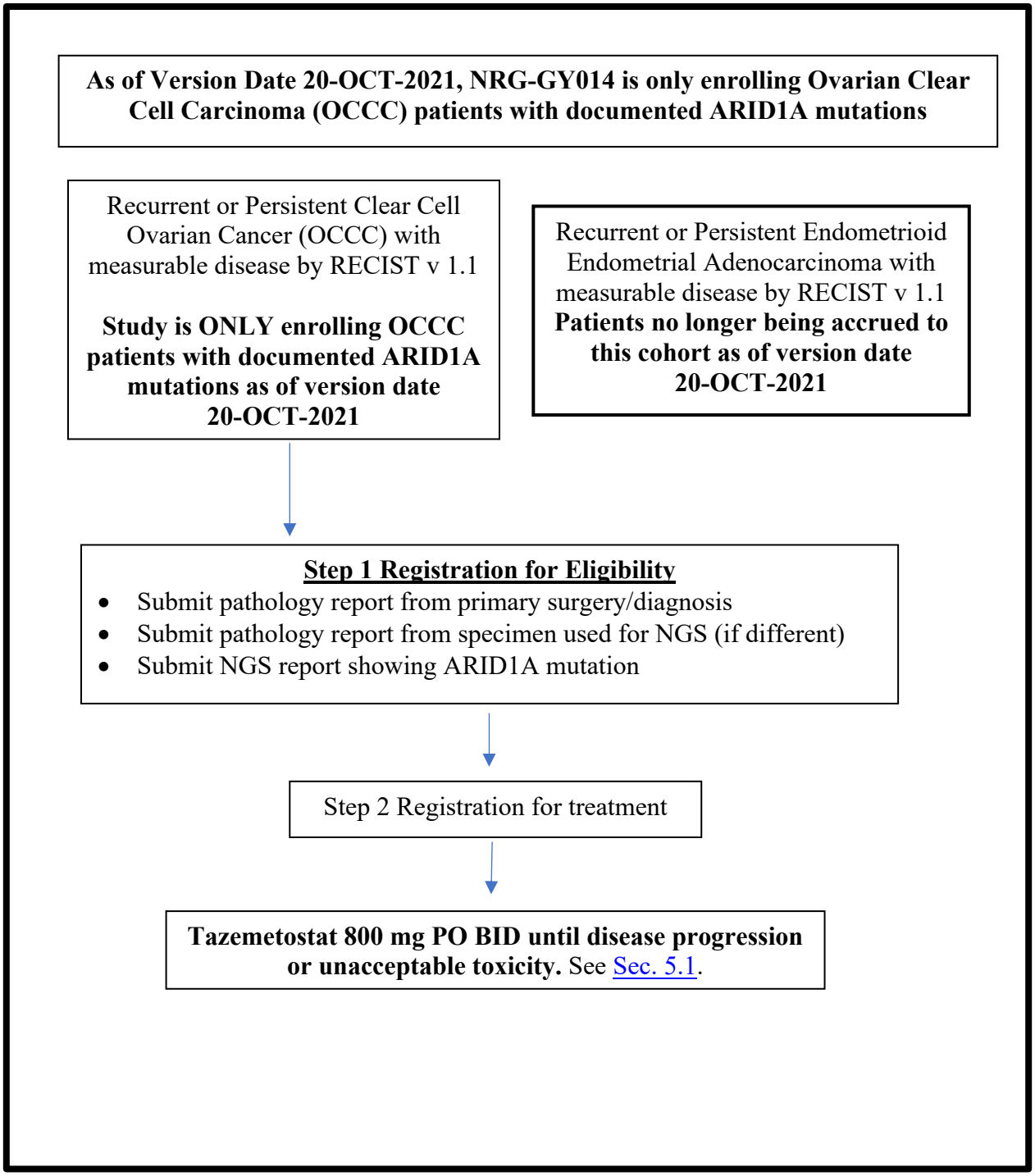
NRG-GY014
SCHEMA (20-OCT-2021)



1. OBJECTIVES (20-OCT-2021)

1.1 Primary Objective

To assess the clinical activity (overall response rate) of tazemetostat in patients with recurrent or persistent endometrioid or clear cell ovarian carcinoma, and patients with recurrent or persistent endometrioid endometrial adenocarcinoma.

1.1.1 As of version date 20-OCT-2021: The primary objective is to assess the clinical activity (response frequency) of tazemetostat in patients with recurrent or persistent clear cell ovarian carcinoma with an ARID1A mutation.

1.2 Secondary Objectives

1.2.1 To examine the nature and degree of toxicity in patients treated with this regimen.

1.2.2 To examine the progression free survival and overall survival for this patient population receiving tazemetostat.

1.2.3 As of version date 20-OCT-2021: <u>additional secondary objective</u>: to examine the 6 month clinical benefit rate in patients treated with this regimen. (20-OCT-2021)

1.2.4 To evaluate BAF250a expression in patient samples as an indicator of *ARID1A* mutation status and correlation with the clinical response to study drug. **Note: this only applies to patients enrolled prior to the 20-OCT -2021 version date. (20-OCT-2021)**

1.3 Exploratory Objectives

1.3.1 Translational Research Integrated Objective: Whether or not the patient has an ARID1A mutation. **(08/13/2019) Note: this only applies to patients enrolled prior to the 20-OCT-2021 version date. (20-OCT-2021)**

1.3.2 To examine the correlation between *ARID1A* mutation and BAF250a expression and to identify potential mutations predictive of response in patients with preserved BAF250a expression. **Note: this only applies to patients enrolled prior to the 20-OCT-2021 version date. (20-OCT-2021)**

2. BACKGROUND

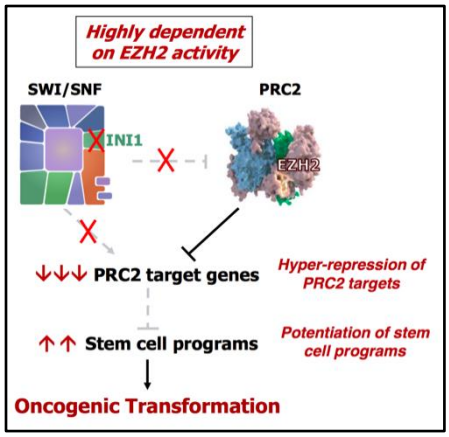
The treatment of solid tumor malignancies has gradually evolved over the past decade. Perhaps best exemplified in the treatment of lung cancer, molecular characterization and utilization of targeted agents has emerged as a preferred therapeutic paradigm. Given the above, The Cancer Genome Atlas (TCGA), a collaboration between the National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI), has generated comprehensive, multi-dimensional maps of the key genomic changes in 33 types of cancer. Recently, the TCGA completed and published the integrated genomic and molecular characterization of cervical cancer (Cancer Genome, Atlas 2017). In addition to data previously released for both ovarian (high grade serous) and endometrial (endometrioid and serous) cancers, this publication completed the molecular and genomic evaluation of the most common gynecologic malignancies, many of which represent an area of un-met clinical need (Cancer Genome Atlas, 2013) (Cancer Genome Atlas, 2011).

The ARID1A Gene

The *ARID1A* gene has been identified as a frequently mutated tumor suppressor in several gynecologic malignancies (Takeda et al, 2016). *ARID1A* encodes the BAF250a protein, a member of the SWItch/sucrose non-fermentable (SWI/SNF) complex, participating in chromatin remodeling and transcriptional regulation (Lowery et al, 2012). Aberrations in chromatin remodeling have been identified in approximately 20% of all human cancers (Bogelstein et al, 2013). Specifically, the SWI/SNF complex is involved in activation or inhibition of transcription, and plays a crucial role in carcinogenesis (Takeda et al, 2016). Most ARID1A mutations are frameshift or nonsense mutations, and in preclinical studies, silencing of *ARID1A* in non-transformed epithelial cells enhanced cellular proliferation and tumorigenesis in mice (Guan et al, 2011). Similarly, *ARID1A* knockdown in esophageal cancer cell lines enhanced cellular proliferation, whereas increased expression in *ARID1A*-deficient cells resulted in an inhibition of proliferation (Streppel et al, 2014). More recently, studies have shown that *ARID1A* mutations are involved in carcinogenesis via the PI3K/AKT pathway, with resultant cellular proliferation and inhibition of apoptosis (Takeda et al, 2016).

Genetic studies have revealed an evolutionarily conserved antagonistic relationship between the SWI/SNF complex and polycomb group proteins (Kim and Roberts, 2016). The loss of SWI/SNF complex subunits (ARID1A, SMARCB1, SMARA4) results in unopposed zeste homolog 2 (EZH2) activity, promoting carcinogenesis, and oncogenic transformation (**Figure 1:** available on epizyme.com) (Kim and Roberts, 2016).

Figure 1: Schematic representing the relationship between the SWI/SNF complex and PRC2. With loss of SWI/SNF activity, there is uninhibited EZH2 activity, resulting in oncogenic downstream signaling.



ARID1A and Endometriosis-Associated Ovarian Cancers (EAOC)

Historically, patients with endometrioid and clear cell ovarian cancer have been included in larger trials exploring new treatment paradigms in advanced or recurrent ovarian cancer, despite differing prognostic and molecular profiles, when compared to the more common high grade serous histology (Storey et al, 2008) (Quirkand Natarajan, 2005) (Sugiyama et al, 2000) (Winter et al, 2007). Given the above, a push has been made to examine these entities

independently. Endometrioid and clear cell ovarian carcinomas are uniquely associated with endometriosis, and have been recently referred to as endometriosis-associated ovarian cancer (EAOC). In a landmark study, Wiegand et al, implicated *ARID1A* as a tumor suppressor gene frequently disrupted in ovarian endometrioid and clear cell carcinomas (Wiegand et al, 2010). In a cohort of 152 cancer specimens, *ARID1A* mutations were identified in 46% of clear cell ovarian cancers, and 30% of the endometrioid ovarian carcinoma specimens (**Table 1**). Importantly, none of the 76 high grade serous cancer specimens exhibited an identifiable mutation (Wiegand et al, 2010). Furthermore, *ARID1A* mutations, and lack of BAF250a protein expression, were identified in neighboring, contiguous pre-neoplastic atypical endometriotic lesions, establishing ARID1A mutation as a potential early event in the transformation of endometriosis into cancer (Wiegand et al, 2010).

