DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

# REQUEST FOR PROJECT TEAM MEMBER APPLICATIONS FOR CONDUCTING CLINICAL TRIALS USING M3814 (NSC# 802447)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) is accepting Project Team Member Applications for clinical and non-clinical projects using M3814 (MSC2490484A, NSC# 802447), an adenosine triphosphate (ATP)-competitive inhibitor of deoxyribonucleic acid protein kinase (DNA-PK) being developed by CTEP as an anticancer agent in collaboration with Merck KGaA (a.k.a., EMD Serono). DNA-PK is vital for the successful repair of double-strand breaks in DNA by nonhomologous end joining (NHEJ) (Curtin, 2012). Pharmacological blockade of DNA-PK leads to an accumulation of sublethal and lethal nuclear DNA damage. M3814 has monotherapy antineoplastic activity in a variety of human tumor cell lines, including small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), head & neck squamous cell cancer (HNSCC), colorectal adenocarcinoma (CRC), breast cancer, as well as hematological cell lines of relapsed or refractory leukemia. Combinations of M3814 and radiotherapy, etoposide, and the anti-PD-L1 antibody avelumab demonstrate substantial *in vitro* activity when given concomitantly, and as such, are of highest clinical interest for CTEP and Merck KGaA.

Available clinical and non-clinical pharmacokinetic data support the use of M3814 by oral administration, with a twice daily (BID) dose of 400 mg as the recommended phase 2 dose (achieves >1 μM drug exposure in humans). Pharmacology safety studies reveal no significant impact on the function of mammalian cardiovascular, respiratory, or central nervous systems after prolonged drug exposure. Pharmacodynamic studies show an up to 90% reduction in human *ex vivo* DNA-PK activity after M3814 exposure. Studies involving M3814 monotherapy in patients with advanced-stage refractory solid tumors or in a M3814-radiotherapy combination in patients needing palliative therapy have shown the drug to be well tolerated. M3814 has also been tested in a separate arm of that same study in combination with radiotherapy in patients with HNSCC with curative intent. Clinical efficacy data are immature.

The current Merck KGaA/EMD Serono drug development plan for M3814 includes final analyses of a completed single-arm monotherapy study (EMR100036-01, NCT02316197), continued accrual to a 3-part study for patients in need of palliative radiotherapy for head and neck/thorax or cutaneous/subcutaneous tumors (EMR100036-02, NCT02516813), and continued accrual to a combined phase 1b single arm /a randomized phase 2 placebo-controlled study of cisplatin-etoposide chemotherapy with or without M3814 in patients with extensive-stage small cell lung cancer (MS100036-0022, NCT03116971) intended for registration. Merck KGaA/EMD Serono also plans a study in solid tumor patients with a combination of M3814-avelumab intravenously 10 mg/kg given once every two weeks.

At the present time, CTEP plans to sponsor up to four phase 1 combination trials of M3814 for the treatment of relapsed refractory ovarian cancer, relapse refractory acute myeloid leukemia (AML), advanced-stage gastrointestinal cancer with liver metastases, or advanced-stage molecularly-targeted cancers. The role of the project team is to evaluate all available evidence to modify and to refine this initial plan. The project team will include:

1. **Clinician Scientists** with expertise in phase 1 or 2 trials and an interest in DNA-damaging chemotherapy or radiotherapy for solid tumors, especially ovarian cancer or gastrointestinal cancer (fill out **Part A** of the attached Application);

2. **Translational scientists** with expertise in biomarker development for DNA-PK, NHEJ, γ-H2AX/NBS1 foci, pro-senescence or pro-apoptosis signaling, or radiotherapy effect upon tumor cells, especially as it relates to ovarian or colorectal cancers or AML (fill out **Part B** of the attached Application);

3. **Clinical pharmacologists** with expertise in phase 1 or 2 trials and an interest in pharmacokinetics, drug-drug interactions, and dose-schedule effect upon tumor pharmacodynamics (fill out **Part B** of the attached Application); and

4. **Basic scientists** with expertise in DNA-PK biology or NHEJ (fill out **Part C** of the attached Application and see the submission instructions at the end of this letter).

Prospective project team members may apply for multiple roles using a single application form by completing all the appropriate parts (Part A, B, or C). The project team will be recruited nationally, and the team will be responsible for prioritizing the research questions regarding M3814 in combination trials, including prioritization of relevant biomarker studies. It is anticipated that clinicians on the project team will be tasked with writing the Letters of Intent (LOIs) describing study design for CTEP approval. It is anticipated that these clinicians will ultimately lead the proposed project team clinical studies. It is also anticipated that other extramural members of the project team will stay involved in the subsequent design and the execution of the proposed trials. The project team should aim to complete its work in three months or less.

