IRB#: AAO5917

NCI Protocol #: 9111
Local Protocol #: AAO5917
NCI Version Date: 12/22/2014
TITLE: A Phase 2 Study of Vorinostat (NSC 701852; IND 71976) in Metastatic Uveal Melanoma
Center: Columbia University Medical Center
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Co-Investigators:
Gary K. Schwartz, M.D.
Yvonne Saenger, M.D.
Maura E. Abbott, NP

Collaborating Institution:

<table>
<thead>
<tr>
<th>Collaborating Consortium</th>
<th>Collaborating Site and Principal Investigator</th>
<th>Site’s Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. Lee Moffitt Cancer Center and Research Institute Phase 2 Consortium</td>
<td>Kristin Ancell, MD Vanderbilt University Medical Center 2220 Pierce Avenue 777 PRB Nashville, TN 37232 Telephone: 615-322-4967 E-mail: <a href="mailto:kristin.k.ancell@vanderbilt.edu">kristin.k.ancell@vanderbilt.edu</a></td>
<td>Data Collection and Specimen Analysis</td>
</tr>
<tr>
<td>Memorial Sloan Kettering</td>
<td>Paul Chapman, M.D.</td>
<td>Data Collection and Specimen Analysis</td>
</tr>
<tr>
<td>N/A</td>
<td>Marc-Henri Stern, MD PhD Institut Curie Immunologie 4ème étage 26 rue d’Ulm 75005 Paris cedex 05 France E-mail: <a href="mailto:Marc-Henri.Stern@curie.fr">Marc-Henri.Stern@curie.fr</a></td>
<td>Specimen Analysis Only</td>
</tr>
</tbody>
</table>

NCI Supplied Agent: N-hydroxy-N’-phenyl-octane-1,8-diolic acid diamide; suberoylanilide hydroxamic acid or SAHA or Vorinostat or Zolinza (NSC 701852; IND 71976)
Protocol Type / Version # / Version Date:  
Original/ Version 1/ Version 09/07/2011  
Amended/ Version 3/ Version 03/21/2012  
Amended/ Version 4/ Version 06/19/2012  
Amended/ Version 5/ Version 08/14/2012  
Amended/ Version 6/ Version 01/25/2013  
Amended/ Version 7/ Version 01/15/2014  
Amended/ Version 8/ Version 04/03/2014  
Amended/ Version 9/ Version 08/07/2014  
Amended/Version 10/Version 12/22/2014  
SOC 5/22/205

REVISION #10
The above-noted protocol has been modified. Specific changes are as follows:

1. **Title Page, Page 1:**
   a. The Protocol details has been updated for CUMC, The Local protocol number AAAO5917 replaces 12 027
   b. IND 71976 has been inserted into the title
   c. The Center has been updated; Address - Columbia University Medical Center replaces “Memorial Sloan Kettering Cancer Center 300 East 66th Street, Office 1071”;
   d. the PI details have been updated,  
      PI Name: the Initial D has been inserted into the name  
      Zip code: 10032 replaces 10065;  
      Phone number: 646 317 6330 replaces 646 888 4161  
      Fax number has been removed  
      Email: rdc2150@cumc.columbia.edu replaces carvajar@mskcc.org
   e. Co-investigators:  
      The following names have been removed: Ping Chi, MD, PhD*, Sandra D’Angelo, MD*, Mark Dickson, MD*, Mary Louise Keohan, MD*, William Tap, MD*, Jedd Wolchok, MD, PhD*, Mrinal Gounder, MD,* Margaret Callahan, MD* Michel Postow, MD* Taha Merghoub, PhD James Harding, MD Murk-Hein Heinemann, MD Brian M. Marr, MD David H. Abramson, MD, Mark Bluth, MD Joseph P. Erinjeri, MD, PhD Klaus J. Busam, MD Katherine Panageas, DrPH Thomas Wiesner, MD, Vanessa Reed

      The following has been inserted: Gary K. Schwartz, M.D. Yvonne Saenger, M.D. Maura E. Abbott NP
IRB#: AAAO5917

2. **Title Page, Page 1 and 2:** Collaborating Institution: MSK statistician study coordinator, Research nurse, data manager and project coordinator details have been removed; a table of collaborating consortiums; site and PI, and roles have been inserted

3. **Title Page, Page 2:** IND 71976 has been inserted into NCI supplied agent

4. **Title Page, Page 2:** / Version 9/ Version 08/07/2014 has been inserted and 06/24/14 3 has been removed

5. **Schema page, Page 3:**
   a. IRB#: 12 027 A(5) has been removed from the header and throughout the document,
   b. below replaces below.
   c. Amended: 06/24/14 has been removed from the footer and the throughout the document

6. **Background, Page 18:** In 2.6.2 “and CUMC” has been inserted into the last sentence of the first paragraph

7. **Patient Selection, Page 20:** “Columbia University,” has been inserted into 3.1.1

8. **Patient Selection, Page 21:** CUMC has been added into 3.1.9

9. **Patient Selection, Page 23:** Section 4.1
   a. “Columbia University“ replaces “MSKCC” in the heading
   b. “Criteria for Subject Eligibility” replaces “Patient Selection”
   c. “Informed Consent Procedures, along with applicable institutional policies and federal regulations.” Replaces “Informed Consent Procedures”
   d. “Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process, Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirmation subject eligibility.” Replaces “During the registration process, registering individuals will be required to complete a protocol specific Eligibility Checklist.
   e. “All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.” Replaces “Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

   All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan Kettering Cancer Center. PPR is available
Monday through Friday from 8:30am – 5:30pm (ET) at 646-735-8000.

10. **Patient Selection, Page 23:** Section 4.1: CPDM Central Registration Procedures was added

11. **Patient Selection, Page 25:** Section 4.2 was removed and the following was inserted
   “Please see the Participating Site Addendum (Appendix E)”

12. **Patient Selection, Page 25:**
   a. “Columbia University” was inserted into 4.3 Recruitment plan in the first sentence,
   b. Columbia University replaced MSKCC in the second sentence of 4.3
   c. Sarcoma was removed in the second sentence of 4.3
   d. “The service holds weekly meetings to identify study participants for open clinical trials. Similar recruitment procedures will be followed at the collaborating institution.” Was removed from the end of the first paragraph of 4.3
   e. “Columbia University will enroll approximately, 10 patients” was inserted into the first sentence of the second paragraph of 4.3 and “20” replaces 30 in the same sentence

13. **Adverse events, page 31:** “IND 71976” has been inserted into the heading for 7.1

14. **Adverse events, page 34:**
   a. CUMC replaces MSKCC in the 3 dot point for 7.3.2
   b. The following has been removed from 7.3.2

Richard D. Carvajal, MD
Memorial Sloan Kettering Cancer Center Telephone: 646-888-4161
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8443 Lead Project Coordinator Memorial Sloan Kettering Cancer Center Fax: 646-227-2423
E-mail: CTO_MSO_MCT@mskcc.org

The MSKCC Research Staff is responsible for submitting all SAEs to the MSKCC IRB/PB within 5 days of learning of the event.

Safety Reports:

• MSKCC will distribute outside safety reports to the participating sites immediately upon receipt.
• MSKCC must submit safety reports to the MSKCC IRB/PB according to institutional guidelines.
• Participating sites must submit safety reports to their institution’s IRBs within 30 days of receipt from MSKCC or per their own institutional guidelines, however all safety reports should be submitted within 90 days

15. **Adverse events, page 36:**
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a. Columbia University Medical Center replaces MSKCC in 7.7 heading
b. CUMC replaces MSKCC in 7.7
c. INC 71976 has been inserted into 8.1

16. Correlative, page 39: CUMC has been inserted into 9.1 in second paragraph

17. Correlative, page 40:
   a. CUMC replaces MSKCC in 4th paragraph for 9.1
   b. “Samples should be assigned a unique code number and be stripped of any
      identifiable information for the specific individual.” Has been inserted into 4th
      paragraph for 9.1
   c. (carvajar@mskcc.org) has been removed
   d. “study team (AAAO5917@columbia.edu)” replaced “MSKCC Research Project
      Coordinator (CTO_MSO_MCT@mskcc.org)”

18. Correlative, page 40:
   a. Samples should be assigned a unique code number and be stripped of any
      identifiable information for the specific individual. Have been inserted into 9.2
   b. Grazia Ambrosini replaces Dr Gary Schwartz
   c. E-mail: AAAO5917@columbia.edu replaces E-mail: gks2123@columbria.edu
   d. CUMC has been inserted into first sentence of 9.5

19. Correlative, page 41:
   a. “and CUMC” has been inserted into first sentence of 9.6
   b. “or in the Schwartz laboratory (see Section 9.2 above)” has been inserted into the
      second sentence of 9.6

20. Study Calendar, page 42: CUMC has been inserted into notes for (f) and (i) for the table

21. Data reporting, page 44: Data and source Documentation has been removed and replaced
    with CUMC Data and source Documentation policies

22. Data reporting, page 50:
   a. Forms replaces Source Documentation
   b. Case Report Source documentation has been deleted and CUMC information has
      been inserted

23. Serious adverse events, Page 60:
   a. CUMC replaced MSKCC in the heading for 14.1
   b. First 2 paragraphs have been removed
   c. Definitions has been inserted

24. Serious adverse events, Page 60: Reporting of Serious Adverse Events has been inserted

25. Protection of Human subjects, page 60: Columbia University Medical Center’s replaced
    MSKCC’s in 15.2

26. Protection of Human subjects, page 61: 15.3.1 has been removed

27. Appendix A, page 67: 80 replaces 70 in percentage column for Grade1

28. Appendix B, page 68:
   a. AAAO5917 replaces 12 027 in first sentence
b. IND 71976 has been inserted
c. NCI Version date 12/22/2014 replaces 04/03/2014

29. Appendix B, page 68: “Samples should be assigned a unique code number and be stripped of any identifiable information for the specific individual” has been inserted into end of first paragraph for Plasma preparation and DNA extraction

30. Appendix E, page 73: Appendix E has been added
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<tr>
<td>N/A</td>
<td>Marc-Henri Stern, MD PhD Institut Curie Immunologie 4ème étage 26 rue d’Ulm 75005 Paris cedex 05</td>
<td>Specimen Analysis Only</td>
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</table>
IRB#: AAAO5917

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E-mail: Marc-Henri.Stern@curie.fr

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Amended/ Version 4/ Version 06/19/2012
Amended/ Version 5/ Version 08/14/2012
Amended/ Version 6/ Version 01/25/2013
Amended/ Version 7/ Version 01/15/2014
Amended/ Version 8/ Version 04/03/2014
Amended/ Version 9/ Version 08/07/2014
Amended/Version 10/Version 12/22/2014
Despite aggressive local control, fifty percent of patients with early stage uveal melanoma will ultimately develop metastatic disease. Preclinical data indicates that vorinostat results in potent inhibition of cell growth at nanomolar concentrations, induction of apoptosis and G1 arrest in uveal melanoma cell lines, with the greatest effects observed in tumors characterized by a GNAQ or GNA11 mutation.

This multicenter, single arm phase II trial is designed to test the hypothesis that vorinostat will result in an overall response rate of 20% in patients with advanced uveal melanoma harboring a GNAQ or GNA11 mutation. The primary objective of the trial is to determine the overall response rate. Secondary objectives include the assessment of progression-free survival, overall survival and safety. As this trial allows patients with any uveal melanoma genotype (including uveal melanomas that are wild-type for GNAQ and GNA11), we will also evaluate, in an exploratory fashion, the hypothesis that those uveal melanomas characterized by activating GNAQ/11 mutations and/or inactivating mutations in BAP1 are more sensitive to therapy with vorinostat than are those cases without such mutations. Using pre-treatment and on treatment biopsies (conducted at only MSKCC), we will examine the effects of vorinostat upon cell cycle progression, apoptosis and activation of oncogenic pathways such as the MAPK pathway. Additionally in an exploratory fashion, collection of serial peripheral blood samples from all patients participating at MSKCC and CUMC will allow for the characterization of circulating tumor DNA as an indicator of treatment response.

All eligible patients will receive vorinostat 300 mg orally twice a day for three consecutive days followed by 4 days of rest, repeated weekly. One cycle is 4 weeks. Toxicity will be assessed every 4 weeks. Disease assessment with cross sectional imaging will be completed every 8 weeks. Patients will continue on study as long as they have stable disease or better and have controlled and acceptable toxicity to the study drug. A detailed schema can be found below.