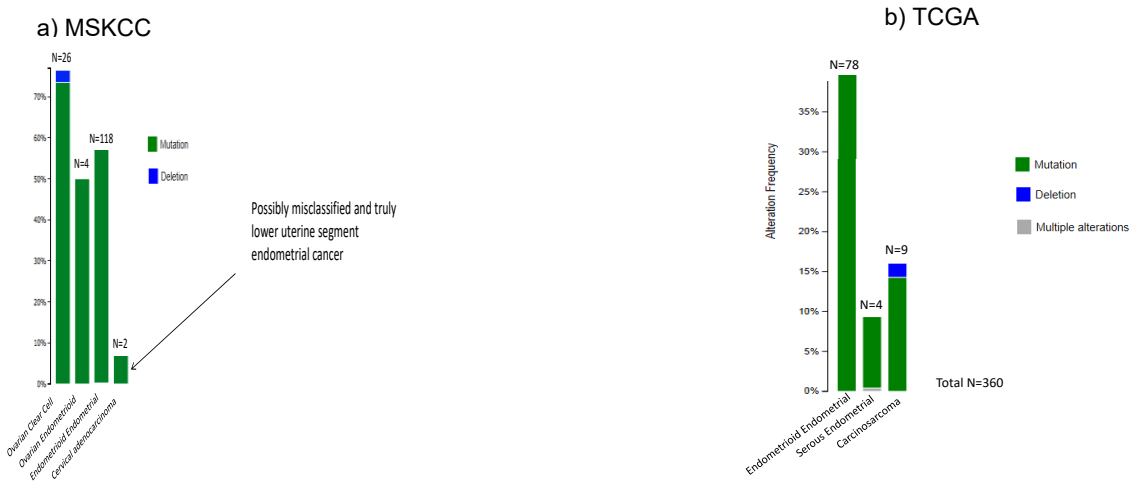
Table 1. Frequency of *ARID1A* mutation in endometrioid and clear cell ovarian cancer

	Endometrioid	**Clear cell**
Wiegland et al.	30%	46%
Rambau et al.	48%	--
Takeda et al.	30%	57%
***Chene et al.**	22%	47%
Mao et al.	30%	57%
Ayhan et al.	55%	75%
***Lowery et al.**	48%	41%

* expression assessed by BAF250a immunohistochemistry alone

In addition to the above, institutional data from the Memorial Sloan Kettering Cancer Center, as well as the endometrial TCGA show *ARID1A* mutation rates ranging from 40-80% in the EAOC cohorts as well as the endometrioid endometrial adenocarcinoma specimens (**Figure 2**) (Cancer Genome Atlas, 2013).

Figure 2: a) Institutional data from the MSKCC and b) data from the endometrial TCGA detailing ARID1A mutation rates in various cohorts



ARID1A and EZH2

Given the prevalence of *ARID1A* mutations in endometrioid and clear cell ovarian cancer, and its implications in carcinogenesis, a therapeutic approach to targeting cancers with such mutations has been explored. Novel treatment strategies targeting enhancer of EZH2 in *ARID1A* mutated cancers have been recently reported (Ayhan et al, 2012). Enhancer of zeste homolog 2 (EZH2) is a histone methyltransferase that mediates gene silencing by catalyzing trimethylation on lysine 27 of histone H3 (H3K27Me3) (Bitler et al, 2016). It is a member of the polycomb group of genes (PcG), and has been implicated in nucleosome modification, chromatin remodeling, and interaction with various transcription factors (Simon and Tamjun, 2002) (Eskander et al, 2013). In a series of eloquent experiments, Bitler et al. were able to show that inhibition of EZH2 methyltransferase activity using GSK126 (a small molecule highly selective inhibitor of EZH2), acts in a synthetic lethal manner in *ARID1A* mutated ovarian cancer cell lines, and that *ARID1A* mutational status correlated with response to the EZH2 inhibitor (Bitler et al, 2015). The authors identified PIK3IP1 (PI3K interacting protein 1) as a direct target of ARID1A and EZH2 that is upregulated by EZH2 inhibition and contributes to the observed synthetic lethality via the inhibition of PI3K-AKT signaling. Furthermore, EZH2 inhibition resulted in the regression of *ARID1A* mutated ovarian cancers in vivo, and decreased the number of disseminated tumor nodules in xenograft models (Bitler et al, 2015). In this context, *ARID1A* mutation status could serve as a biomarker to predict efficacy of EZH2 inhibition in *ARID1A* mutated, recurrent, endometrioid and clear cell ovarian cancer, an area of high unmet clinical need.

ARID1A and Endometrial Cancer

As previously discussed, *ARID1A* mutations have been identified in up to 47% of low grade endometrioid endometrial carcinomas, 60% of high grade endometrioid adenocarcinomas, 11% of serous adenocarcinomas and up to 24% of carcinosarcomas (Takeda et al, 2016). An association between loss of *ARID1A* protein expression and activation of the PI3K/AKT

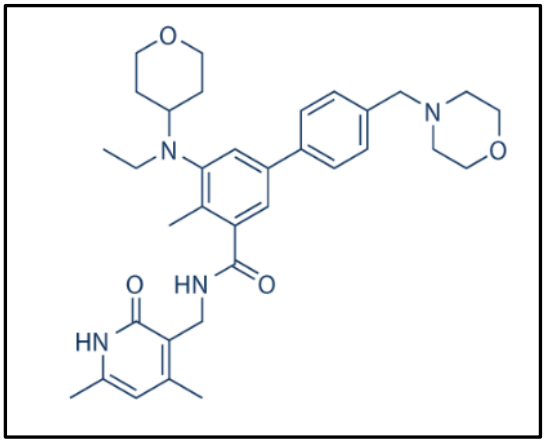
pathway has also been detailed. Mutations of *PTEN* and *PIK3CA* frequently occur in endometrial carcinomas with *ARID1A* mutation, and it is hypothesized that these *ARID1A* mutations induce aberrant activation of the PI3K pathway (Takeda et al, 2016). Additionally, investigators have explored the possibility that *ARID1A* mutation may result in defective mismatch repair, resulting in microsatellite instability and a greater tumor mutational burden. A strong association between *ARID1A* loss and sporadic microsatellite instability (MSI) is thought to result from epigenetic silencing of *MLH1* (Bosse et al, 2013). Furthermore, EZH2 overexpression has been described in both endometrial and ovarian cancer, with an impact on resultant downstream genes (*DK3, SFRP1, E-cadherin*) (Eskander et al, 2013).

The frequency and identification of *ARID1A* mutations in EAOC and endometrioid endometrial adenocarcinoma, as well as the clinical availability of a therapeutic agent capitalizing on *ARID1A* loss, advocates for the development of a clinical trial examining EZH2 inhibitors in this patient population. Given the data outlined above, we propose to explore the efficacy of single agent tazemetostat in patients with recurrent or persistent (1) endometrioid and clear cell ovarian or primary peritoneal cancer and (2) endometrioid endometrial adenocarcinoma.

2.1 Background on tazemetostat

Tazemetostat (EPZ-6438) is a selective, reversible, S-adenosyl methionine (SAM)-competitive small molecule inhibitor of the EZH2 histone methyl transferase enzymatic activity. As outlined above, genetic alterations in proteins of the SWI/SNF complex (including ARID1A) result in an oncogenic dependency on EZH2 activity, lending these solid tumor susceptible to EZH2 inhibition. 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 has 35-fold selectivity over the most closely related HMT, EZH1, and a greater than 4500-fold selectivity over other HMTs. The drug selectively inhibits intracellular H3K27 methylation in a concentration- and time-dependent manner, leading to selective cell killing of cell lines that depend on EZH2 activity.

Figure 3: Chemical structure of tazemetostat (EPZ-6438)



Epizyme is currently evaluating the efficacy of tazemetostat in ongoing clinical trials in adult subjects. The studies focus on subjects with hematologic malignancies (NHL (DLBCL and FL)), solid tumors and mesothelioma. In 2016, at the ASH Lymphoma Biology meeting, data regarding preliminary safety and activity of tazemetostat in patients with relapsed or refractory NHL and advanced solid tumors was presented. Within the cohort of 55 subjects a total of 3, grade 3 or greater treatment-related AEs were reported (1 each of: thrombocytopenia, neutropenia, hypertension). Additional preliminary data evaluating the efficacy of tazemetostat in patients with INI1-negative and SMARCA4-negative rhabdoid tumors and sarcomas (n=11), showed both complete and partial responses, with some subjects experiencing stable disease lasting greater than 6 months. Importantly, INI1 and SMARCA4 are subunits of the SWI/SNF complex, in addition to ARID1A.

Tazemetostat nonclinical pharmacokinetics

The plasma pharmacokinetics of tazemetostat in rats and monkeys was characterized by high-to-moderate clearance, moderate-to-large volume of distribution, and a short half-life of 0.4 to 1.6 hours. Low-to-moderate accumulation of tazemetostat in plasma was observed after repeated doses in male rats. In contrast, there was a 3- to 5-fold decrease in systemic exposure between day 1 and day 28 in monkeys. In vitro, cytochrome P450 (CYP)3A4 is the predominant enzyme responsible for the hepatic metabolism of tazemetostat. The desethyl metabolite, EPZ-6930, was the major metabolite formed in vitro in all species and no metabolite unique to humans was observed.

Tazemetostat clinical pharmacokinetics

Tazemetostat was administered orally at doses of 100, 200, 400, 800, and 1600 mg twice daily (BID) in subjects with advanced solid tumors or with B-cell lymphomas. The drug was rapidly absorbed, with time to maximal plasma concentration (Tmax) of approximately 1-2 hours after administration, and a mean terminal half-life of 3-5 hours. Relative to single day dosing, BID dosing resulted in a decrease in systemic exposure on day 15. Systemic exposure at steady state did not change after day 15. Administration of tazemetostat with food decreased the rate of oral absorption with no relevant effect on total systemic exposure when

compared to drug administration in the fasting state. Drug studies conducted with midazolam suggest that tazemetostat is a weak inducer of CYP3A4/5 mediated metabolism. Thus, potential interactions with concomitantly administered medications that are substrates for CYP3A4/5 will be mild.

Table 12 Summary of Treatment-Related Treatment-Emergent Adverse Events Occurring in ≥5% of Patients in Phase 2 Studies with Tazemetostat

	NHL[a] N=151 n (%)	Solid Tumors[b] N=115 n (%)	Overall N=266 n (%)
Patients with at least 1 TEAE	85 (56)	72 (63)	157 (59)
MedDRA Preferred Term			
Nausea	20 (13)	18 (16)	38 (14)
Fatigue	11 (7)	24 (21)	35 (13)
Asthenia	14 (9)	7 (6)	21 (8)
Thrombocytopenia	19 (13)	0 (0)	19 (7)
Anemia	7 (5)	10 (9)	17 (6)
Diarrhea	11 (7)	5 (4)	16 (6)
Decreased appetite	6 (4)	9 (8)	15 (6)

Source: Appendix 2A_2 Summary of Treatment-Emergent Treatment-Related Adverse Events Occurring in ≥5% of Subjects by Severity, Phase 2; Data cutoff 15 January 2017.

[a] Includes data from the Phase 2 portion of study E7438-G000-101.
[b] Includes data from studies EZH-202 (n=102) and EZH-203 (n=13).
Note: Patients with multiple instances of an AE are counted only once. AEs with a missing relationship are counted as related.
Abbreviations: AE=adverse event, NHL=non Hodgkin lymphoma, TEAE=treatment-emergent adverse event.

Treatment-Related Treatment-Emergent Adverse Events Occurring in ≥ 5% of Patients (taken from Table 12 of p 72 of Epizyme's IB for tazemetostat)

The following side effects or risks have been identified, requiring additional monitoring, or tests, to potentially minimize the occurrence of these events: T-cell lymphoblastic lymphoma or T-cell acute lymphoblastic leukemia (T-LBL/T-ALL):

- A 9-year-old subject treated with tazemetostat in a study being conducted in children developed a type of non-Hodgkin lymphoma, which is also called T-cell lymphoblastic lymphoma (T-LBL) after receiving tazemetostat for 14 months.