## Background/Rationale

DNA-PK is a member of the phophoinositide 3-kinase family [PI3K]). DNA-PK and its protein subunits Ku70 (a.k.a. XRCC6) and Ku80 (a.k.a. XRCC5) regulate NHEJ, a DNA damage response mechanism involved in the repair of double-strand DNA (dsDNA) breaks after radiotherapy or after exposure to some chemotherapeutic agents (Curtin, 2012). If dsDNA breaks are left unrepaired, the break can be cytotoxic due to cell division-related gene loss.

Cytotoxic dsDNA breaks may occur after exposure to ionizing radiation (up to 100 per cell after 350 cGy [Banath & Olive, 2003]), or topoisomerase II poisons (up to 5 per cell after 5μM etoposide or up to 10 per cell after 10μM doxorubicin [Banath & Olive, 2003]), or after the collision of replication forks with single-strand DNA breaks (up to 50 per cell spontaneously [Curtin, 2012]). NHEJ ligates dsDNA breaks with minimal DNA strand end processing, requires only a few nucleotides, occurs mainly in the G0/G1 phase of the cell cycle (but, NHEJ can be recruited for DNA repair in all cell cycle phases [Shrivastav *et al*., 2008]). It is estimated that NHEJ is responsible for the repair of up to 85% of ionizing radiation induced dsDNA breaks (Curtin, 2012).

Ionizing radiation-related and drug-related dsDNA breaks are associated with expression of the phosphorylated histone H2AX (γH2AX, Banath & Olive, 2003; Banath *et al*., 2004). dsDNA breaks are recognized by ataxia-telangiectasia mutated kinase (ATM) and by the MRN complex (formed by MRE11, RAD50, and Nijmegen breakage syndrome protein 1 [NBS1]). Because γH2AX/NBS1 co-localize to treatment-induced dsDNA breaks, CTEP plans correlative studies in the M3814 project team that use its quantitative pharmacodynamic immunofluorescence assay for γH2AX/NBS1 foci, as this has been developed, validated, and tested in human tumor xenograft models for use in clinically-relevant procedures (Kinders *et al*., 2010; LoRusso *et al*., 2016). Moreover, dsDNA breaks slow or halt cell cycle progression. Whether dsDNA break-associated cell cycle disruption pushes tumor cells toward p16-mediated cancer cell senescence and treatment-related resistance (Campisi and d'Adda di Fagagna, 2007) or toward caspase-3-mediated apoptosis (Ichim and Tait, 2016) remains unsettled. Therefore, CTEP seeks expertise on this project team for development of a clinical-grade

quantitative assay to assess pre-therapy and post-therapy tumor p16 level and apoptosis-related proteins (e.g., cleaved caspase-3) in human tumor xenograft models and for use in clinically-relevant procedures. It is anticipated that the latter goal will involve collaboration with project team members from the Frederick National Laboratory.

## M3814

M3814 is an inhibitor of DNA-PK that targets tumor cell DNA damage repair and survival by blocking NHEJ. M3814 is potent (DNA-PK $IC_{50}$ = 46 nM), with clinically-achievable blood levels of the agent being 1 μM in humans (Investigator's Brochure, 2017). Its structure appears in Figure 1.0-1. The human pharmacokinetic profile of M3814 shows a half-life ($t_{½}$) of 5 hours, suggesting twice daily dosing for continuous molecular target control. *In vitro* activity of M3814 has been observed in SCLC, NSCLC, HNSCC, CRC, breast cancer, as well as leukemia. *Ex vivo* dose-dependent inhibition of human peripheral blood mononuclear cell DNA-PK autophosphorylation occurs with a mean $IC_{50}$ of 220 nM (Investigator's Brochure, 2017).