---

**ELIGIBILITY**

**Metastatic Uveal Melanoma**
- Age ≥ 18
- ECOG 0-2
- Measurable Disease RESIST v1.1
- Any number of prior treatments
- Tissue for GNAQ/GNA11/BAP1 typing
- Normal Hematologic, Renal and Hepatic Function

**TREATMENT**

**Vorinostat**
- 300mg PO BID 3 of 7 days q week
- 1 cycle = 4 weeks

**EVALUATION**

- Toxicity by CTCAE v4.0 q4 weeks
- Disease Assessment q8 weeks (i.e. CT-CAP or MRI)

- Pretreatment Evaluation all patients (pts)
- 10 pts mandatory pretreatment biopsy (bx)

- Week 2 Toxicity Assessment all pts
- 10 pts mandatory on treatment bx
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1. **OBJECTIVES**

1.1. **Primary Objectives**

To determine the overall objective response rate (RR) to vorinostat in patients with metastatic uveal melanoma harboring a GNAQ or GNA11 mutation

1.2. **Secondary Objectives**

1.2.1 Overall survival (OS)

1.2.2 Progression Free Survival (PFS)

1.2.3 To determine the tolerability of vorinostat in patients with metastatic uveal melanoma

1.2.4 To correlate overall objective RR with GNAQ, GNA11 and BAP1 mutational status

1.3 **Exploratory Objectives**

1.3.1 To correlate clinical outcome with changes in histone acetylation status by immunohistochemistry

1.3.2 To correlate clinical outcome with changes in known proliferation and apoptotic markers including Ki67 by immunohistochemistry and BIM, survivin, c-myc, Mcl-1, cleaved PARP, γ-H2AX and RAD51 by western blot

1.3.3 To assess for changes in pathways such as the MAPK pathway with treatment

1.3.4 To describe the evolution of circulating cell-free, tumor-derived DNA levels measured by pyrophosphorolysis activated polymerization (PAP) in plasma of patients under treatment for metastatic uveal melanoma

1.4 **Gender and Minority Accrual Estimates for GNAQ/GNA11 Mutated Uveal Melanoma Patients**

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<td>+</td>
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</tr>
<tr>
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<td>12</td>
<td>+</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects</td>
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<td>+</td>
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<th>Racial Category</th>
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<tr>
<td>American Indian or Alaskan Native</td>
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</tbody>
</table>

IRB#: AAAO5917
2. BACKGROUND

2.1 Uveal Melanoma

Uveal melanoma is the most common primary intraocular malignancy in adults, and arises from melanocytes within the choroid plexus of the eye. Melanomas of the ocular and adnexal structures comprise approximately 5% of all melanomas and are biologically distinct from cutaneous melanoma.\(^1\) Approximately 85% of ocular melanomas are uveal (iris, ciliary body, and choroid) in origin, with primary conjunctival and orbital melanomas being less common.\(^1,2\) The incidence in the United States is 4.3 cases per million population, with a higher rate in males (4.9 per million) when compared with females (3.7 per million). This disease is more common in whites and older patients, with a peak incidence seen at the age of 70 years.\(^2\) The development of metastasis in this disease is common and occurs in approximately 50% of patients with posterior uveal melanoma within 15 years after the initial diagnosis and treatment.\(^3\) The median survival from the time of the development of distant metastatic disease is 6 to 12 months.\(^4-6\) No treatment, other than surgery, has been demonstrated to improve survival.\(^7\)

Clinical factors that relate to prognosis include location (primary melanomas of the iris connote a better prognosis than those arising from the choroid, and choroidal melanomas fare better than ciliary body melanomas),\(^8,9\) configuration of the tumor (diffuse configuration suggests poor prognosis),\(^10\) and size.\(^11\) Histopathologic features of importance include tumor cell type (spindle morphology connotes a better prognosis than mixed morphology, and mixed morphology fares better than epithelioid morphology),\(^12,13\) extent of mitotic activity,\(^14\) vascular network (absent better than present),\(^15\) tumor-infiltrating lymphocytes (absent better than present),\(^16\) and the presence of extrascleral extension (absent better than present).\(^9\) Nonrandom changes in chromosomes 1, 3, 6, and 8 have been identified by FISH and CGH in uveal melanomas.\(^17-19\) Monosomy 3 and amplification of 8q have been identified as poor prognostic indicators.\(^18,20\) Other prognostic factors include high expression of HLA class I,\(^21\) c-myc,\(^22\) cyclin D1, p53 MDM2,\(^23\) and IGF-IR.\(^24\)

The development of metastasis in this disease is common and occurs in approximately 50% of patients with posterior uveal melanoma within 15 years after the initial diagnosis and treatment.\(^3\) Uveal melanoma is thought to be particularly resistant to systemic treatment, and no systemic therapy has been demonstrated to improve survival.\(^7\) Drugs commonly used to treat advanced cutaneous melanoma rarely achieve durable responses in patients with uveal melanoma. Nathan et al
compared the outcome between 139 patients with non-uveal melanoma and 16 patients with uveal melanoma who were treated with DTIC, BCNU, cisplatin, and tamoxifen (Dartmouth regimen). The response rates were 33% and 6% respectively. In a review of the MD Anderson Cancer Center experience of 143 treated patients with ocular melanoma, there was only a single objective response observed. Retrospective reviews of the ECOG and SWOG experiences revealed similar findings. Because of the lack of effective systemic treatment options, outcomes are poor once metastatic disease occurs, and the median survival from the time of the development of distant metastatic disease is 6 to 12 months. Thus, it is clear that novel and effective therapies are desperately needed for this disease.

One therapeutic strategy that is of particular interest in this disease is histone deacetylase inhibition (HDACi). As discussed below, there is growing evidence that aberrant epigenetic modulation of gene expression is implicated in the pathogenesis and progression of uveal melanoma. Preclinical data generated by our group is consistent with the hypothesis that HDACi has anti-tumor efficacy in this disease. These effects were predominately seen in GNAQ/GNA11 mutant cell lines. In this protocol, we propose to test the hypothesis that HDACi with vorinostat will lead to clinical benefit in patients with advanced uveal melanoma characterized by a GNAQ or GNA11. Using pre-treatment and post-treatment biopsies conducted only at MSKCC, we will examine the effects of vorinostat upon tumor gene expression profile, with analysis of mediators of cell cycle control and apoptosis.

2.2 Gene Expression is Altered in Uveal Melanoma by Both Chromosomal and Epigenetic Aberrations

Two independent groups have identified microarray gene expression profiles which accurately segregate uveal melanomas into two tumor classes by risk of metastasis. Onken et al identified 62 genes that discriminate between tumors that have a low-risk of metastasis (class 1 tumors) and those that are more aggressive and are associated with a higher risk of metastatic death (class 2 tumors). It has previously been demonstrated that cytogenetic alterations such as monosomy 3 and gains of 8q have important prognostic implications in this disease, with the presence of either alteration associated with poor outcomes. As would thus be expected, poor prognosis class 2 tumors were characterized by the down regulation of genes located on chromosome 3 (MBD4, CTNNB1, eIF2a, RPL24, GC20, RRL15, PIK3R4, FXR1, TKT) and upregulation of genes present on chromosome 8q (RRM2B, C8FW, KIAA1750, FABP5, PRKDC, TAF2). In these cases, aberrant gene expression occurs primarily due to chromosomal gains and losses.

The altered expression of other genes that discriminate between class 1 and 2 tumors do not occur due to such chromosomal alterations, but rather occur through aberrant epigenetic events. PHLDA1 (pleckstrin homology-like domain, family A, member 1) is a gene located at 12q15, a chromosome without common gains or losses in uveal melanoma, and is downregulated in high-risk class 2 tumors. Downregulation of PHLDA1 has been associated with poor outcomes in breast cancer and is associated
with melanoma disease progression.\textsuperscript{31} Although the mechanism of PHLDA1 downregulation in cancer is not fully elucidated, increased transcription has been demonstrated in renal cell carcinoma cells treated with both vorinostat and 13-cis retinoic acid. The effect of HDACi with vorinostat upon PHLDA1 expression suggests that epigenetic alterations may, in part, be responsible for decreased expression in malignancy. Data regarding the epigenetic suppression of gene expression and gene re-expression with epigenetic therapies (in some cases) exist for other genes that discriminate between class 1 and 2 tumors, including GSTM3 (glutathione S-alkyltransferase M3),\textsuperscript{32} SPPI (osteopontin),\textsuperscript{33} ENDRB (endothelin B receptor),\textsuperscript{34,35} as well as BTG1 (B-cell translocation gene 1 protein).\textsuperscript{36} Other relevant genes with expression not directly under epigenetic control (e.g. PDCD4\textsuperscript{37}) are regulated by other epigenetically dysregulated factors such as microRNAs.\textsuperscript{38}

Given these epigenetic events, the use of HDACi or hypomethylating agents are therapeutic strategies worthy of exploration in uveal melanoma. Several groups have investigated the effects of histone deacetylase (HDAC) inhibitors on multiple cutaneous and ocular melanoma cell lines.\textsuperscript{39-42} Ocular melanoma cell lines treated with the HDAC inhibitors depsipeptide, sodium butyrate and trichostatin A exhibited a dose dependent increase in histone acetylation and a corresponding inhibition of cell growth and induction of apoptosis.\textsuperscript{42} As shown in other cell line and tumor models,\textsuperscript{43-49} increased expression of p21, p27 and c-myc were observed with HDACi in uveal melanoma.\textsuperscript{42} The sub-G1 fraction increased in a dose dependent fashion in uveal melanoma, with apoptosis achieved with HDACi that was associated with increased expression of Fas/FasL without changes in bcl-2/bax gene expression.\textsuperscript{42} Further analysis demonstrated impaired migration of uveal melanoma cells with HDACi in association with increased levels of tissue inhibitors of matrix metalloproteinases 1 and 2 (TIMP-1 and TIMP-2) and decreased levels and activity of the matrix metalloproteinases MMP-2, MMP-9, and MT-1/MMP.\textsuperscript{50} This suggests that the use of HDACi in uveal melanoma may decrease the metastatic potential of uveal melanoma.\textsuperscript{50}

### 2.3 Preclinical Data Supporting Testing of Vorinostat in Uveal Melanoma

We have investigated the effects of HDACi using vorinostat on eight ocular melanoma cell lines (Ocm290, Ocm1a, 92.1, OMM1, Mel202, Omm1.3, C918, Mel285), each characterized by GNAQ, GNA11, BRAF and BAP1 status (see Table 1).\textsuperscript{51,52}

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>GNAQ</th>
<th>GNA11</th>
<th>BRAF</th>
<th>BAP1</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCM290</td>
<td>wt</td>
<td>wt</td>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>Ocm1a</td>
<td>wt</td>
<td>wt</td>
<td>V600Q</td>
<td>wt</td>
</tr>
<tr>
<td>92.1</td>
<td>Q209L</td>
<td>wt</td>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>OMM1</td>
<td>wt</td>
<td>Mutant</td>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>Mel202</td>
<td>Q209L</td>
<td>wt</td>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>Omm1.3</td>
<td>Q209P</td>
<td>wt</td>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>C918</td>
<td>wt</td>
<td>wt</td>
<td>wt</td>
<td>wt</td>
</tr>
</tbody>
</table>
Whereas cutaneous melanoma is primarily characterized by activating mutations in BRAF and NRAS in 50% and 20% cases, such changes are rare in uveal melanoma, but oncogenic mutations in the heterotrimeric G protein alpha-subunits of GNAQ and GNA11 have been identified in ocular melanoma. These mutations occur at a high frequency, occur early in oncogenesis, and activate the MAP kinase pathway.

We treated the uveal melanoma cell lines with increasing concentrations of vorinostat. We observed that all cell lines had a dose dependent decrease in cell viability after exposure to vorinostat, with particular sensitivity with IC50s in the 250 to 500 nM range in the cell lines characterized by a GNAQ mutation (Mel202, Omm1.3, 92.1; see Figure 1). Importantly, similar effects in epithelial tumors are observed only at micromolar doses of vorinostat.

**Figure 1**

Apoptosis was evident at 48 hours after treatment with 1 uM of vorinostat; however, this was limited to cells harboring a GNAQ/11 mutation (92.1, Mel202, OMM1; see Figure 2).
As shown in Figure 3, HDACi by vorinostat results in an increase in H4 acetylation predominantly in the GNAQ/11 cell lines. PARP cleavage was only seen in the GNAQ mutant cell lines. Interestingly, the molecular events associated with apoptosis included the induction of Bim, as well as the suppression of c-Myc and survivin (Figure 3). No significant effects upon Bcl2 or Bcl-xl were observed (data not shown). The basis for the cell death remains under investigation; however, as shown in Figure 3, we have observed that vorinostat induces the induction of p-\(\gamma\)H2AX which occurs only in the GNAQ/11 cell lines. This would suggest that vorinostat induces direct DNA damage on the uveal melanoma cells and this is dependent upon the mutational status of the cells. In addition, this is associated with suppression of the DNA repair protein RAD51. This observation argues for the accumulation of DNA double strand breaks in the mutant cell lines and impaired DNA repair resulting in cell death.

Figure 3

A G1 arrest, with an increase in the sub-G1 peak, is also observed in both GNAQ and GNA11 mutant cell lines, with no such effects in the wild-type cell lines (Figure 4).
The G1 cell cycle effect was specific to GNAQ/11 mutant cell lines, and this was associated with a decrease in expression of proteins associated with mitosis including Aurora kinase A and B, as well as Cyclin B1 (data not shown).

2.4 Oncogenic Mutations of BAP1 Are Frequent in Uveal Melanoma and Alter Gene Expression to a Class 2 Phenotype but Are Not Necessary for Apoptosis

Harbour and colleagues have identified inactivating mutations in the gene encoding BRCA1-associated protein (BAP1) on chromosome 3p21.1 in a high proportion of patients with metastatic ocular melanoma. BAP1 is a component of the ubiquitin proteasome system that has been implicated in a variety of cancers, including lung, breast, renal cell carcinoma, and ocular melanoma. BAP1 is a 90 kilodalton (728 amino acids), nuclear-localized, deubiquinating enzyme (DUB) with a unique large C-terminal domain. BAP1 is predicted to coordinate the selective association with multiple potential cellular substrates or regulatory components. Three major functional domains have been identified: a ubiquitin carboxyl-terminal hydrolase catalytic domain, a binding domain for the breast cancer susceptibility gene, BRCA1, and a binding domain for host cell factor-1 (HCF-1), a protein scaffold for histone modifying enzymes. BAP1 participates in the assembly of multi-protein complexes containing numerous transcription factors and cofactors, and activates transcription in an enzymatic-activity-dependent manner, thereby regulating the expression of a variety of genes involved in various cellular processes. Depletion of BAP1 resulted in altered expression of 249 genes, including key mediators of cell cycle progression, DNA replication and repair, cell metabolism, survival and apoptosis.