During pre-clinical animal testing, T-LBL, including lymphoid hyperplasia in the thymus, was observed in one model, rats, but not in other animal models. It was noted by the company that in rats, these events were observed at the highest doses, doses higher than have been used in humans.

The risk for T-LBL/T-ALL occurring in patients treated with tazemetostat is thought to be greater in children but is unknown in adults. The incidence of T-LBL/T-ALL in adults treated with tazemetostat is expected to be uncommon. As of 1 May 2018, this is the only case of T-cell lymphoma that has occurred out of a total of 79 children enrolled in tazemetostat clinical trials. In addition, there have been no cases of T-LBL/T-ALL in the 702 adult patients treated across multiple studies conducted in different types of cancer. The company will continue to monitor all patients treated with tazemetostat very carefully for the development of secondary malignancies.

2.2 Translational Science Background

The Memorial Sloan Kettering Cancer Center has extensive clinical experience surrounding ARID1A assessment as part of GOG protocol 0283. Dr. Hyman, the principal investigator of GOG-0283 completed ARID1A gene sequencing and established a validated, NIH Biomarker Review Committee-approved IHC assay for BAF250a expression. The IHC assay was found to have excellent concordance with *ARID1A* mutational status as detailed in Figure 4 below.

ARID1A Mutation Result	BAF250a Expression		
Frequency	Loss	Retained	Total
Truncating Mutation	7	1	8
Wildtype	0	5	5
Total	7	6	13

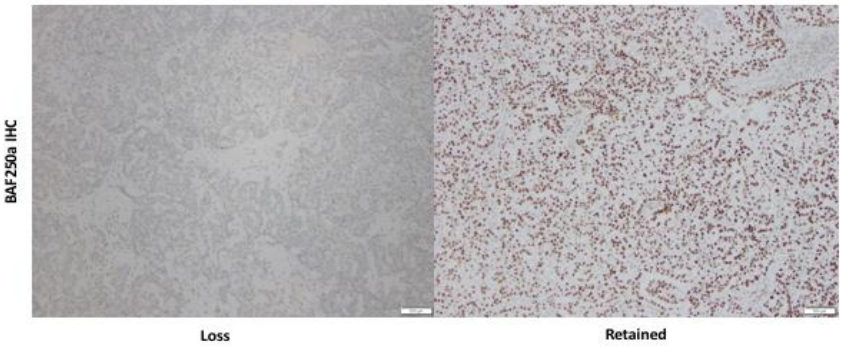


Figure 4: Monograph illustrating BAF250a IHC as well as correlation between ARID1A mutation status and BAF250a expression (courtesy of Dr. Hyman)

2.3 Stage 1 data informing protocol modification for patients enrolled after 20-OCT-2021 version date

Between March 2019 and August 2019, a total of 38 patients were enrolled onto stage 1 of NRG GY014 (n=19 in each cohort). All eligible and evaluable patients in the endometrial cancer cohort were endometrioid histology. Seven of 17 patients (41%) with endometrial cancer were identified as having an *ARID1A* mutation by NGS. Of the 16 patients with BAF250a IHC, absent IHC expression was noted in 2 patients with endometrial cancer, with

variable expression in the remaining 14 patients. Importantly, there were no objective responses identified in the endometrial cancer cohort, irrespective of ARID1A mutation status.

All patients enrolled in the ovarian cancer cohort had clear cell histology. Of the 15 patients in the cohort who were eligible, evaluable, and examined for mutation status, 9 were identified as having an *ARID1A* mutation by NGS (60%). Of the 13 patients with BAF250a IHC, absent IHC expression was noted in 1 patient with ovarian clear cell carcinoma, with variable expression in the remaining 12 patients. There were 2 confirmed objective responses (1 complete response (CR) and 1 partial response (PR)) and one unconfirmed PR in the ovarian clear cell carcinoma cohort (ORR 33%). All 3 patients were identified to have ARID1A mutation by NGS. Furthermore, ARID1A mutation by NGS appeared to be associated with response to single agent tazemetostat in the ovarian cancer cohort. Lastly, an additional 4 patients harboring ARID1A mutations exhibited stable disease > 6 months, resulting in a 6-onth clinical benefit rate of 77.8%. These results prompted revision of the protocol to enroll patients with clear cell ovarian cancer and ARID1A mutations in a prospective manner.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the NRG Oncology Statistics and Data Management Center-Pittsburgh Office (see protocol cover page).

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Submission of tumor tissue is required for all patients. Investigators should check with their pathology department regarding release of tissue biospecimens before approaching patients about participation in the trial. (See Section 10 for details.)

3.2 Eligibility Criteria (09-DEC-2021)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.2.1 Pathologically (histologically or cytologically) proven diagnosis of recurrent or persistent ovarian endometrioid or clear cell carcinoma, OR recurrent or persistent endometrioid endometrial adenocarcinoma. Patients with recurrent endometrial cancer must have MMR immunohistochemistry completed. If they are found to be mismatch repair deficient, they should be offered treatment with immune checkpoint inhibition before consideration for

treatment on trial.

Primary ovarian tumors must be at least 50% endometrioid or clear cell morphology, or have histologically documented recurrence with at least 50% endometrioid or clear cell morphology. Institutional pathology reports must be provided indicating at least 50% endometrioid or clear cell morphology for ovarian tumors (primary or recurrent lesions).

3.2.1.1 As of protocol version date 20-OCT-2021, only patients with recurrent or persistent ovarian clear cell carcinoma (OCCC) with ARID1A pathologic variant or likely pathologic variant mutations per NGS are eligible for entry. (20-OCT-2021)

Institutional pathology reports indicating at least 50% clear cell morphology for ovarian tumors (primary or recurrent lesions) and NGS report must be available for Step 1 registration. (20-OCT-2021) (09-DEC-2021)

All other eligibility criteria (Secs 3.2.2-3.2.14) and ineligibility criteria (Secs 3.31-3.38) must be met for Step 2 registration. (20-OCT-2021) (09-DEC-2021)

3.2.2 All patients must have measurable disease as defined by RECIST v 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be ≥15 mm in short axis when measured by CT or MRI. Refer to Section 13.1.2 for details if in site of previous radiation.

3.2.3 Patients must have had at least one, but no more than 3, prior cytotoxic regimens for management of primary disease. Unlimited prior hormonal therapy, targeted therapy (including immunotherapy) or antiangiogenic therapy will be permitted.

3.2.4 Patients must have completed prior therapy as detailed below:

Prior Therapy	Time from Last Prior Therapy Regimen, if applicable (08/13/2019)
Chemotherapy: cytotoxic	At least 28 days since last dose of chemotherapy prior to Step 2 registration.
Chemotherapy: nitrosoureas	At least 6 weeks since last dose of chemotherapy prior to Step 2 registration.
Chemotherapy: non-cytotoxic (e.g. small molecule inhibitor)	At least 28 days since last dose of chemotherapy prior to Step 2 registration.
Monoclonal antibody(ies)	At least 28 days since last dose of monoclonal antibody prior to Step 2 registration.
Immunotherapy	At least 28 days since last dose of immunotherapy prior to Step 2 registration.
Radiotherapy (RT)	At least 14 days from last local site RT prior to Step 2 registration. At least 21 days from stereotactic radiosurgery prior to Step 2

	registration. At least 12 weeks from craniospinal, ≥50% radiation of pelvis or total body irradiation prior to Step 2 registration. Patients with CNS disease should demonstrate evidence of stabilization after the 28-day time point after definitive treatment. Full recovery of radiation related side effects prior to Step 2 registration. All subjects must have evidence of measurable disease outside of the radiation field at the time of Step 2 registration.

3.2.5 Appropriate stage for study entry based on the following diagnostic workup:
- History/physical examination within 14 days prior to Step 2 registration;
- Imaging of the chest, abdomen and pelvis within 28 days prior to Step 2 registration (See Section 4.1)

3.2.6 Age ≥ 18

3.2.7 ECOG Performance Status of 0, 1 or 2 within 14 days prior to Step 2 registration.

3.2.8 Adequate hematologic function within 14 days prior to Step 2 registration defined as follows: **(08/13/2019)**
- Platelets ≥ 100,000/mcl
- ANC ≥ 1,500/mcl
- Hemoglobin ≥8 g/dL
- Differential with no clinically significant morphologic abnormalities on complete blood count (CBC) testing. Manual differential is encouraged, if clinically indicated, and in cases where an automated differential is abnormal.

3.2.9 Adequate renal function within 14 days prior to Step 2 registration defined as follows: **(08/13/2019)**
- Creatinine ≤ 1.5 x institutional/laboratory upper limit of normal (ULN)

3.2.10 Adequate hepatic function within 14 days prior to Step 2 registration defined as follows:
- AST and ALT ≤ 3 x ULN
- Total serum bilirubin level ≤ 1.5 x ULN; Direct bilirubin ≤ ULN for subjects with total bilirubin > 1.5 x ULN (patients with isolated indirect bilirubin elevations and a history of Gilbert's Syndrome are eligible)

3.2.11 Patients must be able to swallow and retain oral medications and not have gastrointestinal illnesses that would preclude absorption of tazemetostat as judged by the treating physician. **(20-OCT-2021)**

3.2.12 Women of childbearing potential must be willing and able to use adequate contraception (hormonal and barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 6 months after the last dose of study agent. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately. Theoretically, CYP3A induction with tazemetostat use may result in the loss of efficacy in hormonal contraceptives, thus a barrier method of contraception must be used in addition to hormonal contraceptives due to the potential drug-drug interaction with tazemetostat**. (20-OCT-2021)**

3.2.13 The patient or a legally authorized representative must provide study-specific informed consent and authorization permitting release of personal health information prior to study entry.

3.2.14 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial. **(08/13/2019)**

3.3 Ineligibility Criteria (09-DEC-2021)
Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Prior treatment with an investigational EZH2 inhibitor.

3.3.2 Patients who have: **(08/13/2019)**

- A prior history of myeloid malignancies, including myelodysplastic syndrome (MDS).
- Abnormalities known to be associated with MDS (*e.g.* del 5q, chr 7 abn) and myeloproliferative neoplasms (MPN) (*e.g.* JAK2 V617F) observed in cytogenetic testing and DNA sequencing.
- A prior history of T-LBL/T-ALL.

3.3.3 Patients who have had therapeutic paracentesis or thoracentesis within 8 weeks prior to Step 2 registration. **(20-OCT-2021)**

3.3.4 Patients with clinical or radiographic evidence of bowel obstruction. **(20-OCT-2021)**

3.3.5 Severe, active co-morbidity per the treating investigator's discretion.

3.3.6 Pregnant or lactating patients.

3.3.7 Known HIV positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with tazemetostat. In addition, treatments involved in this protocol may be immunosuppressive, increasing the risk of lethal infections in this patient population.