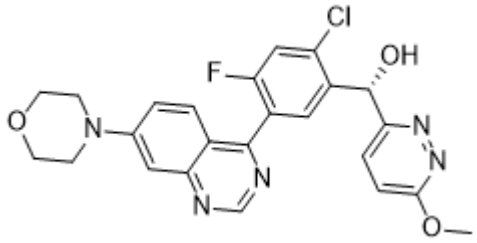


**Figure 1.0-1: Structure of M3814**

Preclinical and Clinical Pharmacology

Good Laboratory Practice (GLP) toxicity studies for distribution and pharmacodynamic response have been evaluated in mammalian models including mouse, rat, guinea pig, dog (beagle), and monkeys prior to studies in humans. Mammalian studies and human *in silico* simulations suggest that M3814 has a bioavailability of 71%. The disposition of M3814 involves high protein binding in all mammalian species investigated, with an unbound fraction of 4% to 6% in human studies. Because M3814 is a P-glycoprotein (P-gp) substrate/inhibitor properties ($IC_{50}$ 1.1 μM), it has properties that might modify absorption of oral agents (e.g., oral etoposide); has poor brain penetrance as its unbound partition coefficient (0.05) across the bloodbrain barrier is very low; and it necessitates phase 1 study to evaluate drug-drug interaction when used in combination with other anticancer therapies. Moreover, drug interaction studies show that M3814 is a substrate of liver CYP3A4 [$f_m$ 0.37-0.53], CYP2C19 [$f_m$ 0.33-0.48] and CYP2C9 [$f_m$ 0.22-0.32]), raising drug-drug interaction possibilities with an agent like etoposide which is also metabolized by liver CYP3A. At the predicted recommended phase 2 dose of 400 mg BID, M3814 might have risk to act as a perpetrator on CYP2C8/CYP2C19 and on the hepatic uptake transporters hOCT1, hOATP1B1 and hOATP1B3. M3814 is predominantly excreted by the kidneys (25% eliminated in the bile). As such, pharmacokinetic analyses on CTEP-sponsored trials are justified and expected on this project team.

| M3814 | $t_{max}$(h) | $t_{1/2}$ (h) | CL/f (l/h) | $V_z$/f (l) |
|---|---|---|---|---|
| | Median (range) | | Mean (CV%) | |
| Single-dose (C1D1) | 1.5 (0.5–4) | 4.5 (1.3–14.7) | 106.8 (98%) | 572 (75%) |
| Multiple-dose (C2D1) | 2 (0–6) | 6.3 (3.7–17.8) | 45.2 (61%) | 423 (57%) |

Clinical Studies of M3814

M3814 has been under investigation as monotherapy or in combination with other therapies in several clinical studies for the treatment of advanced oncologic malignancies; a brief outline is provided below (Table 1.0-1).

**Table 1.0-1:** M3814 clinical trial listing on ClinicalTrials.gov

| NCT | Phase | Agent(s) | Disease/Indication | Study Start -End | Status / Sponsor | Accrual | Abstract* |
|---|---|---|---|---|---|---|---|
| NCT02316197 | I | M3814 monotherapy | advanced solid tumor | Dec 2014 – Jun 2017 | completed / Merck | N=25 | None |
| NCT02516813 | I | M3814 + radiotherapy | HNSCC / thoracic / SC | Sep 2015 – open | open / Merck | N=13 | None |
| NCT03116971 | IIR | M3814 + etoposide/cisplatin | small cell lung cancer | May 2017 – open | open / Merck | N=0 | None |

Abbreviations: HNSCC = head & neck squamous cell carcinoma; SC = cutaneous or subcutaneous tumor not otherwise specified.

While a maximum tolerated dose (MTD) of M3814 has not been identified, a monotherapy recommended phase 2 dose of 400 mg orally (PO) BID has been selected in the first-in-human phase 1 trial in patients with advanced refractory solid tumors (Investigator's Brochure, 2017). Clinical efficacy data are immature. For all M3814 monotherapy studies to date, the most frequent drug-related grade 3 toxicity has been reversible non-serious rash in two treated patients (non-serious maculopapular rash, related - negative upon re-challenge at 300 mg BID; and serious maculopapular rash, related - negative upon re-challenge at 400 mg BID). A single reversible, related grade 4 alkaline phosphatase increase was observed in one patient on Day 1 of treatment. The phase 1 dose escalation starting dose of 100 mg per day, Days 1-21 of a 28-day cycle, has been recommended for future combination studies. Dose escalation steps of 100 mg per day to the targeted 400 mg per day are recommended.

In combination with radiotherapy, pharmacokinetic and pharmacodynamic modeling approaches predict that a biologically effective dose (BED) in humans should be in the range of 50 mg to 400 mg in the clinical setting of six cycles (i.e., 5-days on/2-days off). As there are no expected overlapping systemic toxicities between radiotherapy and M3814, a phase 1 dose escalation starting dose of 100 mg per day of radiotherapy has been recommended for future studies of the combination. Dose escalation steps of 100 mg per day of radiotherapy to the targeted 400 mg per day of radiotherapy are recommended.

The company has tested M3814 in combination with other agents *in vitro*, including cisplatin and topoisomerase II inhibitors like etoposide and doxorubicin (Figures 1.0-2 and 3).