Several investigators have demonstrated that BAP1, in part, exerts its diverse cellular actions via deubiquination of host cell factor-1 (HCF-1). HCF-1, an important cell-cycle regulator, is a chromatin bound protein that functions as a scaffold,
recruiting a number of histone modifying enzymes, including Set1/Ash2 histone methyltransferase complex, the Sin-3 histone deacetylase complex, and MOF histone acetyltransferase.\textsuperscript{64-66} BAP1 also directly regulates chromatin structure via its interaction with several members of the Polycomb family, including ASXL-1 and ASXL-2.\textsuperscript{62} Polycomb proteins are key repressive transcriptional regulators in multiple developmental processes. BAP1 associates with ASXL-1, forming a histone H2A deubiquitinase, named Polycomb repressive deubiquitinase (PR-DUB).\textsuperscript{67} PR-DUB catalyzes the removal monoubiquitin from H2A histones within the nucleosome, resulting in repression of developmental genes. Mutations in the ubiquitin carboxyl-terminal hydrolase catalytic domain of BAP1, however, release this transcriptional suppression. Thus, BAP1 via interactions with HCF-1 and the Polycomb proteins are critically important for normal cellular function.

Inactivating BAP1 mutations were identified in 26 of 31 (84\%) class II uveal melanoma metastatic (high risk) samples, with no corresponding somatic mutations in normal blood DNA samples. Interestingly, only 1 of 26 samples of class I uveal melanoma (low risk) harbored a BAP1 mutation, suggesting that acquisition of a BAP1 mutation may herald the emergence of a class II genetic signature and the transition to a more aggressive clinical course. Microarray analysis comparing 92.1 uveal melanoma cells characterized by a wild-type BAP1 transfected with either control or BAP1 siRNA demonstrated that the gene expression profile of the BAP1 siRNA treated cells shifted towards a class 2 tumor profile versus the class 1 profile observed in the control treated cells, indicating a dominant role for BAP1 in the regulation of expression of these genes.\textsuperscript{55}

BAP1 mutations have not been identified in any available uveal melanoma cell lines. Interestingly, however, the use of RNA interference to suppress BAP1 in the uveal melanoma cell lines did not result in enhanced apoptosis with vorinostat in the cell lines (data not shown). Further investigation is certainly required to better understand the physiologic role of BAP1 and its implications in ocular melanoma. Emerging preclinical data suggest that a potential mechanism for the diverse cellular effects of BAP1 may, in part, be due to modulation of chromatin structure. The observations that high risk ocular melanoma patients have both mutations in BAP1 and have aberrant expression of a variety of known epigenetically-modified genes (i.e. PHLDA1, SPP1, GSTM3, and BTG1) argue for the potential role of HDACi as a therapeutic strategy.

2.5 Vorinostat

2.5.1 Mechanism of Action

Histone acetylation affects the regulation of gene expression, and inhibitors of
HDACs have been found to cause growth arrest, differentiation, or apoptosis of many transformed cells by altering the transcription of a small number of genes. The acetylation status of histones is determined by histone acetyltransferases (HATs) and HDACs. HDACs are enzymes that catalyze the removal of acetyl groups from the lysine residues of proteins, most notably the core nucleosomal histones. Four classes of HDACs have been identified. Class I human HDACs are homologous to the yeast HDAC Rpd3, and include HDAC1, HDAC2, HDAC3, and HDAC8. Class II HDACs include HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10. HDAC11 comprises Class IV HDACs. The key zinc-dependent catalytic residues have been conserved in Classes I, II, and IV HDACs. Class III HDACs, consisting of homologues of yeast Sir2, require nicotinamide-adenine dinucleotide for activity, and differ from Class I and II HDACs in their catalytic site.

Vorinostat is a potent reversible inhibitor of HDAC activity and binds directly to the catalytic pocket of Class I and II HDAC enzymes. X-ray crystallographic studies performed with vorinostat and the HDAC homologue, histone deacetylase-like protein from the thermophilic bacterium *Aquifex aeolicus*, demonstrate that the active site of HDAC consists of a tubular pocket, a zinc binding site, and two Asp-His charging systems. Vorinostat binds to HDAC by inserting the hydroxamic group, most of the aliphatic chain and part of the phenyl amino group in the active site of the enzyme. The hydroxamic group reaches the polar bottom of the pocket, where it coordinates the zinc in a bidentate fashion and also contacts active site residues. The insertion of vorinostat into the active site prevents the binding of the natural substrate and blocks enzymatic deacetylation.

2.5.2 Efficacy of Vorinostat in Nonclinical Studies

Preclinical data indicate that vorinostat is active in inducing differentiation, cell growth arrest, or apoptosis in a wide variety of transformed cells in culture at low micromolar concentrations. Apoptosis has also been observed in vitro in vorinostat–treated human myeloma cells human myelomonocytic cells human neuroblastoma cells, acute T-cell leukemia cells, human cutaneous T-cell lymphoma, human lymphoma cells and cutaneous melanoma and ocular melanoma cell lines. Vorinostat induces both differentiation and apoptosis in human prostate carcinoma and human breast adenocarcinoma cells. The activity of vorinostat was investigated using a 60 cell line screen at the National Cancer Institute (NCI) and IC50s ranging from approximately 38.6 nM to 6.2 μM were obtained for the growth inhibitory activity of vorinostat. Mechanistically, vorinostat causes cell cycle arrest in G1 or G2 phases of the cell cycle in a cell-dependent and dose-related fashion. In vivo, vorinostat administration causes tumor regression, improved survival or remission in murine models of prostate carcinoma, acute promyelocytic leukemia, and mammary tumors.

2.5.3 Vorinostat in Clinical Studies

Vorinostat was approved by the U.S. Food and Drug Administration (FDA) in
October 2006 for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies. Vorinostat has been formulated for both oral and intravenous administration. The initial phase I clinical trial demonstrated tolerability of several oral dosing schedules including, continuous administration of both 400 mg daily and 200 mg twice a day as well as weekly dosing at 300 mg twice day for 3 consecutive days each week. To date over 30 phase I, II and III clinical trials have evaluated the safety and efficacy of the agent with various dosing schedules. The weekly oral dosing schedule (300 mg twice daily for three consecutive days repeated weekly) will be employed for this clinical trial. The rationale for this dose is based on prior trials demonstrating superior tolerability of this regimen.

Pharmacokinetics
An open-label, single-arm, multicenter, phase I study in Japanese patients with malignant lymphoma evaluated the weekly dosing schedule of 300 mg BID for 3 consecutive days followed by a 4-day rest. Concentration time profiles were qualitatively similar on days 1 and 3, indicating no obvious changes in absorption or elimination; the maximum serum concentration ($C_{\text{max}}$) of vorinostat was reached between ~15 minutes and 6 hours post-dose followed by rapid elimination (harmonic mean apparent $t_{1/2}$ of 0.94 to 1.05). Summary PK parameters can be found in below in Table 2. The accumulation ratio of vorinostat following 3 days of multiple oral dose was 1.07 (90% confidence interval; 0.97, 1.18), suggesting very little to no accumulation after administration of vorinostat with this dose regimen.

Table 2: Summary of Pharmacokinetic Parameters at 300 mg BID × 3 days/week in Patients with Solid Tumors

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Day 1 (n=10 fed state)</th>
<th>Day 3 (n=10 fed state)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0-\infty} \ \mu\text{M} \cdot \text{hr}$</td>
<td>3.94 ± 1.56</td>
<td>4.15 ± 2.15$^\dagger$</td>
</tr>
<tr>
<td>$\text{AUC}_{0-12} \ \mu\text{M} \cdot \text{hr}$</td>
<td>3.92 ± 1.52</td>
<td>4.19 ± 1.84</td>
</tr>
<tr>
<td>$C_{\text{max}} \ \mu\text{M}$</td>
<td>1.17 ± 0.43</td>
<td>1.32 ± 0.75</td>
</tr>
<tr>
<td>$T_{\text{max}} \ \text{hr}$</td>
<td>1.99 0.50 5.97</td>
<td>0.99 0.25 6.00</td>
</tr>
<tr>
<td>$t_{1/2} \ \text{hr}$</td>
<td>1.05 ± 0.32</td>
<td>0.94 ± 0.54$^\dagger$</td>
</tr>
<tr>
<td>Accumulation ratio$^\ddagger$</td>
<td>--</td>
<td>1.07 0.97, 1.18</td>
</tr>
</tbody>
</table>

$\text{AUC}_{0-\infty}$, area under the concentration time curve from zero to infinity; $\text{AUC}_{0-12}$ hr, AUC from time to zero to 12 hours; $C_{\text{max}}$, maximum concentration; and $t_{1/2}$, terminal half life.

$\text{AUC}_{0-\infty}$, $\text{AUC}_{0-12}$ hr and $C_{\text{max}}$, geometric mean ± geometric SD, $T_{\text{max}}$, median (range) $t_{1/2}$: harmonic mean± Jackknife SD

$^\dagger$ n=9 (Since the terminal elimination phase was not able to be evaluated in a patient, the $t_{1/2}$ and $\text{AUC}_{0-\infty}$ was not able to be determined.)

$^\ddagger$ $\text{AUC}_{0-12}$ hr, Day 3/$\text{AUC}_{0-12}$ hr, Day 1 (geometric mean)
Safety
The clinical safety of vorinostat is supported by data from 854 patients and 858 patient-exposures in CTCL monotherapy, CTCL combination therapy, hematologic malignancies monotherapy, hematologic malignancies combination therapy, solid tumor monotherapy, and solid tumor combination therapy populations.

Among the 854 patients (858 patient-exposures) with advanced malignancies treated with vorinostat, the most commonly reported adverse experiences were nausea (54.4%), fatigue (49.8%), asthenia (14.1%), diarrhea (48.1%), anorexia (37.8%), vomiting (34.8%), thrombocytopenia (28.3%), platelet count decreased (10.4%), constipation (27.2%), anemia (25.8%), hemoglobin decreased (10.0%), neutropenia (17.2%) and neutrophil count decreased (5.0%). Nausea, the most commonly reported adverse experience was considered by the Investigator to be at least possibly related to study drug for 416 (48.5%) patients. Thirty-five (4.1%) drug-related cases of nausea were Grade 3 or higher. Other Grade 3 or higher drug-related adverse experiences reported in >2% of patients included thrombocytopenia in 101 (11.8%), platelet count decreased in 28 (2.8%), neutropenia in 82 (9.6%), neutrophil count decreased in 17 (2.0%), fatigue 80 (9.3%), asthenia in 26 (3.0%), diarrhea in 33 (3.8%), dehydration in 33 (3.8%), anorexia in 32 (3.7%), anemia in 28 (3.3%), hemoglobin decreased in 10 (1.2%), hypophosphatemia in 28 (3.3%), leukopenia in 23 (2.7%), febrile neutropenia in 19 (2.2%) and hyponatremia in 17 (2.0%) patients.

It should also be noted that a small subset of patient have experienced thromboembolic events as well as QTc prolongation. Thromboembolic events have included cerebrovascular accidents, pulmonary emboli, deep venous thromboses, and myocardial infarctions. It should be noted that these events have occurred at similar frequency to the normal population. Randomized trials of vorinostat are still ongoing and safety data has not yet been unblinded.

Clinical Efficacy
Vorinostat was approved by the U.S. Food and Drug Administration for the treatment of cutaneous manifestations in patients with CTCL who have progressive, persistent or recurrent disease on or following two systemic therapies. Phase I and II clinical studies of vorinostat have demonstrated some anti-tumor efficacy in patients with acute myeloid leukemia (AML), advanced multiple myeloma, B-cell non-Hodgkin's lymphoma, squamous cell laryngeal carcinoma, thyroid carcinoma, breast carcinoma, non-small cell lung carcinoma, glioblastoma multiforme, and myelodysplastic syndrome. Please refer to the Investigator Brochure for more details.

Drug-Drug Interactions
No formal drug-drug interaction studies have been conducted. Vorinostat has a low propensity to cause or be affected by drug-drug interactions. In vivo animal models and in vitro human systems have demonstrated that the major pathways of metabolism of vorinostat involve glucuronidation, and hydrolysis followed by β-oxidation. As vorinostat is not eliminated via cytochrome P450 (CYP) pathways, it is anticipated that vorinostat will not be subject to drug-drug interactions when co-
administered with drugs that are known to be CYP inhibitors or inducers. Since vorinostat was neither a potent inhibitor nor an inducer of CYP enzymes, drug-drug interactions caused by vorinostat are not anticipated. Additionally, vorinostat is not recovered intact in urine to any appreciable extent. Therefore, compounds known to affect renal elimination are not expected to affect the pharmacokinetics of vorinostat.

2.6 Background on Correlative Studies

2.6.1 Assessment of the Molecular Effects of Vorinostat in Patients with Uveal Melanoma

Our preclinical data indicate vorinostat treatment results in inhibition of HDAC in both wild-type and GNAQ/GNA11 ocular melanoma cell lines. Interestingly, vorinostat appears to be a potent inhibitor of cell growth and proliferation only in GNAQ/GNA11 mutated ocular melanoma cell lines. As discussed above, nanomolar concentrations of vorinostat inhibit growth in cell lines characterized by GNAQ/GNA11 mutations. Likewise, mutated cell lines preferentially undergo apoptosis and G1 arrest when compared to wild type. We plan to validate our preclinical data by determining the mutational status for all study participants and using matched pre- and post-treatment tumor samples obtained from patients treated with vorinostat.

Ten patients at MSKCC with metastatic uveal melanoma treated with vorinostat will undergo two mandatory biopsies (assuming that the biopsy procedure does not pose undue danger to the patient). The pre-treatment biopsy will be obtained within 15 days of starting therapy if feasible; however, tumor samples obtained at earlier time-points may be utilized with the permission of the Principal Investigator. The post-treatment biopsy will be performed at day 8, 9 or 10 prior to the evening dose of vorinostat. Up to three core samples will be obtained with each biopsy, providing sufficient tissue for the correlative studies described in Section 9 below.