3.3.8 Treatment with strong and moderate inhibitors or inducers of CYP3A within 14 days of Step 2 registration and during the study treatment (See Section 5.8.2). **(20-OCT-2021)**

4 REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

4.1 PRE-TREATMENT ASSESSMENTS (08/13/2019) (20-OCT-2021) (06-APR-2022)

Assessments	Prior to Step 1 Registration	Prior to Step 2 Registration (calendar days)*	Prior to Treatment (calendar days) (Cycle 1, Day 1)*
Pathology report from primary surgery/diagnosis	X		
Pathology report from specimen used for NGS (if different from above pathology report)	X		
Submission of NGS report showing ARID1A pathologic variant or likely pathologic variant mutation	X		
History and Physical		≤ 14 days	≤ 14 days
Concomitant Medications		≤ 14 days	≤ 14 days
Vital Signs (blood pressure, height, weight, pulse, temperature, respiratory rate)		≤ 14 days	≤ 14 days
Performance Status		≤ 14 days	≤ 14 days
Toxicity Assessment		≤ 14 days	≤ 14 days
CBC with differential/Platelets		≤ 14 days	≤ 14 days
Sodium, Potassium, Chloride, CO_2, Magnesium, BUN, Creatinine, Calcium, Bilirubin, AST/SGOT, ALT/SGPT, Alkaline Phosphatase		≤ 14 days	≤ 14 days
Urine Pregnancy Test (if childbearing potential exists)		≤ 14 days	≤ 72 hours
ECG (if clinically indicated)		≤ 28 days	≤ 28 days
Radiographic Tumor Measurement**		≤ 28 days	≤ 28 days

*** Prior to Step 2 Registration Assessments should be used for Pre Cycle 1, Day 1 as long as they are within the stated Cycle 1, Day 1 window.**

** Radiographic tumor measurements should be obtained via imaging of the chest, abdomen and pelvis to establish the location and extent of disease. See RECIST 1.1 for allowable imaging modalities used to assess disease at baseline (and subsequent assessments). Contrast CT is the preferred modality. PET-CT is **not** permitted for any disease assessment or reassessment.

4.2 ASSESSMENTS DURING TREATMENT * (08/13/2019)

Assessments	Prior to Each Treatment Cycle, Day 1 (after Cycle 1, Day 1)*	Timed (Treatment Cycle Independent)
History and Physical	X	
Concomitant Medications	X	
Vital Signs (blood pressure, height, weight, pulse, temperature, respiratory rate)	X	
Performance Status	X	
Toxicity Assessment	X	
CBC with differential, platelets	X**	
Sodium, Potassium, Chloride, CO_2, Magnesium, BUN, creatinine, Calcium, bilirubin, AST/SGOT, ALT/SGPT, alkaline phosphatase	X	
Patient Medication Calendar (see Appendix V)	X	
Radiographic Tumor Measurement		X***

* Each cycle will be defined as a 28 day period. Visit assessment windows of +/- 3 days will be permitted. Delays of up to 7 days will be allowed and will not be considered a protocol violation for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be rescheduled). Documentation to justify this decision should be provided.

** Every 2 weeks during the first two cycles and then once per cycle (monthly) thereafter with more frequent CBCs as clinically indicated.

*** Every 8 weeks (+/- 7 days) from cycle 1, day 1 (regardless of delays and /or changes in treatment schedule) for the first 12 months; then every 12 weeks (+/- 7 days) thereafter. Radiographic tumor measurements are obtained until disease progression is confirmed; at the investigator's discretion they can be repeated any other time if clinically indicated based on symptoms of physical signs suggestive of new or progressive disease. A tool is provided on the CTSU website to calculate dates of re-imaging. Utilize same imaging modality of abdomen, pelvis and chest (see footnote under Pre-Treatment Assessments) as for pre-cycle 1 baseline assessment.

4.3 ASSESSMENTS IN FOLLOW UP

Assessments	Timed (after progression or discontinuation of treatment)
Vital Status	1
Toxicity Assessment	2
Radiographic tumor measurement	3

[1] Every 3 months for 2 years and then every 6 months for 3 years. Follow-up Forms are collected until study termination.

[2] Patients who discontinue treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. For reporting of delayed toxicity, see Section 7.

[3] In the case that protocol directed therapy is discontinued for reasons other than disease progression, follow radiographic tumor measurement schedule as defined under Assessments During Treatment (until disease progression documented by RECIST 1.1 or until patient initiates a subsequent cancer therapy).

Definition of Disease Assessments

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

TREATMENT SHOULD BEGIN WITHIN 14 DAYS OF REGISTRATION in order to avoid having to repeat the pre-treatment assessments as outlined in Section 4.1.

5.1 Chemotherapy/Hormonal Therapy/Other Agent-Based Therapy

5.1.1 Tazemetostat 800 mg BID administered orally in continuous 28-day cycles until disease progression or unacceptable toxicity.

Tazemetostat can be taken with or without food. Tablets should be taken whole and not chewed or crushed. Doses must be taken twice per day with no less than 8 hours between each dose. If a dose is missed or vomited, skip the dose and take the next scheduled dose. **(09-DEC-2021).**

No grapefruit juice, Seville oranges, or grapefruit can be consumed while on tazemetostat.

See Sections 9.1.10, 9.1.11 and Appendix IV

5.2 Radiation Therapy

Not Applicable.

5.3 Surgery

Not Applicable.

5.4 Device
Not Applicable.

5.5 Imaging
Not Applicable.

5.6 Integral Biomarker Assay
Not applicable.

5.7 Intervention Not Otherwise Categorized
Not applicable.

5.8 General Concomitant Medication and Supportive Care Guidelines

5.8.1 Permitted Supportive/Ancillary Care and Concomitant Medications **(20-OCT-2021)**
All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

- Strong and moderate CYP3A4 inhibitors or inducers are prohibited from 14 days prior to Step 2 registration to the end of the study.

CYP3A induction with tazemetostat use may result in the loss of efficacy in hormonal contraceptives.

Permitted medication(s), include:

- Supportive care measures and symptomatic treatment for any treatment-related toxicity, including short course of glucocorticoids (< 4 weeks), if clinically indicated
- Non-enzyme inducing anti-epileptic drugs
- Prophylactic use of standard antiemetics

Medication(s) to be used with caution:

- In vitro, tazemetostat inhibits MATE1 and MATE2K. Tazemetostat does not inhibit CYP1A2, 2B6, 2C9, 2D6, P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, or BSEP at clinically relevant concentrations. Tazemetostat also induces CYP3A4. Medications that are substrates of CYP3A or P-gp with a narrow therapeutic index and substrates of MATE1 and MATE2K should be used with caution.

Substrates of P- gp, CYP3A, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 with narrow therapeutic index
Digoxin
Phenytoin
Tacrolimus
Warfarin
Carbamazepine
Quinidine
Cyclosporine

Midazolam Triazolam Lansoprazole Omeprazole Tolbutamide Tizanidine Dextromethorphan Nebivolol

The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of.

Appendix IV (Clinical Trial Wallet Card) should be provided to patients.

5.8.2 Prohibited Therapies **(20-OCT-2021) (09-DEC-2021)**

Prohibited medication(s)

- Antineoplastic therapy or other investigational therapy for the treatment of cancer
- Prophylactic use of hematopoietic colony stimulating factors
- In vitro, tazemetostat is metabolized primarily by CYP3A and to a lesser extent by CYP2C8 and CYP2D6. It is a P-gp substrate but not a substrate of BCRP, OAT1B1, OAT1B3, OAT3, OCT2, and MATE1. Therefore, treatment with strong and moderate inhibitors or inducers of CYP3A should be avoided from 14 days prior to the first dose of tazemetostat to the end of the study. Strong inhibitors and inducers of CYP2C8, 2D6, and P-gp should be used with caution.

Strong CYP3A4 inhibitors	**Strong CYP3A4 inducers**
Indinavir Nelfinavir Clarithromycin Itraconazole Ketoconazole Nefazodone Saquinavir Suboxone Telithromycin Boceprevir Cobicistat Danoprevir Ritonavir Grapefruit Jiuce Posaconazole Telaprevir Troleandomycin Voriconazole	Nevirapine Barbiturates Carbamazepine Enzalutamide Oxcarbazepine Modafinil Phenytoin Rifampin Rifabutin Apalutamide Mitotane St. John's wort
Moderate CYP3A4 inhibitors	**Moderate CYP3A4 inducers**

Aprepitant Ciprofloxacin Conivaptan Crizotinib Cyclosporine Diltiazem Dronedarone Erythromycin Fluconazole Fluvoxamine Imatinib Tofisopam Verapamil	Bosentan Efavirenz Etravirine Phenobarbital Primidone

- Non-approved herbal medications or supplements

The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of.

Appendix IV (Clinical Trial Wallet Card) should be provided to patients.

5.9 Duration of Therapy (20-OCT-2021)

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s), as described in Section 6
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator, including non-compliance taking the study drug.

Note:

- Patient has the right to refuse further treatment, but that does not necessitate withdrawing consent for participation in the study (e.g. follow-up) (See Section 8.3.1 re study consent withdrawal)
- If all protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.

6. TREATMENT MODIFICATIONS/MANAGEMENT

Agent	Starting Dose	Dose -1	Dose -2
Tazemetostat	800 mg BID	600 mg BID	400 mg BID

No modification of dose is required for the following grade 3 or greater non-hematologic toxicities:

- Transient fatigue or asthenia (return to grade 1 within 7 days)
- Transient myalgia or arthralgia (return to grade 1 within 7 days)
- Nausea that resolves to < grade 2 within 7 days (with or without anti-emetics)
- Vomiting that resolves to < grade 2 within 48 hours (with or without anti-emetics)
- Diarrhea that resolves to < grade 2 within 48 hours (with or without anti-diarrheal medications)

Other toxicities that, in the opinion of the Investigator are possibly, probably, or definitely related to the study treatment, should be managed per Table 1 below. Toxicities that are felt by the Investigator to be unrelated to tazemetostat but clinically significant should be discussed with the study PI. In the event of an urgent unrelated toxicity, study treatment should be interrupted per Table 1. Dose re-escalation is not permitted.

Table 1: Dose modifications for treatment related toxicities

Toxicity[a]	**During Therapy**	**Approximate Dose Adjustment[b]**
Grade 1		
All occurrences	Continue study treatment	Maintain dose level
Grade 2[c]		
All occurrences	Continue study treatment	Maintain dose level
Grade 3[d] (not including neutropenia)		
1st occurrence	Interrupt study treatment until resolved to Grade ≤ 1 or baseline[b]	Restart at 600 mg BID
2nd occurrence		Restart at 400 mg BID
3rd occurrence	Discontinue study treatment	Not applicable
Grade 3[d] neutropenia (ANC <1000-500/mcl) (XX-APR-2022)		
1st occurrence	Interrupt study treatment until resolved to ANC ≥ 1,500/mcl	Maintain dose level
2nd occurrence		Restart at 600 mg BID
3rd occurrence		Restart at 400 mg BID
4th occurrence	Discontinue study treatment	Not applicable
Grade 3 Thrombocytopenia with bleeding and Grade 4 Thrombocytopenia (Platelets <25,000-50,000)		
1st occurrence	Interrupt study treatment until resolved to ≥75,000/mcl	Restart at 600 mg BID
2nd occurrence		Restart at 400 mg BID
3rd occurrence		Restart at 400 mg BID
4th occurrence	Discontinue study treatment	Not applicable
Grade 4		
All occurrences	Interrupt study treatment until resolved to Grade ≤ 1 or baseline and discuss with study chair	Pending discussion with study chair

ANC = absolute neutrophil count; BID = twice daily

a. Excluding alopecia, nausea, vomiting or diarrhea not receiving adequate treatment
b. A delay of tazemetostat for more than 14 days due to any toxicity requires discontinuation of study treatment.
c. Any case of grade 2 toxicity where investigator believes that an interruption or dose modification is warranted should be discussed with study chair.
d. Excludes Grade 3 anemia: Subjects are allowed to continue tazemetostat at the current dose level with transfusions per investigator discretion.