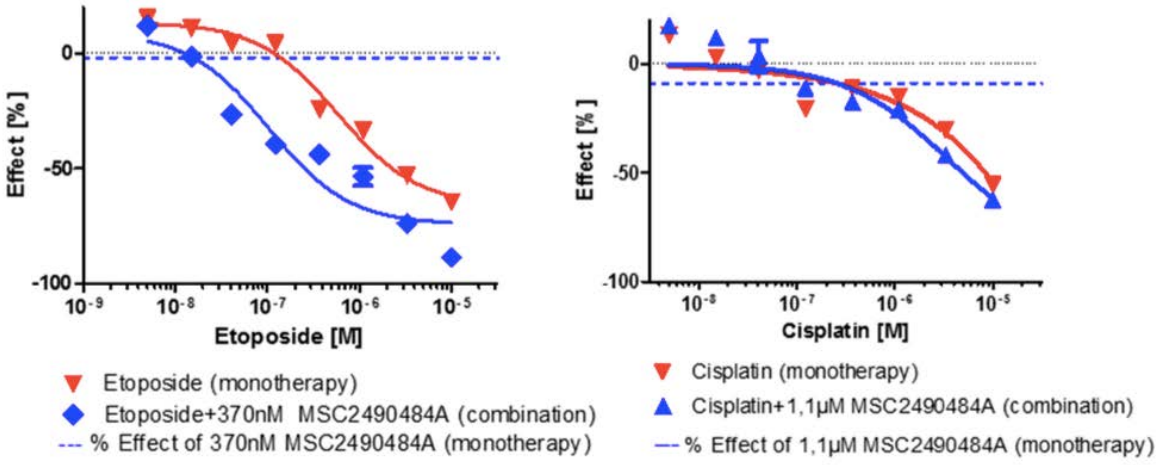


**Figure 1.0-2: M3814 in combination with etoposide and cisplatin**

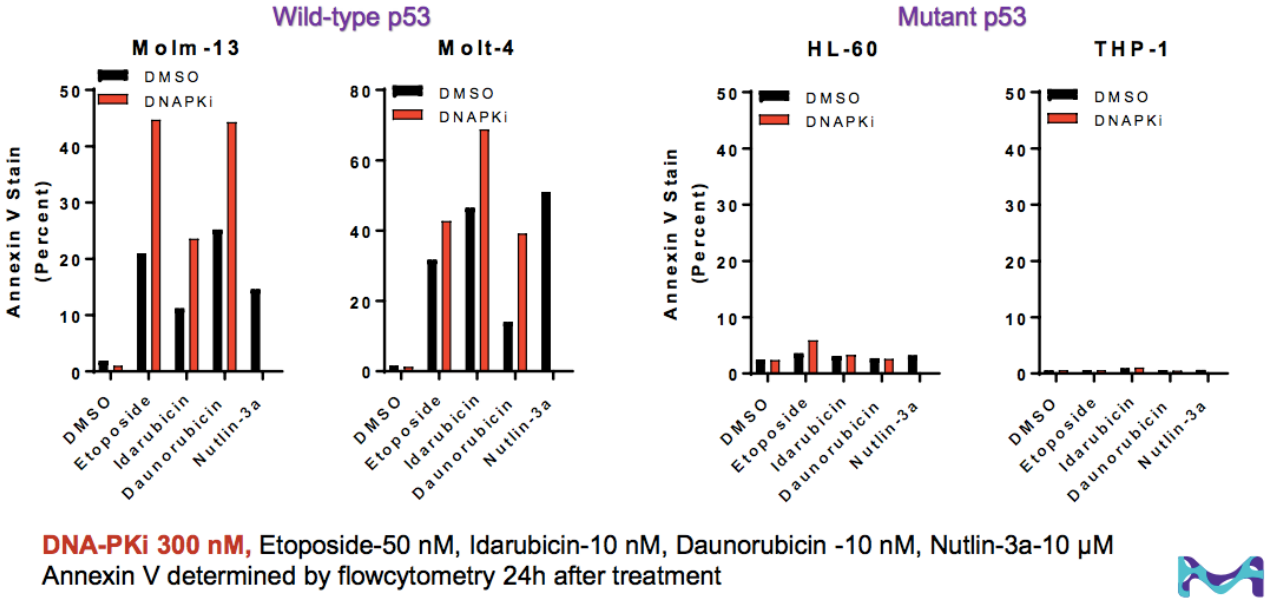


**Figure 1.0-3: p53-dependent apoptosis in acute myeloid leukemia**

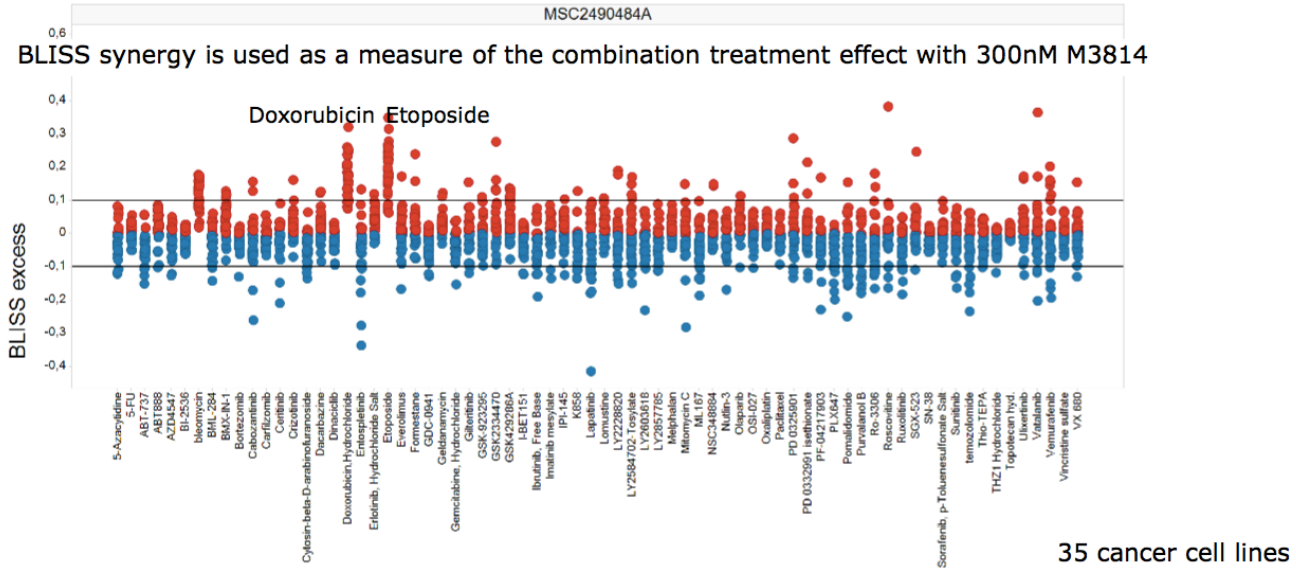


**Figure 1.0-4: BLISS synergy index in 35 cancer cell lines**

A Bliss independence model analyzes drug combination data and compares an observed combination response (Y(O)) with a predicted combination response (Y(P)). This model assumes that there is no effect from drug-drug interactions. A combination effect is declared synergistic if Y(O) is greater than Y(P). Merck KGaA has explored M3814 (300 nM) in combination with many anticancer drugs (Figure 1.0-4), and identifies synergy with doxorubicin and etoposide. CTEP is interested in further testing of M3814 and other drug combinations in ovarian, colorectal, and HNSCC cancer cell lines.

## CTEP's Plans for M3814 Development

CTEP would like to utilize a M3814 project team to develop up to four clinical trials with M3814 as well as to devise appropriate pharmacokinetic and pharmacodynamic biomarker studies for those trials. The role of the project team is to evaluate all available evidence to modify and to refine this initial clinical development plan. CTEP is willing to discuss different or additional M3814-agent combination trials, and the M3814 project team applicants can suggest such studies either in the response to this