2.6.2 Evaluation of circulating cell-free, tumor derived DNA in patients with Uveal Melanoma

It is now well established that human tumor cells, through a variety of physiologic events such as apoptosis, necrosis and secretion, release single and double stranded fragments of DNA into the circulation. These oligonucleotides, which can range in size from 70 to 21,000 base pairs, have been detected in plasma samples as circulating, cell-free, tumor-derived DNA (ctDNA) in a variety of human cancers. Interestingly, ctDNA share the specific genetic and epigenetic abnormalities as their tumor cell of origin, and thus, are readily distinguished from cell-free DNA derived from normal cells. Point mutations, methylation patterns, and microsatellite alterations have all been indentified in ctDNA and have the potential to function as biomarkers for both tumor burden and even treatment response.
As discussed above, 80% of uveal melanomas harbor mutations in GNAQ and GNA11.\textsuperscript{51} These genetic alterations are found predominately at nucleotide position 626 on codon 209 and are the product of a missense mutation (i.e. \textit{GNAQ}\textsuperscript{626A>T}, \textit{GNAQ}\textsuperscript{626A>C}, and \textit{GNA11}\textsuperscript{626A>T}), which results ultimately in glutamine being replaced by leucine or proline (i.e. GNAQ Glu209Leu, GNA11 Glu209Leu, and GNAQ Glu209Pro). Recently, Madic and colleagues developed and validated a method using real-time PCR using bi-directional pyrophosphorolysis-activated polymerization (PAP) that detects and quantifies tumor specific GNAQ/GNA11 mutations in ctDNA in patients with uveal melanoma.\textsuperscript{84} Activating mutations in GNAQ/GNA11 were detected in the plasma samples of 20 of 21 (95%) patients with metastatic uveal melanoma, while such ctDNA was absent in 20 healthy donors. Interestingly, the level of ctDNA strongly and significantly correlated with tumor burden as assessed by cross sectional imaging. This indicates that tumor volume is a major determinate of ctDNA.

In collaboration with investigators at the Institut Curie, Paris France we propose to prospectively measure ctDNA in patients with metastatic uveal melanoma. The primary objective is to describe the evolution of ctDNA levels measured by PAP in plasma of patients under treatment for metastatic uveal melanoma. Additionally, we will evaluate the early changes of circulating tumor DNA levels as early indicator of efficiency or non-efficiency of treatment and correlate circulating DNA levels with tumor imaging of metastases. Patients on this study at MSKCC and CUMC will be required to submit peripheral blood samples prior to treatment, at various time points on treatment, and at progression.

\section*{2.7 Summary}

In summary, there are no effective systemic treatment options for ocular melanoma. Novel effective therapies for metastatic uveal melanoma are desperately needed. Preclinical data demonstrated that inhibition of histone deacetylase with vorinostat is an effective therapy in uveal melanoma, and that efficacy may be dependent upon GNAQ/11 mutational status. Mechanistically, this appears to be due to the induction of apoptosis and G1 cell cycle arrest as a result of direct DNA damage in the setting of modulation of expression of both pro- and anti-apoptotic proteins and suppression of RAD51, which is a critical part of the DNA repair process. The role of BAP1 remains to be defined. However, as GNAQ/11 mutations occur in 80% of all patients with uveal melanoma, we believe these observations should have a significant impact on the development of vorinostat in the treatment of patients with this disease.

In this phase II study, we will test the hypothesis that HDACi will lead to clinical benefit as defined as objective RECIST response in patients with uveal melanoma treated with vorinostat. The preclinical data indicate that cell lines with a GNAQ and GNA11 mutations are more sensitive to HDACi than are wild type cell lines. In order to assure the trial is not biased towards the null hypothesis, the assessment of overall response will be restricted only to patients with metastatic uveal melanomas harboring a GNAQ or GNA11 mutation. Wild type GNAQ and GNA11 uveal
melanoma patients will still be included on this trial, given the modest preclinical activity observed in the wild type cell lines and the present lack of effective therapies for this disease. Wild type uveal melanoma patients will not be included in the final statistical analysis of the primary endpoint of the trial. In an exploratory fashion, we will evaluate the hypothesis that uveal melanoma characterized by activating GNAQ/11 mutations are more sensitive to therapy with vorinostat than are those cases without such mutations. Using pre-treatment and post-treatment biopsies (conducted only at MSKCC), we will examine the effects of vorinostat upon the cell cycle, apoptotic cell death, and activation of the MAPK kinase pathway. Finally, we will describe the evolution of circulating cell-free, tumor-derived DNA levels measured by pyrophosphorolyis activated polymerization (PAP) in plasma of patients under treatment for metastatic uveal melanoma.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have metastatic histologically or cytologically confirmed uveal melanoma. (If histologic or cytologic confirmation of the primary is not available, confirmation of the primary diagnosis of uveal melanoma by the treating investigator can be clinically obtained, as per standard practice for uveal melanoma). Pathologic confirmation of diagnosis will be performed at Columbia University, MSKCC or Vanderbilt University Medical Center.

3.1.2 Patients must have measurable disease as defined by RECIST version 1.1. (See Section 11 for the evaluation of measurable disease.)

3.1.3 Age ≥18 years. Because limited dosing or adverse event data are currently available on the use of vorinostat in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric single-agent trials, if applicable.

3.1.4 ECOG performance status ≤ 2 (Karnofsky ≥ 60%, see Appendix A).

3.1.5 Life expectancy of greater than 3 months

3.1.6 Patients must have normal organ and marrow function as defined below:

- Leukocytes ≥3,000/mcL
- Absolute neutrophil count ≥1,500/mcL
- Platelets ≥100,000/mcL
- Hemoglobin ≥ 9.0 g/dL not requiring transfusions within the past 2 weeks
- Total bilirubin ≤ 1.5 X institutional upper limit of normal
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Requirement</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (SGOT)/ALT(SGPT)</td>
<td>≤ 3.0 X institutional upper limit of normal if the patient has Gilbert’s Syndrome</td>
<td>AST (SGOT)/ALT(SGPT) ≤ 2.5 X institutional upper limit of normal if no liver metastasis present ≤ 5 X institutional upper limit of normal if liver metastases are present</td>
</tr>
<tr>
<td>Creatinine</td>
<td>≤ 1.5 mg/dL</td>
<td></td>
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</tbody>
</table>

3.1.7 Ability to understand and the willingness to sign a written informed consent document.

3.1.8 Vorinostat is toxic to the developing human fetus. For this reason and because Class D agents are known to be teratogenic, women of child-bearing potential and men must agree to use effective contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of vorinostat administration.

3.1.9 Tumor GNAQ, GNA11 and BAP1 mutational status must be determined on all patients. If initial testing is performed locally or not available, MSKCC or CUMC patients must consent to provide a tumor block or unstained slides to either MSKCC or CUMC for central review of mutational status. If tissue is not available, a pre-treatment biopsy will be necessary for eligibility.

Patients enrolled at Vanderbilt University Medical Center may have GNAQ and GNA11 mutational status determined on a CLIA-approved assay at Vanderbilt University Medical Center, CUMC, or MSKCC. Tissue must be sent to MSKCC for BAP1 mutational status determination.

The determination of mutational status may be performed retrospectively and will not delay patient treatment on study as long as tissue is available for molecular analysis.

3.2 Exclusion Criteria

3.2.1 Patients may have had any number of prior therapies. At least 3 weeks must have elapsed since the last dose of systemic therapy. At least 6 weeks must have elapsed if the last regimen included BCNU or mitomycin C. At least 6 weeks must have elapsed if the last regimen included an anti-CTLA4 antibody. Patients must have experienced disease progression on their prior therapy in the opinion of the treating investigator.
3.2.2 Patients who are receiving any other investigational agents.

3.2.3 Patients with active or untreated brain metastases. Treated brain metastases must have been stable for at least 2 months.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to vorinostat.

3.2.5 Patients receiving HDAC inhibitors or compounds with HDAC inhibitor like activity, such as valproic acid, are ineligible. Patients who have received such agents may enroll on this study after a 14-day washout period.

3.2.6 Patients on warfarin will be excluded from the trial if they cannot be switched to an acceptable alternative medication (i.e. LMWH). Prolongation of prothrombin time (PT) and International Normalized Ratio (INR) were observed in patients receiving vorinostat concomitantly with coumarin-derivative anticoagulants.

3.2.7 Pregnant women are excluded from this study because vorinostat is a Class D agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with vorinostat, breastfeeding should be discontinued if the mother is treated with vorinostat.

3.2.8 HIV-positive patients on combination antiretroviral therapy will be eligible unless the CD4 count is < 200 cells/mm$^3$ within one month of study enrollment (as requested by CTEP). These patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.9 A second malignancy requiring active therapy.

3.2.10 No concomitant anti-cancer chemotherapy or other systemic drugs. Palliative radiation therapy will be allowed as long as the patient meets all other eligibility criteria.

3.2.11 Refractory nausea and vomiting, chronic gastrointestinal diseases (e.g. inflammatory bowel disease), or significant bowel resection that would preclude adequate absorption.

3.2.12 QTc >475 milliseconds.

3.2.13 Patients who cannot swallow capsules.

### 3.3 Inclusion of Women and Minorities
Both men and women of all races and ethnic groups are eligible for this trial.

4. RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

4.1 Columbia University Research Participant Registration

CUMC Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirmation subject eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

CPDM Central Registration Procedures:
Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@columbia.edu or fax to 212.305.5292, with the subject line “AAAO5917 Pending Subject Registration Request (PHI)”. Upon receipt, applicable subject information as well as a “pending eligibility” status will be entered into HICCC’s institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable.
The completed/signed IRB approved HIPAA Authorization form

Completed/signed CPDM ICF checklist

Completed/signed HICCC personal census form

Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

The completed/signed study specific Eligibility Checklist (signed by an Physician level Investigator)

Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:

- Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)

- Copy of pathology and surgical reports

- Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)

- Protocol deviation/waiver approvals (if applicable)

Please note: subject line of email or fax should include the following: “AAAO5917 Complete Subject Registration Request (PHI)”.

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment.

All applicable finalized registration/eligibility information will then be entered into HICCC’s institutional CTMS database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible subjects, as well as subject’s who withdraw consent prior to
enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

4.2 Participating Sites Registration Process

Please see the Participating Site Addendum (Appendix E)

4.3 Recruitment Plan

Patients will be recruited at Columbia University, Memorial Sloan Kettering Cancer Center and Vanderbilt University Medical Center. It is expected that 18-40 patients will be recruited to this study. At Columbia University, patient recruitment will be done by the Melanoma service. It is anticipated that Columbia University will enroll approximately 10 patients, MSKCC will enroll approximately 20 patients and Vanderbilt University Medical Center will enroll approximately 10 patients.

5. TREATMENT PLAN

5.1 Vorinostat Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

If all eligibility criteria are met, study participants will initiate vorinostat 300 mg twice a day for 3 consecutive days of treatment followed by 4 days of rest repeated weekly. Four weeks of therapy is considered one full cycle.

- Patients will be provided with a Medication Diary for vorinostat (Appendix B), instructed in its use, and asked to bring the diary with them to each appointment.

- Patients will be advised to take vorinostat with food.

- Any dose of vorinostat that is missed or vomited should not be replaced. Missed doses should be recorded on the Medication Diary but will not be considered violations of the protocol.

- Patients will be instructed that vorinostat can be stored at room temperature.
Patients will be advised to drink plenty of water or take rehydration fluids to avoid dehydration if diarrhea occurs.

No premedication or other supportive medications are required.

5.2 **General Concomitant Medication and Supportive Care Guidelines**

Patients are permitted to receive appropriate supportive care measures as deemed necessary by the treating Physician, including, but not limited to, the items outlined below:

- **Nausea and/or Vomiting** is a common adverse reaction with vorinostat. The use of early and aggressive anti-emetics is recommended. Antiemetic agents including, but not limited to, 5HT-3 antagonists, lorazepam, diphenhydramine or phenothiazines.

- Treat **diarrhea** promptly with appropriate supportive care, including loperamide. Instruct patients to begin taking loperamide at the first signs of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day, or 3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. Daily dose should not exceed 16 mg/day. Loperamide should not be taken prophylactically. Advise patients to drink plenty of clear fluids to help prevent dehydration caused by diarrhea. Avoid loperamide if there is the presence of blood or mucus in the stool or if diarrhea is accompanied by fever. If diarrhea occurs during treatment with vorinostat, the dose should be modified as per Section 6.3.

- Altered taste and decreased food and liquid intake are associated with vorinostat administration. **Dehydration** is a major dose limiting toxicity. These toxicities can be actively managed with fluid management and nutritional consultation, as appropriate. To prevent dehydration, patients should consume at least 2 liters of fluid orally, on a daily basis, in particular during the days that patients are being treated with vorinostat. If patients are experiencing dysgeusia, popsicles or oral electrolyte fluid replacement may be recommended.

- Treatment with vorinostat can cause dose-related **anemia** which may result in fatigue, lethargy or shortness of breath. If hemoglobin is reduced during treatment with vorinostat, the dose should be modified or therapy discontinued, as outlined in Section 6. Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.

- Generally, prophylactic use of colony-stimulating factors including
granulocyte colony-stimulating factor (G-CSF), pegylated G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF) for neutropenia should not be utilized during the first cycle of therapy. These factors may be utilized if clinically indicated in subsequent cycles.

- Treatment with vorinostat can cause dose-related thrombocytopenia. If platelet counts are reduced during treatment with vorinostat, the dose should be modified as per Section 6. Transfusion of platelets may be used if clinically indicated to support patients.

- Hyperglycemia has been observed in patients receiving vorinostat. Serum glucose should be monitored, especially in diabetic or potentially diabetic patients. Adjustment of diet and/or therapy for increased glucose may be necessary.

- Hypokalemia or hypomagnesaemia should be corrected prior to administration of vorinostat.

- Pulmonary embolism (19/858 patients) and deep vein thrombosis (20/858 patients) have been reported. Investigators should be alert to the signs and symptoms of PE and DVT, particularly in patients with a prior history of thromboembolic experiences.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue indefinitely or until one of the following criteria applies:

- Disease progression,

- Intercurrent illness that prevents further administration of treatment,

- Unacceptable adverse event(s),

- Patient decides to withdraw from 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.

- Pregnancy

5.4 Duration of Follow Up

Patients removed from the study treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients will be
followed in clinic or by telephone on an approximately every 12 week schedule (+/- 2 weeks) until death for the purposes of survival follow-up.