- If a new case of T-LBL/T-ALL occurs in patients then the patient will be discontinued from treatment, a case assessment will be conducted to better understand the event, and enrollment will be suspended.
  - Patients on study who continue to derive clinical benefit will be maintained on therapy.
- For any MDS/AML or other myeloid malignancies like MPN:
  The patient will be discontinued from treatment, and a case assessment will be conducted to better understand the event.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agent administered in NRG-GY014, tazemetostat, is being made available under an IND sponsored by DCTD, NCI. For patients receiving tazemetostat, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in section 7.4.2 of the protocol.

7.2 Adverse Events and Serious Adverse Events

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Tazemetostat (NSC 791066) (07-JUL-2020) (20-OCT-2021) (11-JAN-2023)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 941 patients.* Below is the CAEPR for Tazemetostat.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, November 16, 2022[1]

Adverse Events with Possible Relationship to Tazemetostat (EPZ-6438) (CTCAE 5.0 Term) [n= 941]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Bronchial infection		
	Upper respiratory infection		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
	Creatinine increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	Weight loss		

Adverse Events with Possible Relationship to Tazemetostat (EPZ-6438) (CTCAE 5.0 Term) [n= 941]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyperglycemia		
	Hypertriglyceridemia		
	Hyponatremia		
	Hypophosphatemia		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
		Treatment related secondary malignancy[2]	
	Tumor pain		
NERVOUS SYSTEM DISORDERS			
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Cough	***Cough (Gr 2)***
		Dyspnea	***Dyspnea (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		
		Photosensitivity	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Treatment related secondary malignancies includes Peripheral T-cell lymphoma (PTCL), T-cell lymphoblastic lymphoma (T-LBL), and B-cell acute lymphoblastic leukemia (B-ALL). It may be worth noting that the adult patient observed with B-ALL may be due to an underlying Diffuse large B-cell lymphoma (DLBCL).

Adverse events reported on Tazemetostat trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Tazemetostat caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia
CARDIAC DISORDERS - Chest pain - cardiac; Left ventricular systolic dysfunction
EAR AND LABYRINTH DISORDERS - Vertigo
ENDOCRINE DISORDERS - Hypothyroidism
EYE DISORDERS - Dry eye; Periorbital edema; Vision decreased; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastric perforation; Gastrointestinal disorders - Other (defecation urgency); Hemorrhoids; Mucositis oral; Rectal hemorrhage; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Flu like symptoms; General disorders and administration site conditions - Other (early satiety); General disorders and

administration site conditions - Other (general physical health deterioration); Localized edema; Malaise; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Gallbladder obstruction; Hepatobiliary disorders - Other (hepatocellular injury)
INFECTIONS AND INFESTATIONS - Conjunctivitis; Device related infection; Esophageal infection; Infections and infestations - Other (lower respiratory tract infection); Lung infection; Pharyngitis; Sepsis; Sinusitis; Skin infection; Soft tissue infection; Thrush; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; CPK increased; Electrocardiogram QT corrected interval prolonged; Investigations - Other (c-reactive protein increased); Serum amylase increased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperkalemia; Hyperlipidemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Metabolism and nutrition disorders - Other (diabetic metabolic decompensation); Metabolism and nutrition disorders - Other (polydipsia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Muscle cramp; Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage
NERVOUS SYSTEM DISORDERS - Dizziness; Dysesthesia; Dysgeusia; Dysphasia; Hydrocephalus; Lethargy; Memory impairment; Nervous system disorders - Other (vocal cord paralysis); Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Radiculitis; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Depression; Hallucinations; Insomnia; Psychiatric disorders - Other (mood swings)
RENAL AND URINARY DISORDERS - Proteinuria; Renal and urinary disorders - Other (polyuria); Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (vulvovaginal rash)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Nasal congestion; Oropharyngeal pain; Pleural effusion; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (tachypnea)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Hair color changes; Hair texture abnormal; Hirsutism; Hyperhidrosis; Hypertrichosis; Nail ridging; Pruritus; Purpura; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (HSV oral infection); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin hyperpigmentation; Urticaria
VASCULAR DISORDERS - Hot flashes; Hypertension; Superior vena cava syndrome; Thromboembolic event; Vascular disorders - Other (peripheral venous disease)

Note: Tazemetostat (EPZ-6438) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Note: AESI: Based on preclinical findings in toxicology studies, FDA has requested the following Adverse Events of Special Interest (AESI) to be reported in an expedited manner: 1) T-cell lymphoma; and 2) abnormal bone growth. It should be noted that abnormal bone growth has not been observed in clinical trials of tazemetostat (EPZ-6438).

7.4 Expedited Reporting of Adverse Events (06-APR-2022)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via https://ctepcore.nci.nih.gov/ctepaers/security/login

Submitting a report via CTEP-AERS serves as notification to NRG and satisfies NRG requirements for expedited adverse event reporting.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to CTEP for this study by telephone at 301-897-7497 and to the NRG Regulatory Affairs by phone at 215-854-0770. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.4.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting Requirements, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a complete report within 3 days.
- Supporting source documentation is requested by the IND Sponsor for this study (CTEP/DCTD) and NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to CTEP at 301-230-0159 and to NRG Regulatory Affairs at 215-854-0716.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.
-

7.4.2 Expedited Reporting Requirements for Adverse Events (06-APR-2022)

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 3 Calendar Days

Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via electronic submission within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur **more than** 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

7.4.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.4.4 Secondary Malignancies

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

Please see Section 7.3 for reporting of AESIs.

8. REGISTRATION AND STUDY ENTRY PROCEDURES (08/13/2019) (07-JUL-2020)

8.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR – MD, DO, or international equivalent;
- NPIVR – advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP – clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (such as the Roster Update Management System [RUMS], OPEN, Rave, acting as the primary site contact, or with consenting privileges;
- Associate (A) – other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) – individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				

Documentation Required	IVR	NPIVR	AP	A	AB
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval.

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

8.2 CTSU Registration Procedures (06-APR-2022)

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

8.2.1 IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU

website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

8.2.2 Downloading Site Registration Documents:

- Download the site registration forms from the NRG-GY014 page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To review/download site registration forms:Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen:
  - Enter the protocol # NRG-GY014 in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select NRG, and protocol # NRG-GY014.
- Click on *Documents*, *Protocol Related Documents,* and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

8.2.3 Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

8.2.4 Checking Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the sites 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

8.3 Patient Enrollment (20-OCT-2021) (09-DEC-2021) (06-APR-2022)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB

approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN for Step 1 registration, site staff should verify the following:

- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).
- All eligibility criteria, as determined by pre-screening and patients' medical history/pathology report, must be met prior to Step 1 registration (See Sec 4.1).

Sites will be notified via email to proceed with Step 2 registration after study chair review of the submitted pathology and NGS reports. **Please make sure to supply the email for the individual who should be notified of the approval to proceed to Step 2 registration as requested in OPEN.**

Prior to accessing OPEN for Step 2 registration, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.3.1 Patient-Initiated Consent Withdrawal from the Study **(20-OCT-2021)**

If a patient chooses to have no further interaction regarding the study (i.e., allow no future follow up data to be submitted to NRG Oncology), the study applicable form should be completed in Medidata Rave to report the patient's consent withdrawal.

NOTE: This should not be done if the patient has only chosen to stop protocol treatment and is willing to still be followed. (See Section 5.9)

8.4 Data Submission / Data Reporting (20-OCT-2021) (06-APR-2022)

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;

- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave* Home and click to accept the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

9.0 DRUG INFORMATION

9.1 Tazemetostat (EPZ-6438, E7438), NSC #791066 (06-APR-2022)

9.1.1 Chemical Name or Amino Acid Sequence: N-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-yl)methyl]-5-[ethyl(tetrahydro-2H-pyran-4-yl)amino]-4-methyl-4'-(morpholin-4-ylmethyl)biphenyl-3-carboxamide hydrobromide

Classification: Enhancer of zeste homolog 2 (EZH2) Inhibitor

CAS Registry Number: 1467052-75-0

Molecular Formula: C34H45BrN4O4 (Hydrobromide salt)
C34H44N4O4 (Free base)

M.W.: 653.65 (Hydrobromide salt)
572.74 (Free base)

9.1.2 Approximate Solubility: Soluble in 0.1 N hydrochloride (HCl) solution, very slightly soluble in water and ethanol, and practically insoluble in phosphate buffered saline (PBS, pH 7.4).

9.1.3 Mode of Action: Tazemetostat is a selective, reversible, S-adenosylmethionine (SAM)-competitive small molecule inhibitor of the enhancer of zeste homolog 2 (EZH2), a histone methyltransferase (HMT). Tazemetostat selectively inhibits intracellular H3K27 methylation.

9.1.4 Description: The tazemetostat HBr salt form is a white powder.

9.1.5 How Supplied: Epizyme supplies and PMB, CTEP, DCTD, NCI distributes tazemetostat as film-coated tablets.

Film-coated tablets are red, round, and biconvex with a diameter of approximately 10 mm containing 200 mg of drug substance (as free base). Tablets are supplied in 240-count white HDPE bottles with desiccants and child resistant, tamper-evident polypropylene screw caps. The excipients are lactose monohydrate, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate, hypromellose, talc, polyethylene glycol, titanium dioxide, and ferric oxide (red).

9.1.6 Storage: *Film-coated tablets:* Do not store above 25°C (77°F). Brief excursion (less than 4 hours) up to 30°C is allowable. Store in the original package and protect from moisture.

If a storage temperature excursion is identified, promptly return tazemetostat tablets to below 25°C (77°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.1.7 Stability: Stability studies are ongoing. Dispense tablets in the original manufacturer's container. If tablets are transferred to a pharmacy vial, they should be assigned a 30-day expiration.

9.1.8 Route of Administration: Oral without regard to meals. Doses must be taken twice per day with no less than 8 hours between each dose. If a dose is missed or vomited, skip the dose and take the next scheduled dose. **(20-OCT-2021)**

9.1.9 Method of Administration: The tablets should be taken whole and not cut, crushed or chewed.

9.1.10 Potential Drug Interactions: **(20-OCT-2021)** In vitro, tazemetostat is metabolized primarily by CYP3A and to a lesser extent by CYP2C8 and CYP2D6. It is a P-gp substrate but not a substrate of BCRP, OAT1B1, OAT1B3, OAT3, OCT2, and MATE1. Therefore, treatment with strong and moderate inhibitors or inducers of CYP3A should be avoided from 14 days prior to the first dose of tazemetostat to the end of the study. Strong inhibitors and inducers of CYP2C8, 2D6, and P-gp should be used with caution.