5.5 **Criteria for Removal from Study Treatment**

If at any time the patient develops progressive disease on vorinostat he/she will be taken off study treatment and referred for alternative therapy. If at any time the patient develops unacceptable toxicity he/she will be removed from study treatment (see Section 6.2).

If the patient is unable to follow the requirements of the protocol for treatment or evaluation he/she will be removed from study treatment.

If at any time the patient becomes pregnant on vorinostat, she will be taken off the study treatment and referred to alternative therapy.

6. **DOISING DELAYS/DOSE MODIFICATIONS**

6.1 **Required Laboratory Parameters for Initiation of a Treatment Cycle**

A cycle of therapy may be initiated provided that the patient meets the following criteria on Day 1 of each cycle:

- ANC ≥ 1,000/mcL
- Platelets ≥ 100,000/mcL
- Non-hematologic toxicity recovered to ≤ tolerable grade 2 (or baseline)
- No evidence of progressive disease

6.2 **Dosing Delays/Dose Modifications for Vorinostat**

Vorinostat is generally well tolerated, with only 20% patients requiring a dose reduction. Dosing is based on adverse events during the prior treatment cycle. If multiple adverse events are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single adverse event.

Patients may continue vorinostat for Grade 1 or tolerable Grade 2 toxicity without a dose reduction. For intolerable Grade 2, Grade 3 or Grade 4 toxicity, vorinostat must be withheld until the toxicity has resolve to Grade 1 or tolerable Grade 2. At the discretion of the treating physician, vorinostat may then be resumed at 200 mg twice daily for three consecutive days, followed by 4 days of rest, repeated weekly. If Grade 3 or Grade 4 toxicity recurs, the patient will be removed from the study treatment.

**Table 3: Dose Modification**
<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Vorinostat Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>300 mg BID x 3 days, repeated weekly</td>
</tr>
<tr>
<td>-1</td>
<td>200 mg BID x 3 days, repeated weekly</td>
</tr>
</tbody>
</table>

In the event of an adverse event at least possibly related to the agent, the doses of vorinostat should be adjusted according to the guidelines shown in the Dose Delays/Dose Modifications tables that follow. If an adverse event is not covered in the table, doses may be reduced or held at the discretion of the investigator for the subject's safety.

Subjects with adverse events that are manageable with supportive therapy may not require dose reductions (e.g., nausea/vomiting may be treated with antiemetics, diarrhea may be treated with loperamide, and electrolyte abnormalities may be corrected with supplements rather than by dose reduction).

Subjects will be withdrawn from the study treatment if they fail to recover to CTC Grade 0, Grade 1 or tolerable grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a treatment-related adverse event within 21 days OR they experience agent related adverse events requiring dose modification despite one previous dose reduction (i.e. would require a second dose reduction) unless the investigator and CTEP monitor agree that the subject should remain in the study because of evidence that the patient is/may continue deriving benefit from continuing study treatment (i.e. patient has PR, CR, SD ≥ 3 months). The appropriate reduced dose will be determined after discussion between the principal investigator and CTEP monitor.

### 6.3 Management of Common Hematologic and Non-Hematologic Adverse Events Associated with Vorinostat

<table>
<thead>
<tr>
<th>Event</th>
<th>AE Grade or Observation</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/Vomiting (if antiemetic is not effective)</td>
<td>Grade 1 or 2</td>
<td>Maintain dose; continue antiemetic therapy with standard dose ondansetron, metoclopramide or prochlorperazine.</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4, or intolerable Grade 2</td>
<td>Hold vorinostat until grade 1 or tolerable grade 2, then reduce 1 dose level and resume treatment; Consider addition of lorazepam.</td>
</tr>
<tr>
<td></td>
<td>Recurrent Grade 3 or 4 after 1 dose reduction</td>
<td>Remove patient from study.</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Grade 1 or 2</td>
<td>Maintain dose; continue anti-diarrheal treatment. Loperamide (4 mg at first onset, followed by 2 mg every 2 – 4 hrs until diarrhea free for 12 hrs)</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 or</td>
<td>Hold vorinostat until &lt; tolerable grade 2,</td>
</tr>
<tr>
<td>(if anti-diarrheal treatment is ineffective)</td>
<td>intolable Grade 2</td>
<td>loperamide; reduce 1 dose level and resume treatment ¹.</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Recurrent Grade 3 or 4 after 1 dose reduction</td>
<td></td>
<td>Remove patient from study.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fatigue</th>
<th>Grade 1 or 2</th>
<th>Maintain dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4 or intolable Grade 2</td>
<td>Hold vorinostat until ≤ tolerable grade 2, then reduce 1 dose level and resume treatment</td>
<td></td>
</tr>
<tr>
<td>Recurrent Grade 3 or 4 after 1 dose reductions</td>
<td>Remove patient from study.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematologic</th>
<th>Grade 1 or 2</th>
<th>Maintain dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4 or intolable Grade 2</td>
<td>Hold vorinostat until ≤ grade 2, then reduce 1 dose level and resume treatment. Transient transfusion support and growth factor is acceptable if the patient is experiencing clinical benefit</td>
<td></td>
</tr>
<tr>
<td>Recurrent Grade 3 or 4 after 1 dose reductions</td>
<td>Remove patient from study.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematologic: Platelets</th>
<th>≥ 100,000/mcL</th>
<th>Maintain dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100,000/mcL</td>
<td>Hold vorinostat until ≥ 100,000/mcL, then reduce 1 dose level and resume treatment.</td>
<td></td>
</tr>
<tr>
<td>Recurrent thrombocytopenia &lt; 100,000/mcL after 1 dose reduction</td>
<td>Remove patient from study.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other non-hematological toxicity</th>
<th>Grade 1 or 2</th>
<th>Maintain dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade 2 of concern (e.g., QT prolongation, electrolyte abnormalities)</td>
<td>Hold vorinostat until ≤ grade 1 or tolerable grade 2, then reduce 1 dose level and resume treatment</td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4 or intolable Grade 2</td>
<td>Hold vorinostat until ≤ tolerable grade 1, then reduce 1 dose level and resume treatment ²</td>
<td></td>
</tr>
<tr>
<td>Recurrent Grade 3 or 4</td>
<td>Remove patient from study.</td>
<td></td>
</tr>
</tbody>
</table>

¹ If event has not improved to ≤ tolerable grade 2 or baseline within < 21 days, patient should be removed from the study.
² Patients with medically concerning grade 3 or 4 AEs related to vorinostat may be taken off study at investigator’s discretion.

**7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS**

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) in addition to routine reporting.
The Comprehensive Adverse Event 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](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf) for further clarification. Frequency is provided based on 1076 patients. Below is the CAEPR for Vorinostat (SAHA, Zolinza).

**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 2.8, December 18, 2013

<table>
<thead>
<tr>
<th>Adverse Events with Possible Relationship to Vorinostat (SAHA, Zolinza) (CTCAE 4.0 Term)</th>
<th>Specific Protocol Exceptions to Expedited Reporting (SPEER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely (&gt;20%)</td>
<td>Less Likely (&lt;20%)</td>
</tr>
<tr>
<td>BLOOD AND LYMPHATIC SYSTEM DISORDERS</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>GASTROINTESTINAL DISORDERS</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Nausea</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>INFECTIONS AND INFESTATIONS</td>
<td></td>
</tr>
<tr>
<td>Infection²</td>
<td></td>
</tr>
<tr>
<td>INVESTIGATIONS</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>Alanine aminotransferase increased (Gr 2)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>Aspartate aminotransferase increased (Gr 2)</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>Creatinine increased (Gr 2)</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>Lymphocyte count decreased (Gr 4)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>Neutrophil count decreased (Gr 4)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>Platelet count decreased (Gr 3)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Weight loss (Gr 2)</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>White blood cell decreased (Gr 4)</td>
</tr>
<tr>
<td>METABOLISM AND NUTRITION DISORDERS</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>Anorexia (Gr 2)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Dehydration (Gr 2)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Hyperglycemia (Gr 2)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td></td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Hypophosphatemia (Gr 3)</td>
</tr>
<tr>
<td><strong>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Muscle weakness (Gr 2)</td>
</tr>
<tr>
<td><strong>NERVOUS SYSTEM DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>Dizziness (Gr 2)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>Dysgeusia (Gr 2)</td>
</tr>
<tr>
<td><strong>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>Cough (Gr 2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
</tr>
<tr>
<td><strong>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>Skin and subcutaneous tissue disorders - Other (skin necrosis)</td>
</tr>
</tbody>
</table>

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. Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

3. Muscle weakness includes Generalized muscle weakness, Muscle weakness left-sided, Muscle weakness lower limb, Muscle weakness right-sided, Muscle weakness trunk, and Muscle weakness upper limb under the MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS SOC.

4. Prolongation of prothrombin time and International Normalized Ratio have been observed in patients using vorinostat concomitantly with coumarin-derivative anticoagulants.

Also reported on vorinostat (SAHA, Zolinza) trials but with the relationship to vorinostat (SAHA, Zolinza) still undetermined:

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Febrile neutropenia

**CARDIAC DISORDERS** - Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (supraventricular arrhythmia); Chest pain - cardiac; Left ventricular systolic dysfunction; Myocardial infarction; Palpitations; Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Ventricular fibrillation

**EAR AND LABYRINTH DISORDERS** - Tinnitus; Vertigo

**EYE DISORDERS** - Blurred vision; Eye disorders - Other (retinal tear)

**GASTROINTESTINAL DISORDERS** - Abdominal distension; Anal hemorrhage; Bloating; Cheilitis; Colitis; Dysphagia; Esophageal hemorrhage; Esophagitis; Flatulence; Gastric hemorrhage; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (duodenitis); Lower gastrointestinal hemorrhage; Mucositis oral; Oral hemorrhage; Oral pain; Small intestinal obstruction; Stomach pain; Upper gastrointestinal hemorrhage

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Chills; Edema limbs; Gait disturbance; General disorders and administration site conditions - Other (failure to thrive); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain

**HEPATOBIILIARY DISORDERS** - Hepatic failure

**IMMUNE SYSTEM DISORDERS** - Immune system disorders - Other (angioedema)

**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Bruising; Vascular access complication; Wound dehiscence

**INVESTIGATIONS** - Activated partial thromboplatin time prolonged; Alkaline phosphatase increased; Cardiac
troponin I increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased;
Investigations - Other (increased lactate dehydrogenase); Lipase increased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia;
Hypermagnesemia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Metabolism and nutrition disorders - Other
(decreased total protein); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Chest wall pain;
Musculoskeletal and connective tissue disorder - Other (muscle spasms); Musculoskeletal and connective tissue
disorder - Other (myositis); Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms
benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Tumor pain
NERVOUS SYSTEM DISORDERS - Abducens nerve disorder; Ataxia; Cognitive disturbance; Depressed level of
consciousness; Dysphasia; Encephalopathy; Facial muscle weakness; Facial nerve disorder; Headache; Intracranial
hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders - Other
(Guillain-Barre syndrome); Nervous system disorders - Other (head injury); Nervous system disorders - Other
(polyneuropathy); Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence;
Stroke; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Euphoria; Personality change;
Psychosis
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Proteinuria; Urinary frequency;
Urinary incontinence; Urinary retention; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Pelvic pain; Uterine
hemorrhage; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage;
Epistaxis; Hypoxia; Pharyngeal mucositis; Pleural effusion; Pleuritic pain; Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Nail loss; Palmar-plantar
erythrodysesthesia syndrome; Purpura; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (brittle
nails)
VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypertension; Hypotension; Thromboembolic
event; Visceral arterial ischemia

Note: Vorinostat (SAHA, Zolinza) 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.

The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report ONLY AEs higher than this grade expeditiously via CTEP-AERS. 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.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales
found in the revised NCI Common Terminology Criteria for Adverse Events
(CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment
areas should have access to a copy of the CTCAE version 4.0. A copy of the
CTCAE version 4.0 can be downloaded from the CTEP web site

- For expedited reporting purposes only:
  - AEs for the agent that are **bold and italicized** in the CAEPR (i.e., those listed
    in the SPEER column, Section 7.1) should be reported through CTEP-AERS
only if the grade is above the grade provided in the SPEER.

- Other AEs for the protocol that do not require expedited reporting are outlined in Section 7.1.

- **Attribution** of the AE:
  - Definite – The AE is *clearly related* to the study treatment.
  - Probable – The AE is *likely related* to the study treatment.
  - Possible – The AE may be related to the study treatment.
  - Unlikely – The AE is *doubtfully related* to the study treatment.
  - Unrelated – The AE is clearly NOT related to the study treatment.

### 7.3 Expedited Adverse Event Reporting

#### 7.3.1 Expedited AE reporting for this study must use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP Web site ([http://ctep.cancer.gov](http://ctep.cancer.gov)). The reporting procedures to be followed are presented in the “NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs” which can be downloaded from the CTEP Web site ([http://ctep.cancer.gov](http://ctep.cancer.gov)). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

#### 7.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

In addition to reporting to CTEP-AERS:

- Participating sites are responsible for submitting all SAEs to their local IRB per institutional guidelines.
- Participating sites are responsible for reporting all SAEs to the MSKCC PI via fax or e-mail within 3 calendar days of learning of the event.
- Participating sites should notify the CUMC PI of any grade 5 event immediately.

**SAE contact information for the Coordinating Center is listed in Appendix E:**

#### 7.3.3 Expedited Reporting Guidelines: Expedited Reporting Requirements for
Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention\(^1,2\)

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

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**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 CTEP-AERS within the timeframes detailed in the **table below**.

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 Timeframes</th>
<th>Grade 2 Timeframes</th>
<th>Grade 3 Timeframes</th>
<th>Grade 4 &amp; 5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization ≥ 24 hrs</td>
<td>10 Calendar Days</td>
<td>24-Hour 5 Calendar Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not resulting in Hospitalization ≥ 24 hrs</td>
<td>Not required</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

1Serious 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 5 calendar days for:**

- All Grade 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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.

Effective Date: May 5, 2011

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**7.4 Routine Adverse Event Reporting**
All Adverse Events must be reported in routine study data submissions. AEs reported through CTEP-AERS must also be reported in routine study data submissions.

7.5 Secondary Malignancy

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 following treatment with an agent under an NCI IND/IDE 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.

7.6 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.

7.7 Serious Adverse Event (SAE) Reporting for Columbia University Medical Center patients only

See Section 14, “Serious Adverse Event (SAE) Reporting For CUMC.”

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 Vorinostat (NSC 701852; IND 71976)

Chemical Name: N-hydroxy-N’-phenyl-octane-1,8-diotic acid diamide; suberoylanilide hydroxamic acid

Other Names: SAHA, MK-0683
Classification: Histone deacetylase inhibitor
CAS Registry Number: 149647-78-9
Molecular Formula: C_{14}H_{20}N_{2}O_{3}
M.W.: 264.32
Approximate Solubility: Water ≤ 5 mg/mL

Mode of Action: Histone deacetylases (HDACs) are a family of enzymes that regulate chromatin remodeling and gene transcription via the dynamic process of acetylation and deacetylation of core histones. Vorinostat, a potent inhibitor of HDAC activity, binds directly to the catalytic pocket of HDAC enzymes. It causes G1 or G2 phase cell-cycle arrest, apoptosis, or differentiation in cultured transformed cells.

How Supplied: Merck and Co. supplies and CTEP, NCI, DCTD distributes vorinostat. The agent is available as a white, opaque gelatin, size 3 capsule with “568” over “100 mg” printed within the radial bar in black ink on the capsule body, containing 100 mg of vorinostat. The inactive ingredients contained in each capsule are microcrystalline cellulose, sodium croscarmellose, and magnesium stearate. Vorinostat 100 mg capsules are supplied in high-density polyethylene (HDPE) bottles containing 120 capsules.

Storage: Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published (see Package Insert). There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. Vorinostat capsules should not be opened or crushed. Direct contact of the powder in vorinostat capsules with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly as outlined in the references. Personnel should avoid exposure to crushed and/or broken capsules.

Stability: Shelf life stability studies of the intact bottles are on-going.

Route of Administration: Orally. Unless otherwise stated in the protocol, vorinostat capsules must be administered whole. Administer vorinostat with food if possible.

Potential Drug Interactions: Prothrombin time and INR prolongations have been reported in patients taking vorinostat concomitantly with coumarin derivative anticoagulants. Monitor these patients more frequently for alterations in their coagulation parameters.

Special Handling: Clean powder spills from broken or damaged vorinostat capsules carefully minimizing inhalation. Wash spill area at least three times with ethyl alcohol, followed by water.

Patient Care Implications: Because vorinostat’s dose limiting toxicities are anorexia, dehydration, diarrhea, and fatigue, patients should maintain adequate fluid and food intake.
Encourage patients to seek a nutritional consult.

Treat diarrhea promptly with appropriate supportive care, including loperamide. Instruct patients to begin taking loperamide at the first signs of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day, or 3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. Daily dose should not exceed 16 mg/day. Loperamide should not be taken prophylactically. Advise patients to drink plenty of clear fluids to help prevent dehydration caused by diarrhea. Avoid loperamide if there is the presence of blood or mucus in the stool or if diarrhea is accompanied by fever. If diarrhea occurs during treatment with vorinostat, the dose should be modified as per Section 6.3.

Patients should not have taken valproic acid, another histone deacetylase inhibitor, for at least two weeks prior to study enrollment.

8.1.1 **Availability**

Vorinostat is an FDA approved agent for CTCL supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Vorinostat is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3). The IND (#71976) for this protocol is held by CTEP.

8.1.2 **Agent Ordering and Agent Accountability**

8.1.2.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), 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 investigator at that institution.

Agent may be requested electronically to PMB. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application [https://eapps.ctep.nci.nih.gov/OAOP/pages/login.jspx](https://eapps.ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the
establishment of a CTEP Identity and Access Management (IAM) account https://eapps-ctep.nci.nih.gov/iam/ and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfHerHours@mail.nih.gov anytime.

8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator’s Handbook for Procedures for Drug Accountability and Storage.)

9. CORRELATIVE/SPECIAL STUDIES

The first 10 patients at MSKCC with metastatic uveal melanoma who have accessible sites of tumor who are treated with vorinostat will undergo two mandatory biopsies (assuming that the biopsy procedure does not pose undue danger to the patient). The pre-treatment biopsy will be obtained within 15 days of starting therapy for patients; however, tumor samples obtained at earlier time-points may be utilized with the permission of the Principal Investigator. The post-treatment biopsy will be performed at day 8, 9 or 10 prior to the evening dose of vorinostat. Up to three core samples will be obtained with each biopsy, providing sufficient tissue for the correlative studies described below. Tissue will be divided such that a portion is designated for immunohistochemistry (IHC) and the remainder flash frozen in liquid nitrogen for Western blots. All unused tumor tissue will be destroyed 10 years after the completion of the trial.

9.1 GNAQ/GNA11/BAP1

Determination of Gnaq, Gna11 and BAP1 mutational status will be required for all patients on this study. This analysis can be performed retrospectively utilizing 10 unstained slides from paraffin embedded tissue. For patients who do not have biopsy-confirmation of metastatic disease, a core biopsy (up to 3 cores) will be performed prior to study entry to confirm metastatic disease and to provide sufficient tissue for Gnaq/Gna11 and BAP1 analysis and other correlative studies. For patients who have previously undergone a fine needle aspiration confirming the presence of metastatic disease but which is insufficient for molecular analysis, another mandatory pre-treatment core biopsy (up to 3 cores) will be required for Gnaq/Gna11 and BAP1 analysis and other correlative studies.

Tumor Gnaq and Gna11 status for all patients treated on this study will be determined using a CLIA certified assay at MSKCC, CUMC or Vanderbilt University Medical Center. Testing conducted at MSKCC will be done in the MSKCC Molecular Diagnostics Laboratory. A turnaround time of 5-10 business days from the time of tissue submission to reporting of the Gnaq and Gna11 results is expected at MSKCC. DNA from normal tissue (if available) will be analyzed to demonstrate the somatic nature of identified mutations and novel
polymorphisms. Currently, a CLIA certified assay for BAP1 is not available and BAP1 mutational analysis for all patients (enrolled at MSKCC, CUMC and Vanderbilt University Medical Center) will be performed by Thomas Wiesner, MD in the laboratory of Ping Chi, MD.

IHC for BAP1 will be performed on all samples in the laboratory of Pathology under the supervision of Klaus Busam, MD at MSKCC. Briefly, formalin-fixed paraffin-embedded sections will be stained with commercial BAP1 antibody (Santa Cruz, sc-28383) and a corresponding detection immunostain followed by appropriate analysis per the Manufacturer’s instruction. Sections will be scored based on nuclear staining intensity as follows: the percentage of positive tumor cells will be multiplied by a factor of 1 to 3 (0, no staining; 1, faint staining; 2, moderate staining; and 3, strong staining), giving a final score between 0 and 300. Samples will be run in duplicate and a final composite result (average of the two numbers) will be given to each case. Cases will be scored negative if the result is 0.

Samples for patients enrolled at the collaborating institution will be shipped to CUMC via overnight carrier. This material will be packaged in a way to ensure they do not break. All slides must be shipped with appropriate identifiers including a pathology report from the collaborating institution and the tumor tissue shipment provided by the 12-027 CUMC research staff. Samples should be shipped to arrive Mondays through Fridays. Samples should be assigned a unique code number and be stripped of any identifiable information for the specific individual. All shipments should be directed to the address listed on the tissue sample shipment form. Dr. Richard D. Carvajal and the study team (AAA05917@columbia.edu) will be notified by e-mail the day the slides are sent. This e-mail will contain the following information:

- Subject Initials
- Subject Number
- Shipment Date
- Shipment Tracking Number
- Contents of Shipment

9.2 Validation of Target Inhibition

Western blot analysis for acetylated-H4 will be performed on 10 paired samples in the laboratory of Dr. Gary Schwartz. As outlined in Section 2.5, we anticipate vorinostat treatment will increase acetylation of histone 4 in both patients with wild-type and Gnaq/Gna11 mutated uveal melanoma. In cell lines, Gnaq/Gna11 mutants appear more sensitive to HDACi and exhibit relatively higher levels of acetylated H4. Histone acetylation status will be correlated with best overall objective response as well as Gnaq, Gna11 and BAP1 mutational status. Based on our preclinical findings, we anticipate that higher levels of acetylated-H4 will be observed in Gnaq/Gna11 mutants, but not in wild-type tumors, and will be associated with improved clinical outcome.

Frozen specimens will be shipped in batches. Samples should arrive Mondays through Fridays. Samples should be assigned a unique code number and be stripped of any identifiable information for the specific individual. Ship specimens to:
9.3 Markers of Proliferation and Apoptosis

Using 10 or more matched tumor samples, changes in proliferation will be assessed using Ki67 by IHC, and assessment of apoptosis will be performed western blot by assessing PARP cleavage, as well as levels of BIM, Survivin, c-myc and Mcl-1 using published methods in the laboratory of Gary K. Schwartz. These results will be correlated with tumor mutation status (Gnaq mutant, Gna11 mutant, Gq/11 wild-type and BAP1 status) and clinical outcome (best overall response).

Ship specimens as per instructions in Section 9.2.

9.4 Assessment of Effects upon Signaling Pathways

Other studies may be performed utilizing tumor tissue obtained from the 10 mandatory pair biopsies enrolled onto this study at MSKCC, including, but not limited to, evaluation of the MAPK and PI3K pathways.

The analysis will be conducted in the laboratory of Dr. Gary Schwartz. Ship specimens as per instructions in Section 9.2.

9.5 Optional Tumor Biopsies

In addition to the mandatory biopsies described above, all patients enrolled on this study at MSKCC (in addition to the 10 patients who undergo mandatory paired biopsies), CUMC and Vanderbilt will have the option to undergo biopsies prior to treatment, nine days (± 1) into treatment, and at progression of disease. These biopsies will only be suggested if the biopsy procedure does not pose undue danger to the patient and if funding is available for additional analysis. The purpose of these biopsies will be to assess for target inhibition, markers of proliferation and apoptosis, and effects on signaling pathways as delineated above.

The analysis for MSKCC biopsies will be conducted in the laboratory of Dr. Gary Schwartz. MSKCC specimens should be shipped as per instructions in Section 9.2. The analysis for Vanderbilt biopsies may be conducted locally or in the laboratory of Dr. Gary Schwartz (shipping instructions located in Section 9.2).

9.6 Assessment of ctDNA

Two lavender top tubes of peripheral blood will be collected for all MSKCC and CUMC patients 1) prior to the start of vorinostat, 2) on treatment at week 3 and then at the beginning
of every odd numbered cycle, and 3) at progression of disease. All samples will be submitted to the Wolchok laboratory for processing and storage as per Appendix C or in the Schwartz laboratory (see Section 9.2 above). Samples will be sent in bulk throughout the course of the study to the Institut Curie, France as per Appendix C. The analyses for ctdDNA will be conducted as per published methods in the Laboratory of Immunology of Institut Curie Hospital.

10. STUDY CALENDAR

Baseline evaluations (including baseline imaging studies) are to be conducted within 28 days prior to administration of protocol therapy. MRI or CT scan with contrast of the brain should be performed if there are signs/symptoms concerning for brain metastases. If 30 days or more have elapsed since patient signed the informed consent and HIPAA Authorization form at screening, the patient will have to re-consent by signing the current IRB approved version of the informed consent. The schedule of procedures and treatment for patients receiving vorinostat is outlined in the calendar below:

<table>
<thead>
<tr>
<th></th>
<th>Cycle 1</th>
<th>Cycle 2</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Radiologic Evaluation⁵</td>
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42
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<tr>
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<td>Adverse Event Evaluation</td>
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<tr>
<td>Radiologic Evaluation h</td>
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</tr>
</tbody>
</table>

\(a\): Vorinostat will be administered at 300mg BID for 3 consecutive days followed by 4 days of rest, repeated weekly. Four weeks is one cycle.

\(b\): All blood work and examinations may be performed +/- 3 days from the scheduled date.

\(c\): Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT (AST), SGPT (ALT), sodium.

\(d\): Serum pregnancy test for women of child-bearing potential.

\(e\): An EKG will be performed at baseline for all patients and again at the beginning of each cycle to monitor for QTc prolongation. The Cycle 1 week 1 EKG does not need to be conducted if the baseline EKG was conducted within 14 days of treatment start date. Additional EKGs will be performed as clinically indicated.
f. If there is no available or insufficiently previously collected banked tumor tissue available for baseline Gnaq/Gna11/BAP1 analysis, patients will undergo a baseline tumor biopsy. Ten patients at MSKCC treated with vorinostat will require a pre- and a post-treatment biopsy. The post-treatment biopsy will be performed at day 8, 9 or 10 prior to the evening dose of vorinostat. All patients at CUMC MSKCC and Vanderbilt will also have the option to undergo optional tumor biopsies prior to treatment, nine days (± 1) into treatment, and at progression of disease as per Section 9.5.

g. MRI or CT imaging of the brain will be performed at baseline at the discretion of the treating physician and should be performed if there are signs/symptoms of brain metastases.

h: CT of the chest, abdomen and pelvis with contrast OR CT of the chest without contrast and MRI of the abdomen and pelvis will be performed at baseline, 8 weeks, and again every subsequent 8 weeks (+/- 1 week). After completing six cycles of therapy, the treating physician will have the option to perform staging scans every 8 – 16 weeks (+/- 1 week) starting from the Cycle 6 Week 4 scan, and continuing thereafter, if deemed appropriate.

i: For patients at MSKCC and CUMC: Two 10 cc lavender top tube (EDTA) will be collected prior to treatment, at week 3 on treatment, at the beginning of every odd numbered cycle (e.g., cycle 3, 5, 7 etc) and at progression.

j: The CBC at week 2 is only for patients who undergo an on treatment research biopsy; this CBC should be obtained prior to biopsy. Any laboratory is an acceptable alternative for this blood sample as long as normal ranges are provided.

k: In the event that the patient’s health deteriorates such that the follow-up visit is not feasible, a note will be placed in the subject’s medical record documenting the situation. This will not be considered a protocol violation.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients will be re-evaluated for response every 8 weeks. After completing six cycles of therapy, the treating physician will have the option to perform staging scans every 8 – 16 weeks (+/- 1 week) starting from the Cycle 6 Week 4 scan, and continuing thereafter, if deemed appropriate. Confirmatory scans should also be obtained 4 weeks following initial documentation of objective response. Patients will be re-evaluated for response until progression is documented, the start of new anticancer therapy, or death.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee Version 1.1. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST version 1.1 criteria, as defined below. In contrast, measurable disease in lymph nodes is determined based on the lymph node short axis.