In vitro, tazemetostat inhibits MATE1 and MATE2K. Tazemetostat does not inhibit CYP1A2, 2B6, 2C9, 2D6, P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, or BSEP at clinically relevant concentrations. Tazemetostat also induces CYP3A4. Medications that are substrates of CYP3A or P-gp with a narrow therapeutic index and substrates of MATE1 and MATE2K should be used with caution.

9.1.11 Special Handling: Adequate precautions must be taken to avoid direct contact of tazemetostat powder to skin/mucous membranes.

9.1.12 Patient Care Implications:

Prolonged exposure to sunlight should be avoided during treatment with tazemetostat. Patients should wear protective clothing, sunscreen, and avoid tanning beds.

Females of childbearing potential should agree to remain abstinent (refrain from heterosexual intercourse) or use adequate contraceptive methods while receiving tazemetostat and for 6 months after the last dose of tazemetostat. Female subjects that use hormonal contraceptives should also use an additional barrier method. Women should not breastfeed during treatment and for 1 week after the last dose of tazemetostat.

9.1.13 Adverse Events

Please see Section 7.3. for the Tazemetostat CAEPR.

9.1.14 Agent Ordering

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Sites may order initial agent supplies after a subject has been enrolled onto the study. Please provide the subject ID number in the comment box of the order.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

9.1.15 Agent Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

9.1.16 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

9.1.17 Useful Links and Contacts

- *CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/*
- *NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov*
- *PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm*
- *PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/*
- *CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/index.jsp*
- *CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov*
- *IB Coordinator: IBCoordinator@mail.nih.gov*

- *PMB email: PMBAfterHours@mail.nih.gov*
- *PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)*

10. PATHOLOGY/BIOSPECIMEN (20-OCT-2021)

10.1 Central Pathology Review
Not Applicable.

10.2 Biospecimen Selection for Integral Biomarker Testing (20-OCT-2021)
As outlined in section 2.3 above, analysis of data obtained from stage 1 of the study resulted in protocol modification. As of version date 20-OCT-2021, all patients with clear cell ovarian cancer enrolled on trial will be required to have a document ARID1A pathologic variant or likely pathologic variant mutation based on NGS assessment.

10.3 Biospecimen Selection for Integrated Biomarker Testing (20-OCT-2021)
NOTE: As of version date 20-OCT-2021, Sections 10.3.1-10.3.5 are no longer applicable.

10.3.1 Integrated Biomarker to be Tested (08/13/2019)
BAF250a expression will be evaluated by immunohistochemistry (IHC) as an indicator of *ARID1A* mutation status and correlated with clinical response to study drug.

ARID1A mutation analysis will be evaluated by MSK-IMPACT.

10.3.2 Integrated Biomarker Testing Requirements and Reporting (08/13/2019)
Formalin-fixed, paraffin-embedded (FFPE) tumor tissue and DNA extracted from whole blood will be used for BAF250A IHC and *ARID1A* mutation analysis (i.e., MSK-IMPACT). See Mandatory Biospecimen Submission Table (Section 10.4.1) for details.

IHC test results will be considered positive (RETAINED) if any of the tumor nuclei are immunoreactive and negative (LOSS) if all tumor nuclei show no staining. The result will be interpreted as a technical failure and subsequently repeated on an additional slide if all nuclei on the slide show no immunoreactivity.

10.3.3 Method of Integrated Biomarker Testing (08/13/2019)
Only one tumor type will be tested. If more than one tumor type is submitted, the more advanced and most recently obtained tumor type will be tested (e.g., a metastatic lesion rather than a primary; recurrent or persistent tumor rather than a primary or metastatic tumor from a previously untreated patient).

IHC will be used to measure BAF250a expression. One slide will be stained for BAF250a (Sigma, Catalog # HPA005456) and one with hematoxylin and eosin (H&E). The H&E will confirm there is normal tissue present on the slide to serve as a normal control. All stained slides will be reviewed by a gynecologic pathologist.

MSK-IMPACT (Cheng, 2015; FDA DEN170058) will be used to determine *ARID1A*

mutation status. This next generation sequencing (NGS) assay is comprised of ≥467 genes including alternate components of the SWI/SNF pathway (e.g., *ARID1B*, *ARID2*, *SMARCA4*, *SMARCB1*, *SMARCD1*, and *PBRM1*).

10.3.4 Location of Integrated Biomarker Testing

Integrated biomarker testing will be done by Dr. David Hyman at Memorial Sloan Kettering Cancer Center.

10.3.5 Biospecimen Submission for Integrated Biomarker Testing (08/13/2019)

Four unstained sections (charged, 5µm) of FFPE tumor tissue are needed for IHC; additional unstained sections and DNA isolated from whole blood will be used for MSK-IMPACT. Clear cell or endometrioid carcinoma AND normal tissue must be present in the tissue section placed on each slide. See Mandatory Biospecimen Submission Table (Section 10.4.1) for details.

10.4 Biospecimen Submission Tables

Biospecimens listed below should not be submitted until after patient registration and Bank ID assignment.

A detailed description of biospecimen procedures can be found in Appendix VI.

10.4.1 Mandatory Biospecimen Submissions (08/13/2019) (20-OCT-2021)

The patient must give permission to participate in this **mandatory** study component. Participating sites are required to submit the patient's biospecimens as outlined below.

Required Specimen (Specimen Code)	Collection Time Point	Sites Ship Specimens To
FFPE TUMOR – Submit *one* of the following		
FFPE Primary Tumor (FP01)[1,2] 1st Choice: block 2nd Choice: 20 unstained consecutive slides (charged, 5µm)	Archival tumor collected prior to the patient receiving any treatment *Submit **one** - Primary preferred; submit metastatic if primary not available*	NRG BB-Columbus within 8 weeks of registration[3]
FFPE Metastatic Tumor (FM01)[1,2] 1st Choice: block 2nd Choice: 20 unstained consecutive slides (charged, 5µm)		
FFPE Primary Neoadjuvant Tumor (FPT01)[1,2] 1st Choice: block 2nd Choice: 20 unstained consecutive slides (charged, 5µm)	Archival tumor collected after the patient received neoadjuvant treatment, but prior to the patient receiving study treatment *Submit **one** if tumor collected prior to the patient receiving any treatment is not available*	
FFPE Metastatic Neoadjuvant Tumor (FMT01)[1,2] 1st Choice: block 2nd Choice: 20 unstained consecutive slides (charged, 5µm)		
FFPE Recurrent Primary Tumor (FRP01)[1,2] 1st Choice: block 2nd Choice: 20 unstained consecutive slides (charged, 5µm)	Archival tumor collected prior to the patient receiving study treatment	

FFPE Recurrent Metastatic Tumor (FRM01)[1,2] 1st Choice: block 2nd Choice: 20 unstained consecutive slides (charged, 5µm)	*Submit **one** if tumor collected prior to the patient receiving any treatment or tumor collected after the patient received neoadjuvant is not available*	
FFPE Persistent Primary Tumor (FPP01)[1,2] 1st Choice: block 2nd Choice: 20 unstained consecutive slides (charged, 5µm)		
FFPE Persistent Metastatic Tumor (FPM01)[1,2] 1st Choice: block 2nd Choice: 20 unstained consecutive slides (charged, 5µm)		
BLOOD		
Whole Blood (WB01) 7-10mL drawn into purple top (K2EDTA) tube(s)	Prior to or after starting study treatment	NRG BB-Columbus the day the specimen is collected[3]

1 A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the NRG BB-Columbus.

2 **Clear cell AND normal tissue must be present in the FFPE submitted for biomarker testing**
.

3 NRG BB-Columbus / Protocol NRG-GY014, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

10.5 Exploratory Biomarker Testing (08/13/2019)

10.5.1 SWI/SNF Pathway Mutation Analysis (08/13/2019) (20-OCT-2021)

DNA isolated from FFPE and whole blood will be used to identify potential mutations predictive of response, with preserved BAF250a expression **(for patients enrolled prior to the 20-OCT-2021 version date)**. The next generation sequencing (NGS) assay to be used, MSK-IMPACT, comprises n≥467 other genes including alternate components of the SWI/SNF pathway (e.g., *ARID1B*, *ARID2*, *SMARCA4*, *SMARCB1*, *SMARCD1*, and *PBRM1*).

10.6 Banking Biospecimens for Future Research

Details regarding the banking and use of biospecimens for future research can be found in Appendix VI.

11. SPECIAL STUDIES (NON-TISSUE)

Not Applicable.

12. MODALITY REVIEWS

Not Applicable.

13. ASSESSMENT OF EFFECT

13.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (uni-dimensional

measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

13.1.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment on study.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

13.1.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan, as ≥20 mm by chest x-ray, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal/pelvic masses (identified by physical exam and not CT or MRI), are considered as non-measurable.

Notes:
Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

13.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, subsequent image acquisitions should use the same type of scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

NRG Oncology will not allow PET-CT use for RECIST 1.1 response criteria.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of

FDG-PET imaging can be identified according to the following algorithm:

a. *Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.*
b. *No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.*
c. *FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.*

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

13.1.4 Response Criteria

13.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters (i.e. the nadir) while on study.

13.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s)

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of only "non-target" lesions is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

13.1.4.3 Evaluation of Best Overall (unconfirmed) Response

The best overall response is the best time point response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum recorded since the treatment started. The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

Time Point Response for Patients with only Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

13.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since date of study entry, including the baseline measurements.

13.1.6 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first.

13.1.7 Survival

Survival is defined as the duration of time from study entry to time of death or the date of last contact.

14. DATA AND RECORDS

14.1 Data Management/Collection

Data collection for this study will be done exclusively through Medidata Rave®. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS (Regulatory Support System). To access iMedidata/Rave, the site user must have an active CTEP-IAM account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization rosters at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts also will receive a separate invitation from iMedidata to activate their account. Account activation instructions

are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

14.2 NRG Data Management Forms

Refer to the CTSU member website for the table of Required Form and Materials.

14.3 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7.4 for information about expedited and routine reporting.

14.4 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

15. STATISTICAL CONSIDERATIONS

15.1 Study Design (-20-OCT-2021)

The data showed promise of activity in Cohort A among the patients with ARID1A mutated clear cell ovarian cancer, so the study will examine this population with more patients.

The original study involved two distinct cohorts to be examined separately and independently. Cohort A included patients with clear cell or endometrioid histology who had recurrent or persistent ovarian or peritoneal cancer (measurable disease by RECIST v1.1). Cohort B included patients who had recurrent or persistent endometrioid endometrial adenocarcinoma (measurable disease by RECIST v1.1). Each cohort included unselected subsets of *ARID1A* mutation positive patients and *ARID1A* wild types. These patients could have been accrued in two stages. The first stage targeted a sample size of 16 patients but allowed between 12 and 19 patients to enroll. If 1 or fewer patients out of 12 to 14 patients responded (objective complete or partial responses), or if 2 or fewer patients out of 15 to 19 responded, then the drug was considered clinically uninteresting in that cohort and stopped early for futility. Otherwise the study was designed to continue with the cohort assuming medical judgment indicated. If the study proceeded, then a cumulative sample size of 40 patients would have been targeted but allowed to deviate from 36 to 43 patients. If 6 or fewer patients responded out of 36 to 39 patients, or 7 patients or fewer responded out of 40 to 43, then the drug would have been deemed clinically uninteresting and not worthy of further investigation. Otherwise, the drug could have been deemed clinically interesting with medical judgment indicating and considered for further study with that cohort.

The study is not randomized so there were no stratification factors.

There is no robust historical data available on what the anticipated response probability will be in this patient population, so we tested whether the proportion responding was indicative of treatment activity for the agent in the patient population based on a wider group of recurrent patients. The null hypothesis for both cohorts was that the probability of a patient responding to treatment is 10% or less (i.e. Ho: $p \leq 0.10$). The alternative hypothesis was that the probability of response is 30% or more (i.e. Ha: $p \geq 0.30$). Using the decision rules listed above, the study had a 71% chance of stopping early when the treatment is not active (i.e. p=0.10). The overall probability of a type I error (alpha) is 5% for each cohort. On the other hand, if the drug is active with p=0.30, then the decision rules had a 90% chance of correctly declaring the regimen interesting and worthy of further investigation.

Design for the Cohort of Patients with Ovarian Clear Cell Carcinoma (OCCC) ARID1A pathologic variant or likely pathologic variant Mutation:

A cumulative sample size of 40 patients with ovarian clear cell carcinoma is targeted as the second stage of the trial for Cohort A. To be eligible for the second stage, patients must be ARID1A mutant. The population being targeted is different from the original population. Following the rules of the original design, accrual is allowed to deviate from 36 to 43 patients. If 6 or fewer patients responded out of 36 to 39 patients, or 7 patients or fewer responded out of 40 to 43, then the drug would have been deemed clinically uninteresting and not worthy of further investigation. Otherwise, the drug will be deemed clinically interesting with medical judgment indicating and considered for further study with that cohort.

It is difficult to assess the operating characteristics of the design because the populations in each stage are different. For simplicity, let's assume the Ho: $p_1 \leq 0.10, p_2 \leq 0.10$ where p1 and p2 are the probabilities of response for ARID1A mutant and wild type patients, respectively, under the hypothesis that the drug is not active in either population. In addition, we will assume that Ha: $p_1 \geq 0.30, p_2 \leq 0.10$ under the alternative hypothesis. This hypothesis implies that the drug is active for ARID1A mutant patients but not for ARID1A wild type. Lastly, let's assume that 19 patients were enrolled in Stage 1 with 10 patients who were wild types and that 21 are enrolled in Stage 2. The first stage decision rules were not necessarily followed, so a simplifying assumption will be that the number of responses among the ARID1A mutant patients is $X_1 \sim Bin(n = 9 + 21, p_1)$ and the number of responses among the ARID1A wild type patients is $X_2 \sim Bin(n = 10, p_2)$. Let $T = X_1 + X_2$, the total number of responses. The distribution of the total number of responses is given by:

$$f_T(t) = \sum_{x_2=max(0,t-n_1)}^{min(n_2,t)} f_{x_1}(t - x_2) \cdot f_{x_2}(x_2)$$

When Ho is true, $P(T \leq 7) = 0.958$, which leads to acceptance of the null hypothesis. The probability of a type I error is 0.042. When Ha is true, $P(T \leq 7) = 0.177$, which would lead to rejection of Ha. The power of the study is 0.823.

15.2 Study Endpoints

15.2.1 Primary Endpoint (20-OCT-2021

Tumor response as defined by RECIST v 1.1. If the patient fails to respond (including stable disease), she will be classified as a non-responder for the purposes of the decision rule.

15.2.2 Secondary Endpoints (20-OCT-2021)

Tumor response in patients with *ARID1A* mutations using tumor response as defined by RECIST v 1.1 (including stable disease). If the patient fails to respond, she will be classified as a non-responder for the purposes of the study. **NOTE: This is not a secondary endpoint as of version date 20-OCT-2021.**

6-month progression free survival (clinical benefit rate)

Adverse events according to grade of toxicity by organ or organ system.

Progression-free survival.

Overall survival.

15.2.3 Translational Research Endpoints **(08/13/2019) (20-OCT-2021)**

Integrated Endpoint: *ARID1A* mutational status.

BAF250a expression by IHC.

NOTE: This is not a translational research endpoint as of version date 20-OCT-2021

15.3 Sample Size and Power Calculations (20-OCT-2021)

The sample size and power justification for the original design was provided in the paper by Chen and Ng (1998). The revised power calculations use elementary probability.

15.4 Study Monitoring of Primary Objectives 20-OCT-2021)

The objective of the original interim analysis was treatment/study futility. The subsequent study is the second stage evaluation.

The study will be monitored on a quarterly basis by the Early Phase Monitoring Committee (EPTOC).

Interim Analysis for the DMC **NOTE: this does not apply to the study after version date 20 OCT, 2021**

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis.

Since this is not a randomized study, it will be monitored according to the SOP involving single arm studies.

15.5 Accrual/Study Duration Considerations (20-OCT-2021)

The original study was open from 3/29/2019 to 8/2/2019, a duration of 126 days. During this time, 9 patients with ovarian cancer had ARID1A mutations. Based on this result, we anticipate a monthly accrual rate of 2.17 patients per month.

For the original study, the anticipated period of active accrual for Cohort A is 8 months and 12 months respectively for the first and second stage of accrual. The anticipated period of active accrual for Cohort B is 5.3 months and 8 months respectively for the first and second stage of accrual.

For the ARID1A mutated cohort, the anticipated period of active accrual is approximately 10 months.

15.6 Secondary, Translational Research, or Exploratory Endpoints (including correlative science aims) (08/13/2019)

See section 15.2.

15.6.1 Translational Research Integrated Hypotheses and Endpoints: (08/13/2019) (20-OCT-2021)

The null and alternative hypotheses for patients with *ARID1A* are that the probability of response is 10% or less (Ho: $p \leq 0.10$) and 30% or more (Ha: $p \geq 0.30$), respectively. The endpoints are whether or not the patient has an objective tumor response.

The integrated biomarker in the original study is now the integral biomarker.

15.6.2 Definitions of Integrated TR Endpoints and How These Will Be Analyzed (08/13/2019) (20-OCT-2021)

For the definition of the TR endpoints, see section 15.2.

The following points were considered in the original study: The number of patients who are *ARID1A* mutant was not fixed in the original trial. If 16 patients are accrued and the probability of a patient being mutant is 50%, then the chances that the number of people with *ARID1A* mutations being between 4 and 11 is 95%. Within this subset of patients, 90% 1-sided CIs (i.e. CIs of the form $[0, p_U]$) will be constructed for the probability of response. If this CI contains the value of 30% or higher, then the study could be amended to screen patients for *ARID1A* mutations. If the total number of patients with *ARID1A* mutations is 6 or less, then the study will reopen for patients with *ARID1A* mutations. The chances of obtaining 6 or fewer patients with *ARID1A* mutations within a sample of 16 are 23%. The sample size is essentially too small to exclude the possibility of a 30% response rate, regardless of the number of observed responses. If 7 to 11 patients are accrued with *ARID1A* mutations, then 1 or more responses are necessary within this subset before consideration is given to amending the study. If 12 to 15 patients have *ARID1A* mutations, then 2 or more responses are necessary

before consideration is given to amending the study. If 16 patients have *ARID1A* mutations, then 3 or more responses are necessary before consideration is given to amending the study. In this setting, the study has about a 67.6% probability of being amended when the true probability of response is 10% within this subset, and a 95.9% probability of being amended when the true probability of response is 30%.

For the analysis of the ARID1A mutated cohort, the biomarker is now integral so that all additional patients are required to be ARID1A mutated. We anticipate 28 to 32 cases.

For Secondary Endpoints
Adverse events will be tabulated by organ or organ system and grade of toxicity. Comparisons between cohorts may be conducted while emphasizing that the study is not randomized.

Progression-free survival (PFS) and overall survival (OS) will be characterized by quartiles and the median of the distribution with confidence intervals. Kaplan-Meier plots will show an estimate of the survival function for these populations.

An analysis of strictly the ARID1A mutated patients in the second stage will be conducted. If 5 or more out of 21 patients are observed with responses, this analysis will deem the regimen interesting and worthy of further investigation. If the number of evaluable patients deviates from 21, then the 1-sided test will be conducted at the 10% level of significance. This analysis will be a secondary analysis. This study has about 80% power when the probability of response is 30%.

TR Endpoints
Associations between BAF250a and ARID1A mutations may be examined with contingency table analysis (e.g. potentially including Chi-square analyses or Spearman's correlation). Tables may be created to examine response by type of ARID1A mutation among those tumors that express BAF250a to identify potential mutations predictive of response in patients with preserved BAF250a expression.

15.7 Gender/Ethnicity/Race Distribution

15.7.1 Endometrial Patients (20-OCT-2021)

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	0	0	0	3
White	16	0	1	0	16
More Than One Race	0	0	0	0	0
Total	19	0	0	0	19

15.7.2 Ovarian Cancer Patients

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	1	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	0	0	0	2
White	40	0	0	0	40
More Than One Race	0	0	0	0	0
Total	43	0	0	0	43

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APPENDIX I FIGO OVARIAN CANCER STAGING 2014

STAGE I: Tumor confined to ovaries

IA Tumor limited to 1 ovary, capsule intact, no rumor on surface, negative washings.

IB Tumor involves both ovaries otherwise like 1A.

IC Tumor limited to 1 or both ovaries

IC1 Surgical spill
IC2 Capsule rupture before surgery or tumor on ovarian surface
IC3 Malignant cells in the ascites or peritoneal washings

STAGE II: Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer

IIA Extension and/or implant on uterus and/or Fallopian tubes

IIB Extension to other pelvic intraperitoneal tissues

STAGE III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

IIIA Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis

IIIA1 Positive retroperitoneal lymph nodes only
IIIA1(i) Metastasis ≤ 10 mm
IIIA1(ii) Metastasis > 10mm

IIIA2 Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes

IIIB Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.

IIIC Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.

STAGE IV: Distant metastasis excluding peritoneal metastasis

IVA Pleural effusion with positive cytology

IVB Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity).

Other major recommendations are as follows:

- Histologic type including grading should be designated at staging
- Primary site (ovary, Fallopian tube or peritoneum) should be designated where possible
- Tumors that may otherwise qualify for stage I but involved with dense adhesions justify upgrading to stage II if tumor cells are histologically proven to be present in the adhesions

APPENDIX II FIGO STAGING OF ENDOMETRIAL CARCINOMA 2009

Stage I* Tumor confined to the corpus uteri.
IA* No or less than half myometrial invasion
IB* Invasion equal to or more than half of the myometrium
Stage II* Tumor invades cervical stroma, but does not extend beyond the uterus**
Stage III* Local and/or regional spread of the tumor
IIIA* Tumor invades the serosa of the corpus uteri and/or adnexae[#]
IIIB* Vaginal and/or parametrial involvement[#]
IIIC* Metastases to pelvic and/or para-aortic lymph nodes[#]
IIIC1* Positive pelvic nodes
IIIC2* Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV* Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA* Tumor invasion of bladder and/or bowel mucosa
IVB Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

*Either G1, G2, or G3.