11.1.1 Definitions

**Evaluable for toxicity.** All patients will be evaluable for toxicity from the time of their first treatment with vorinostat.

**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.)

11.1.2 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 $\geq 20$ mm by chest x-ray or as $\geq 10$ mm with CT scan, MRI, or 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 might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq 15$ 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 $\geq 10$ to $<15$ mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: 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, but 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.

### 11.1.3 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 \( \geq 10 \) 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).

**PET-CT** At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.
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.

11.1.4 Response Criteria

11.1.4.1 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 progressions).

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

11.1.4.2 **Evaluation of Non-Target Lesions**

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

**Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

**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 “non-target” lesions only 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).

11.1.4.3 **Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.
| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Overall Response when Confirmation is Required*
<table>
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<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
<td>≥4 wks. Confirmation**</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>PR</td>
<td></td>
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<td>CR</td>
<td>Not evaluated</td>
<td>No</td>
<td>PR</td>
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<tr>
<td>PR</td>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Non-CR/Non-PD/Not evaluated</td>
<td>No</td>
<td>SD</td>
<td>Documented at least once ≥4 wks. from baseline**</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
<td>no prior SD, PR or CR</td>
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<td>Any</td>
<td>PD***</td>
<td>Yes or No</td>
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<td>Any</td>
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* 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.

11.1.5 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 the treatment started, including the baseline measurements.

11.1.6 Response Review

For trials where the response rate is the primary endpoint, it is strongly
recommended that all responses be reviewed by an expert(s) independent of the study at the study’s completion. Simultaneous review of the patients’ files and radiological images is the best approach.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 12.1.

Data Collection
The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system (CTMS) that will be used for data collection. CRFs for the study will be built into the CTMS for data entry. The system has full auditing capabilities which is web-based and housed on a server in a fully HIPAA compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity of patients via an interface with the electronic medical patient index. Staff with the appropriate IRB defined roles can run reports within the system for reporting purposes.

Data Reporting
Case Report Forms will be completed for each subject enrolled into the clinical study through the CTMS. It is the investigator’s responsibility for ensuring that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate and authentic.

Data and Safety Monitoring Committee
The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee is chair is appointed by the HICCC Director. The committee consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to
ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

For multicenter research, the principal investigator will assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. The report will document that a review of data and outcomes across all centers took place on a given date. It will summarize the DSMC’s review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It will also inform site investigators of the study the DSMC’s conclusion with respect to progress or need for modification of the protocol.

Quality Control and Quality Assurance
Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures. The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings.

Internal On-site Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).

- The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.

- The Compliance Coordinator will communicate with the site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.

- The assigned Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and
documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF’s accurately reflect source documents, that all toxicities have been reported to date, and that all SAE’s/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

Confidentiality
Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (e.g., that the subject is alive) at the end of their scheduled study period.

The subject binders will be maintained with in the CPDM offices, a secured floor within the Herbert Irving Pavilion and only the investigator and study staff will have access to the file.

Source Documents
Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Case Report Forms
The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”.

Records Retention
Records relating to a specific research activity, including research records collected by
IRB#: AAAAA5917

Investigators, must be maintained for at least three years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This minimum retention period applies whether or not any subjects were enrolled in the study. If the research is FDA regulated, records should be retained for at least two years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least two years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies); Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least seven years, per CUMC and NYP policy which is based on state law.

12.1 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix D.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

12.2 Collaborative Agreements Language

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.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary endpoint is overall response rate in patients with GNAQ/GNA11 mutant uveal melanoma as defined as the rate of complete and partial responses. In this phase II trial, we will utilize a Simon mini-max two-stage design in which a 5% response rate is considered not promising, a 20% response rate is considered promising, and the probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) are set at 0.10 and 0.10, respectively. In the first stage of this design, 18 patients with GNAQ/GNA11 mutant tumor will be accrued. If at least 1 patient with GNAQ/GNA11 mutant tumor achieves an objective response among these 18 patients, then an additional 14 patients will be accrued to the second stage. As GNAQ/GNA11 mutational analysis is being performed retrospectively in this study, it is anticipated that up to 8 patients with GNAQ/GNA11 wild-type tumor will be accrued. Patients with GNAQ/GNA11 wild-type uveal melanoma who are accrued during the study will not be included in the primary endpoint of overall response rate. An additional patient with known GNAQ/GNA11 mutant tumor will be accrued for every patient with GNAQ/GNA11 wild-type tumor included in this study. At the end of the trial, if 3 or less responses are seen in patients with GNAQ/GNA11 mutant uveal melanoma, the study will be declared negative. This design yields at least a 0.90 probability of a positive result if the true response rate is at least 20% and yields a 0.90 probability of a negative result if the true response rate is 5%. At the end of the trial, the response rate along with 90% confidence interval will be estimated.
13.2 Sample Size/Accrual Rate

This study design requires the accrual of up to 32 patients with uveal melanoma harboring a GNAQ or GNA11 mutation. Patients with wild type GNAQ and GNA11 uveal melanomas will also be enrolled on this study; however, not be counted towards the primary endpoint. This means that a maximum of 40 patients can be enrolled on this study to meet the primary endpoint (20% wild type, 80% GNAQ/GNA11 mutated). This study will be a multicenter phase II study conducted at MSKCC and Vanderbilt University Medical Center. The Melanoma Service at MSKCC sees between 2 and 4 patients with uveal melanoma monthly, with 75% or more presenting to us with metastatic disease. We anticipate accrual of 1-2 patients monthly at MSKCC for a total study accrual of 2-3 patients per month.

13.3 Stratification Factors

Not applicable

13.4 Analysis of Secondary Endpoints

Overall survival defined as the time from start of treatment to death or last follow-up will be estimated. Progression-free survival as the time from start of treatment to date of progression, death or last follow-up will be estimated. Progression-free survival and overall survival curves will be generated using Kaplan-Meier methodology.

Toxicity will be reported by type, frequency and severity according to the NCI Common Toxicity Criteria 4.0.

Gnaq/Gna11/BAP1 mutation status will be determined by sequencing. Associations of each unique mutation status with overall response will be assessed using Fisher’s exact test.

13.5 Analysis of Exploratory Endpoints

Additional exploratory studies will be reported in a descriptive fashion. These assays will be performed even if a negative result is obtained for the primary endpoint.

13.6 Reporting and Exclusions

13.6.1 Evaluation of toxicity – All patients will be evaluable for toxicity from the time of their first treatment with vorinostat.

13.6.2 Evaluation of response – All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from
toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database. Patients in category 9 will be considered to have a treatment failure (disease progression and will be evaluated in for the primary endpoint.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 90% confidence intervals should also be provided.

14. SERIOUS ADVERSE EVENT (SAE) REPORTING FOR CUMC

14.1 Definitions

**Adverse Event:**
An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including abnormal sign, symptom or disease, temporally associated with the subject’s participation in research, whether or not considered related to the subject’s participation in the research. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

**Serious Adverse Event:**
Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
• life-threatening
• requires inpatient hospitalization/prolongation of existing hospitalaation, unless:
  o routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
  o elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  o treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above/below and not resulting in hospital administrations
  o social reasons and respite care in the absence of any deterioration in the patient’s general condition
• results in persistent or significant disability or incapacity
• a congenital anomaly or birth defect
• an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious events should be regarded as non-serious adverse events.

**Unanticipated Problem:**
An unanticipated problem is any incident, experience or outcome involving risks to subjects or others in any human subjects research that meets all of the following criteria:

• Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
• Related or possibly related to participation in such research (e.g., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
• Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

**Adverse Event Reporting Period:**
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures (e.g., after the first dose of study treatment) to the end of the study treatment (e.g., last dose of study treatment) and/or follow-up.
**Baseline/Preexisting Condition:**
A baseline/preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or if the character of the condition worsens during the study period.

**General Physical Examination Findings:**
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

**Post-study Adverse Event:**
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject’s personal physician, believes might reasonably be related to participation in this study.

**Abnormal Laboratory Values:**
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.).

**Hospitalization, Prolonged Hospitalization or Surgery:**
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of
the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

**Recording of Adverse Events:**
At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

14.2 Reporting of Serious Adverse Events

14.2.1 IRB Notification by Sponsor-Investigator

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator’s acquiring knowledge of the unanticipated problem in accordance with IRB policy. Additionally, the sponsor-investigator will submit a summary of all Unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

14.2.2 DSMC Reporting by the Sponsor Investigator

Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting should occur within 24 hours of knowledge of the SAE occurring at our institution or affiliate sites.

15. PROTECTION OF HUMAN SUBJECTS

15.1 Inclusion of Children in Research

This protocol/project does not include children because the number of children is limited and because the majority are already accessed by a nationwide pediatric
cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

15.2 Privacy

Columbia University Medical Center’s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

15.3 Informed Consent Procedures

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information.

In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.
16. REFERENCES

# Appendix A: Performance Status Criteria

## Performance Status Criteria

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Percent</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal activity. Fully active, able to carry on all pre-disease performance without restriction.</td>
<td>100</td>
<td>Normal, no complaints, no evidence of disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease.</td>
</tr>
<tr>
<td>1</td>
<td>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).</td>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70</td>
<td>Cares for self, unable to carry on normal activity or to do active work.</td>
</tr>
<tr>
<td>2</td>
<td>In bed &lt;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.</td>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most of his/her needs.</td>
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<tr>
<td></td>
<td></td>
<td>50</td>
<td>Requires considerable assistance and frequent medical care.</td>
</tr>
<tr>
<td>3</td>
<td>In bed &gt;50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
<td>40</td>
<td>Disabled, requires special care and assistance.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>Severely disabled, hospitalization indicated. Death not imminent.</td>
</tr>
<tr>
<td>4</td>
<td>100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
<td>20</td>
<td>Very sick, hospitalization indicated. Death not imminent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>Moribund, fatal processes progressing rapidly.</td>
</tr>
<tr>
<td>5</td>
<td>Dead.</td>
<td>0</td>
<td>Dead.</td>
</tr>
</tbody>
</table>
Appendix B: Vorinostat

Name: _______________ Date: _______________ Study ID/ MRN: _______________

Medication Diary for IRB AAAO5917: A Phase 2 Study of Vorinostat (NSC 701852; IND 71976) in Metastatic Uveal Melanoma (NCI Protocol #9111; NCI Version Date: 12/22/2014)

Number of Capsules Given: ______ Medication Bottle(s) returned: Circle Yes or No

Total Daily Dose: ______ Number of Capsules returned: _____________

(To be Completed by RN)

PLEASE FILL OUT AND BRING THIS SHEET AT YOUR NEXT VISIT.

- Please take dose by mouth twice daily for 3 consecutive days followed by 4 days of rest each week. Do not chew the capsules. Please allow for adequate time (8-12 hours) between your AM and PM dosing time and record below. You are encouraged to remain consistent with your daily dosing schedule throughout your treatment.
- Please bring this diary with you to each appointment. A new copy of the Medication Diary will be given to patients as needed.
- Any dose missed or vomited should not be replaced.
- Please store capsules at room temperature.
- Please take with food.

<table>
<thead>
<tr>
<th>CYCLE #: _______</th>
<th># of WEEKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAY</td>
<td>DATE</td>
</tr>
<tr>
<td>Example</td>
<td>01/01/2010</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Day 1</td>
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<td>Day 2</td>
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<td>Days 4 to 7</td>
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<td>Day</td>
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<td>Day 17</td>
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<td>Day 24</td>
<td>AM</td>
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<tr>
<td>Day 25-28</td>
<td></td>
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</tr>
</tbody>
</table>

Patient Signature: ___________________________ Date: __________

Consenting Professional/Research RN Signature: ______________ Date: __________

Consenting Professional/Research RN Comments: ___________________________
Appendix C: Processing of Samples for ctDNA Analysis

Plasma preparation and DNA extraction

Plasma samples should be prepared as described by Diehl and Coll. Blood is centrifuged at 820g for 10 minutes. The supernatant is then transferred to sterile tubes, centrifuged at 16,000g for 10 minutes at room temperature, and the supernatant should be stored at -80°C. The overall process from blood collection to plasma storage should not exceed 3 hours. Samples should be assigned a unique code number and be stripped of any identifiable information for the specific individual.

DNA extraction from plasma of patients should be accomplished using the Qiagen QIAamp circulating nucleic acid kits or an acceptable alternative. Extraction should be performed according to the manufacturer instructions. Nucleic acids should be stored and shipped at -20°C.