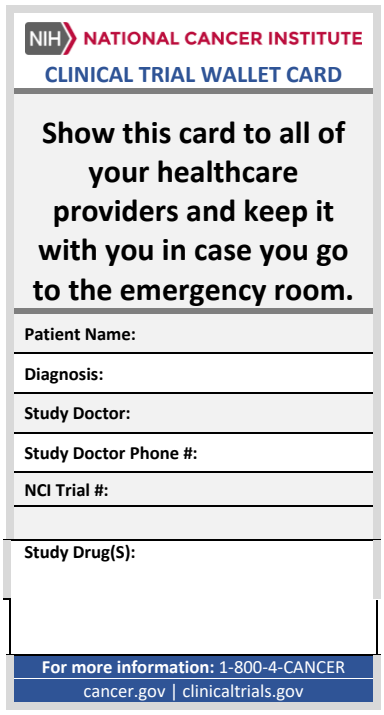
**Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

[#]Positive cytology has to be reported separately without changing the stage.

APPENDIX III PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX IV CLINICAL TRIAL WALLET CARD (20-OCT-2021)



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

APPENDIX V- PATIENT MEDICATION CALENDAR – TAZEMETOSTAT (20-OCT-2021) (09-DEC-2021) (06-APR-2022)

This is a calendar on which you are to record the number of tazemetostat tablets you take each day. The instructions on how to take the tazemetostat are below.

Use the calendar to record date, time and number of tazemetostat tablets taken each day. You will start by taking 800 mg (four 200 mg tablets) of tazemetostat twice each day for 28 days. This 28-day time period is called a cycle. It is possible your doctor may reduce the amount of tazemetostat you take while participating in this study. Your doctor will discuss the new treatment plan with you at that time. Medication should be taken as instructed without skipping any medications. If you have missed a dose please mark down as "0" in the # slot for that day. If your doctor changes the amount of tazemetostat you take, please be sure to write down the correct number of pills and correct amount taken in the columns below.

Tazemetostat can be taken with or without a meal, but there must be at least 8 hours between doses. Tablets must be swallowed whole and must not be cut, crushed or chewed.

If a dose is missed or vomited, skip the dose and take the next scheduled dose.

You should not take CYP3A inhibitors or inducers while on this study. You will be given a clinical trial wallet card to share with any of your healthcare providers,

You should not drink or eat grapefruit juice, Seville oranges or grapefruit while on this study.

Note to staff: Please give patient a drug log at initial enrollment and every week 4 visit. Instruct patient how to complete the diary log. If they are taking the first dose at a visit complete the log with them. Remind them they must bring the log back at each visit along with pill bottles, empties included.

Please note: Medication Calendar should be brought to each appointment along with medication bottles (empty included).

NRG-GY014 PATIENT MEDICATION CALENDAR-TAZEMETOSTAT

Patient Name_____ Patient Study ID_____

Instructions: Take ___ tablets 2 times a day (at least 8 hours apart)

Day	Date	First Dose Time	# of 200mg tablets	Second Dose Time	# of 200mg tablets	Comments
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						

Patient Signature _____ Date _____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient started this cycle _____ This is cycle #_____
3. Patient's planned total daily dose for this cycle_____
4. Total number of tablets taken this month_____
5. Number or pills returned/unused this month _____
6. Physician/Nurse/Data Manager's Signature_____

APPENDIX VI – TRANSLATIONAL SCIENCE BIOSPECIMEN PROCEDURES (20-OCT-2021) (09-DEC-2021)

I. Obtaining a Bank ID for Translational Science Biospecimens

One Bank ID (N# # # # # # # # #) is assigned per patient per study. All translational science biospecimens and accompanying paperwork must be labeled with this coded patient number.

A Bank ID is automatically assigned once the Specimen Consent is completed and indicates that a patient has agreed to participate in the translational science component.

Please contact User Support (support@nrgoncology.org) if you need assistance.

II. Requesting Translational Science Biospecimen Kits

Kits are not provided for this protocol. A pre-paid FedEx air bill is provided for the submission of whole blood via the online Kit Management system (https://kits.bpc-apps.nchri.org/).

III. FFPE Tissue Shipped to the NRG BB-Columbus

Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the specimen type (e.g., primary, metastatic, recurrent, persistent).

- Archival **primary (FP01)** and **metastatic (FM01)** tumor should be collected prior to the patient receiving any treatment.

- **Primary neoadjuvant (FPT01)** and **metastatic neoadjuvant (FMT01)** tumor should be collected after the patient received neoadjuvant treatment, but prior to the patient receiving study treatment.

- **Recurrent** and **persistent** tumor should be collected prior to the patient receiving any study treatment. Recurrent or persistent tumor collected from the site of primary disease should be labeled **recurrent primary (FRP01)** or **persistent primary (FPP01)**, respectively. Recurrent or persistent tumor collected from a site other than the site of primary disease (e.g., lymph node) should be labeled **recurrent metastatic (FRM01)** or **persistent metastatic (FPM01)**, respectively.

Only one block may be submitted per tissue type.

All FFPE tissue should be submitted with the corresponding pathology report.

Mandatory FFPE Biospecimen Requirement (08/13/2019)

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then 20 unstained slides (charged, 5µm) should be submitted. All tissue sections must be cut sequentially from one block.

Note: Clear cell AND normal tissue must be present in the FFPE tissue submitted for biomarker testing.

Completing Form TR for FFPE Biospecimens

The type of biospecimen (block or slides) should be specified on Form TR. If submitting slides, the slide type, thickness, and count should also be specified.

Labeling FFPE Tissue
A waterproof permanent marker or printed label should be used to label each translational science tissue biospecimen with:

Bank ID (N# # # # # # # # #)*
Patient ID (e.g., AB###-GY014-#####)
specimen code (see section 10.4.1)
collection date (mm/dd/yyyy)
surgical pathology accession number
block number

**Leading zeros may be omitted when labeling biospecimens with the Bank ID. For example, N00000010 may be written as N10.*

Note: If labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

IV. Whole Blood Shipped to the NRG BB-Columbus
1. Label the lavender/purple top (EDTA) collection tube(s) as described below. Multiple tubes may be used to collect the required amount.
2. Draw 7-10mL of blood into the labeled lavender/purple top tube(s). A minimum of 3mL is needed for processing.
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.
4. Ship whole blood to the NRG BB-Columbus the day the biospecimen is collected. If the whole blood absolutely cannot be shipped the day it is collected, the tube(s) should be refrigerated (4°C) shipped within 24 hours. Do not collect whole blood the day before a holiday.

Labeling Whole Blood
A waterproof permanent marker or printed label should be used to label each translational science whole blood biospecimen with:

Bank ID (N # # # # # # # # # #)*
Patient ID (e.g., AB###-GY014-#####)
specimen code (WB # #)
collection date (mm/dd/yyyy)

**Leading zeros may be omitted when labeling biospecimens with the Bank ID. For example, N00000010 may be written as N10.*

V. Submitting Form TR
A specimen transmittal form (i.e., Form TR) for each biospecimen will be available in the **Translational Research Folder in Rave**, once the Specimen Consent (located in the Baseline

Folder) has been completed.

An electronically (i.e., Rave) completed copy of Form TR must accompany each biospecimen shipped to the NRG BB-Columbus (or alternate laboratory). **Handwritten forms will not be accepted.**

Note: A copy does not need to be sent to the NRG BB-Columbus (or alternate laboratory) if biospecimens are not collected.

Form TR **must** be printed from the Translational Research Form screen in Rave using the **"PDF File" link at the top of the form**. Clicking this link will generate a single page PDF. Do not use the "Printable Version" or "View PDF" links at the bottom of the form or any other method to print the form, as these formats will not be accepted.

Note: Biospecimens will not be marked as received in Rave without receipt of a corresponding electronically completed Form TR. **Incomplete forms or those containing incorrect information will not be processed.**

Retain a printout of the completed form for your records.

Please contact User Support if you need assistance (Email: support@nrgoncology.org; Phone: 716-845-7767).

VI. Shipping Translational Science Biospecimens
Translational science biospecimens should not be shipped until after patient registration and Bank ID assignment.

An electronically completed copy of Form TR must be included for each translational science biospecimen.

All translational science biospecimens should be shipped to:

NRG BB-Columbus / Protocol NRG-GY014
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205
Phone: 614-722-2865
FAX: 614-722-2897
Email: BPCBank@nationwidechildrens.org

A. FFPE Tissue Shipped to the NRG BB-Columbus
FFPE tissue and a copy of the corresponding pathology report should be shipped using your own container at your own expense to the NRG BB-Columbus at the address above.

Do not ship FFPE tissue for Saturday delivery.

B. Whole Blood Shipped to the NRG BB-Columbus
Whole blood biospecimens should be shipped to the NRG BB-Columbus at the address above.

Whole blood biospecimens can be shipped to the NRG BB-Columbus **Monday through Friday for Tuesday through Saturday delivery**. Do not ship whole blood the day before a holiday. Use your own shipping container to ship biospecimens via **FedEx priority overnight**.

When shipping whole blood biospecimens, **your site must comply with IATA standards** (www.iata.org). If you have questions regarding your shipment, contact the NRG BB-Columbus at BPCBank@nationwidechildrens.org or by phoning 866-464-2262.

To ship whole blood biospecimens you will need (1) a sturdy shipping container (e.g., a cardboard or styrofoam box), (2) a leak proof biohazard envelope with absorbent material*, (3) a puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) an Exempt Human Specimen sticker, and (5) a pre-paid FedEx air bill.

**If you will be shipping whole blood biospecimens from more than one patient, please put each biospecimen in a separate plastic zip-lock bag before placing the biospecimens in the shipping bag. You may include up to four different blood biospecimens in one biohazard envelope.*

If you do not have these materials available at your site, you may order them from any supplier (e.g., Saf-T-Pak; Phone: 800-814-7484; Website: www.saftpak.com).

Shipping Whole Blood Using Your Own Shipping Container
1. Place the whole blood biospecimen in a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the bag.
2. Wrap the biohazard envelope in bubble wrap or another padded material.
3. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.
4. Place the Tyvek envelope in a sturdy shipping container (e.g., cardboard FedEx box).
5. Insert a copy of Form TR for each biospecimen.
6. Attach an Exempt Human Specimen sticker to the outside of the shipping container.
7. Print a pre-paid FedEx air bill using the Kit Management link (https://kits.bpc-apps.nchri.org/). Attach the air bill.
8. Make arrangements for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

VII. Banking Translational Science Biospecimens for Future Research
Biospecimens will remain in the NRG BB-Columbus and made available for approved research projects if the patient has provided permission for the use of her biospecimens for future health research.

Note: Testing of banked biospecimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

The patient's biospecimen consent choices will be recorded on the signed informed consent document and electronically via the Specimen Consent form. At the time of biospecimen selection for project distribution, the most recent consent information will be used.

Sites can amend a patient's choices regarding the future use of her biospecimens at any time if the patient changes her mind.

If the patient revokes permission to use her biospecimens, the NRG BB-Columbus will destroy or return any remaining biospecimens. The patient's biospecimens will not be used for any further research; however, any biospecimens distributed for research prior to revoking consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her biospecimens distributed prior to revoking consent.

Note: If return of biospecimens is requested, shipping will be at the site's expense.

APPENDIX VII – COLLABORATIVE AGREEMENT

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). -Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.