Shipment of DNA to Institut Curie

Samples will be shipped in bulk to the Institut Curie throughout the study. Samples should be sent on dry ice to:

Marc-Henri Stern, MD PhD
Institut Curie
Immunologie 4ème étage
26 rue d’Ulm
75005 Paris cedex 05 France

Prior to shipment, the research team at the Institut Curie should be notified by email at:

maud.milder@curie.net
aurore.rampanou@curie.fr
delphine.louis@curie.net
isabelle.peguillet@curie.net
Appendix D: CTEP Multicenter Guidelines

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair
• The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
• The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
• The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
• The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center
• Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
• Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
• The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
• The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
• The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
• Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration...
Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.
Appendix E: Guidelines for Affiliate Institutions in Multicenter Studies

1. Multi-site Communication:

The CPDM Office at CUMC provides administration, data management, and organizational support for the affiliate sites in the conduct of a multicenter clinical trial. The CPDM Office will coordinate, at minimum, regularly scheduled conference calls with affiliate sites. The following issues will be discussed, as appropriate:

- Enrollment information
- Cohort updates (e.g., DLTs)
- Adverse events (e.g., new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

2. New Protocol Distribution, IRB Submission, Modifications, and Annual Renewals

- Protocol specific documents are distributed to affiliate sites once CUMC IRB approval has been obtained.
- The affiliate site must submit a draft of site specific revisions to protocol and/or consent form documents for review and approval by the sponsor-investigator prior to submission to the local IRB. Draft documents should be sent to the study specific email address. The site will be provided confirmation that they are approved to submit to their local IRB. Protocol amendments must be approved by the affiliate site’s local IRB within 90 days of distribution to the site by the sponsor-investigator.

3. Regulatory Documents:

Prior to Site Initiation:

Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected, prior to the initiation of an affiliate site.

- CV of PI, Co-I’s and other research staff listed on FDA 1572 (signed and dated copy within 2 years)
- Medical Licenses of PI and Co-I’s (current copy)
- Human subjects training certificates for PI and Co-I’s
- CLIA/Laboratory Certifications for Local Laboratories listed on FDA 1572
- Local Laboratory Director’s CV and License
- Local Laboratory Reference Ranges
- IRB roster or statement of compliance
- FDA Form 1572, if applicable (wet ink originals required)
- Financial Disclosure forms for all members listed on FDA 1572 (wet ink originals required)
Ongoing Regulatory Documentation: Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected throughout the course of the study.

- IRB approval letters for all protocol modifications and all renewals
- IRB-approved consent forms
- Current IRB roster, if statement of compliance is not provided as part of site initiation
- FDA Form 1572, if applicable as updates are required
- Updated investigator and site information where relevant (e.g., CV, medical licensure and Financial Disclosure for new sub-investigator, local laboratory information)

Regulatory documents may be sent to AAAO5917@columbia.edu or to the following address if wet ink originals are required:

Clinical Protocol & Data Management Office
161 Fort Washington Ave.
Herbert Irving Pavilion
Mezzanine Level, M-203
New York, NY 10032

4. Site activation

Columbia University will schedule a site initiation visit once IRB approval has been submitted from the affiliate site.

5. Central Registration Procedures- Affiliate Institution Research Participant Registration Process:

All Affiliate Institutions must register subjects with the coordinating center (CUMC) prior to any administration of study drug/intervention/local institution registration. Please see instructions below:

1. Within 48 hours of obtaining consent (excluding holidays and weekends), the Affiliate Institution CRN and/or CRC is required to submit the following documents to the coordinating center’s designee (CUMC’s study specific Clinical Research Coordinator or Clinical Research Nurse). The coordinating center’s designee will review the documents for accurateness, and subsequently submit the documents to the CPDM Central Registration Office via email at CPDMRegistration@columbia.edu (or via fax at 212.305.5292), with a request to register the patient “pending eligibility.” The title of the email should read, “AAAO5917 Pending Subject Registration Request (PHI)”. The following documents should be submitted with the pending registration request, as applicable:
   a. Redacted Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable
   b. Redacted Signed HIPAA (or institutional equivalent)
c. MCT CPDM Velos Note to File form

2. The Affiliate Institution’s investigator/research nurse/data manager/coordinator must contact the coordinating center’s designee (CUMC’s study specific Clinical Research Coordinator or Clinical Research Nurse) via telephone or email to communicate the following:
   • Notify of pending registration request
   • Confirm method of registration request submission (email or fax)
   • Communicate expected time-line of registration request submission (e.g., same day, next day, within the hour, etc.)

3. To complete registration, the Affiliate Institution’s investigator/research nurse/data manager/coordinator should then submit the following documents to the CUMC study specific designee:
   • A signed Affiliate Site Eligibility Checklist (signed by the investigator)
   • Copies of redacted source documentation necessary for each item to be verified on the CUMC specific Eligibility Checklist, including but not limited to:
     o Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
     o Copy of pathology and surgical reports
     o Copy of clinic note(s) capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms. (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)
     o Protocol deviation/waiver approvals (if applicable)
   • Please note: subject line of email or fax should include the following: “AAAO5917 Complete Subject Registration Request (PHI)”.

4. Upon receipt of the above mentioned documents, the designated study specific Clinical Research Coordinator will review all documents and verify patient eligibility. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable affiliate site study team personnel for clarification prior to enrollment. Upon verification, the CUMC study specific designee will then forward all documents to the CPDM Central Registration Office for central registration (as described above). The CPDM Central Registration Registrar will review all applicable documents and communicate to the CUMC study specific designee in order to clarify any items. The CUMC study specific designee will communicate with the applicable site study team personnel for additional clarifications necessary prior to enrollment.

5. Upon receipt of the subject registration notification email, the CUMC study specific designee will forward the notification email (which will include the study specific patient ID) to the affiliate site’s Principal Investigator, Consenting Professional, and
applicable research personnel. This notification should be filed in the patient research binder accordingly. Protocol therapy may not be initiated prior to receipt of this notification from the coordinating center.

6. All screenfail/ineligible subjects, as well as subject’s who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration Office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

6. Protocol Deviation/Subject Waiver request for Affiliate Sites:

The Affiliate site MUST submit a prospective deviation request to the CUMC lead PI for review and submission to the HICCC DSMC and CUMC IRB. Approvals must be obtained from all entities prior to implementation at the Affiliate site. If a prospective protocol deviation request is submitted for review (from an Affiliate site), the PI/site memo(s), HICCC DSMC approval(s) and correspondence and CUMC IRB eligibility deviation approval letter(s) should be forwarded to the Affiliate site for documentation. The Affiliate site is also required to obtain prospective local IRB approval as per institutional policies/procedures prior to implementing the proposed deviation and registering/enrolling the subject via CUMC Central Registration. All documents and determinations must be clearly documented in the study subject’s medical record, research chart and regulatory binder, as described.

7. Guidelines for Affiliate Site Monitoring

On-Site MCT Monitoring:
1. Initial, recurrent, and close-out on-site monitoring visits will also be conducted at Affiliate sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
   a. The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.
2. The Compliance Coordinator will communicate with the Affiliate site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.
3. The Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled at the Affiliate site and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the participating site PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly
obtained, eligibility is met (via the central registration process), and all study procedures
are conducted according to the study protocol. The Compliance Coordinator will also
verify that the data reported in the CRF’s accurately reflect source documents, that all
toxicities have been reported to date, and that all SAE’s/UPs/deviations/violations have
been reported according to Coordinating Center, local IRB and HICCC DSMC
requirements. The Compliance Coordinator will issue queries and ensure resolution in a
timely and efficient manner. The Compliance Coordinator will also monitor for
applicable regulatory compliance and research pharmacy compliance (if applicable) and
communicate any deficiencies as appropriate.

4. An SIV (or) teleconference will be scheduled and conducted prior to study drug being
made available (if applicable) and before any subjects are enrolled on a study at the
Affiliate site.

MCT Remote Monitoring:
- When necessary (due to logistical constraints), Affiliate sites will be monitored remotely
  by a designated Compliance Coordinator. Sites will be informed of this remote
  monitoring process on a site by site basis.
- Affiliate sites will be monitored by the Compliance Coordinator on both a regulatory
  level, as well as a clinical data/source documentation review level.
- Redacted source documents (applicable to supporting the protocol specific CRF data
  requirements) will be sent to the designated Compliance Coordinator via fax or secure
  email for all subjects enrolled at Affiliate sites. Timelines for submission procedures will
  be defined on a case by case basis.
- The Compliance Coordinator will review all submitted redacted source documents
  against the data entered on the protocol specific CRFs. The Compliance Coordinator will
  issue queries when/if necessary.
- The Affiliate site research staff will respond to queries within 30 days. If queries remain
  outstanding, the Compliance Coordinator will send a delinquent query reminder for the
  outstanding items.
- The remote monitoring procedures will include review of applicable redacted source
documentation and supporting applicable documents to determine compliance regarding:
  a. Informed consent procedures
  b. Eligibility criteria
  c. Protocol specific treatment compliance
  d. Protocol specific toxicity/outcome documentation/compliance
  e. Protocol specific schedule of events (e.g., baseline visits, pre-treatment, on study,
     follow-up)
  f. Participating site IRB documents (e.g., IRB amendment approvals, annual
     renewals, SAE/UP submissions, violation/deviation submissions, INDSR
     submissions, etc.).
  g. Required specimen submissions (e.g., tissue specimens, research blood
     specimens, etc.)
  h. Pharmacy accountability records
  i. Adherence to the CRF submission timeframes to CUMC (within the protocol
     specified timeframes)
Affiliate site remote monitoring reports will be sent to the lead PI, HICCC DSMC, and Affiliate sites after each remote monitoring review. Reports will include information regarding data submission timeliness/accuracy, protocol adherence items, query resolution status, regulatory status, and overall Affiliate site performance. These reports will be generated by the Compliance Coordinator and reviewed with the Compliance Core Manager prior to dissemination.

8. Dose Level Determinations:

The sponsor-investigator will review enrollment for each dose level cohort during the regularly scheduled conference call with the affiliate sites. The dose level for newly enrolled subjects will be determined by the study statistician upon notification that a subject has signed informed consent to participate in the study. The assigned dose level for any subject to begin study treatment will be communicated to the affiliate site along with the determination by Central Registration that the subject is eligible for enrollment in the study. If a Dose Limiting Toxicity (DLT) is identified in a subject, the affiliate site must notify the sponsor-investigator via email at the study specific email address within 1 business day of identification. The lead site will communicate that a DLT has been experienced within 1 business day.

9. Adverse event reporting

Sponsor reporting: Notifying participating investigators at affiliate sites of adverse events

It is the responsibility of the study sponsor to notify all affiliate sites, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Serious Adverse Event Reporting

Each participating investigator is required to abide by the reporting requirements set by Columbia University Medical Center. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Participating investigators must report each serious adverse event to the Columbia University Medical Center Overall Principal Investigator within 24 hours of learning of the occurrence using the SAE Report Form. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Gary K. Schwartz
Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the Investigator’s Brochure for the study drug (new occurrence) and is thought to be related to the investigational agent, the sponsor-investigator may urgently require further information from the investigator for reporting to Health Authorities.

Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the Columbia University Medical Center Overall Principal Investigator on the toxicity Case Report Forms.

Reporting to the Institutional Review Board (IRB) and the Data and Safety Monitoring Committee:

All Unanticipated Problems (UPs) will be reported to the CUMC IRB. SAEs not constituting UPs will reported to the HICCC DSMC.

Each affiliate site will be responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB’s reporting requirements, though must submit the required reports to their IRB no later than 7 calendar days following the occurrence of the UP or the Principal’s Investigator’s acquiring knowledge of the UP. Copies of each report and documentation of IRB notification and receipt must be included in the regulatory binder.

Expected AEs must be reported at the time of continuing review of a protocol.

Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The CUMC
Principal Investigator will review all applicable IND Safety Reports and has the responsibly for forwarding the IND Safety Reports to the Affiliate Institutions. The Affiliate Institution investigators are to review, send a copy to their IRB according to their local IRB’s policies and procedures, and file a copy with their regulatory documents. All Affiliate site INDSR submissions, along with IRB acknowledgment (per local policies and procedures) are to be forwarded to CUMC for placement within the trial master file.

**Reporting to Hospital Risk Management**

Affiliate Site investigators will report to their local Risk Management Office any subject safety reports or sentinel events that require reporting according to institutional policy.

10. **Confidentiality**

Each affiliate site will be assigned a site number. Each subject that signs consent should be assigned a unique code number consisting of site number followed by a number with each new subject being assigned the next sequential number (e.g., 04-10). All sites will be required to enter their data in the Velos eResearch, the Clinical Trial Management System used for all Cancer-related clinical research at CUMC. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials.

Subject confidentiality must be maintained according to HIPAA regulations and GCP recommendations.

Except when required by law, study information shared with persons and organizations outside of Columbia University Medical Center must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier. If the results of this research project are published or presented at a scientific or medical meeting, the patient not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

11. **Data Reporting Plan**

Columbia University Medical Center (CUMC) is deeply committed to research integrity and strong credibility when it comes to the discovery of new treatment concepts, implementation of new clinical research techniques, and acceptance of its researcher's findings by the medical establishment. In accord with these ethics, CUMC encourages and supports its investigators in the sharing of final research data and/or details of newly developed clinical treatments.

CUMC's policies that pertain to patient data sharing conform to CUMC IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the Principal Investigator, Statistician, Data Safety and Monitoring Board (DSMC), and, in
other instances, the CUMC IRB.

Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the CUMC’s guidelines for Protecting the Rights and Privacy of Human Subjects.

12. Data Acquisition and Submission

Informed consent, including HIPPA authorization, must be obtained on all subjects prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. Velos eResearch will be used as the electronic clinical trials and data management system. Affiliate sites will enter data directly into Velos eResearch via customized case report forms for the study. The research staff will generate reports from Velos eResearch to ensure timely submission of data by affiliate sites. This resource allows for the timely analysis of particular data sets for safety analysis.

Data should be submitted to CUMC according to Table 4:

<table>
<thead>
<tr>
<th>Table 4: Data Submission Timelines for Therapeutic Studies</th>
<th>Baseline</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3/Odd “X”</th>
<th>Cycle 4/Even “X”</th>
<th>SAE</th>
<th>End of Treatment</th>
<th>Long-Term Follow up</th>
<th>Off Study</th>
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13. **Record Keeping and Record Retention**

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.