PTMA or during the project team process if the applicant is accepted to the team. In a similar fashion, applicants for a basic science or translational position on the project team may suggest alternative trials, combinations, or biomarker strategies based on their experience in the field.

CTEP is interested in M3814 due to its potent inhibition of DNA-PK among a broad number of malignancies. M3814 has favorable *in vivo* pharmacokinetic ($t_{½}$ = 5 hrs) and pharmacodynamic (post-M3814 exposure <10% DNA-pK activity) profiles. Tumor growth delay or regression effects in human tumor-bearing xenograft mammals have been demonstrated. The relatively short half-life of M3814 might also contribute to better tolerability of M3814 in combination with other therapies. M3814 associates with minimal adverse events when given BID, which favors multiple cycles of on-therapy time.

M3814 demonstrates cell lethal synergy with etoposide. Etoposide is a semisynthetic derivative of podophyllotoxin from the rhizome of the wild mandrake (*Podophyllum peltatum*), and forms a ternary complex with DNA and the topoisomerase II enzyme (which aids in DNA unwinding). Etoposide prevents re-ligation of the DNA strands, and by doing so, causes dsDNA breaks. 3-day oral etoposide given every two weeks as

palliative treatment in women with advanced-stage refractory ovarian cancer has a 4% response rate (Hillcoat *et al*., 1985). CTEP and Merck KGaA are interested in a phase 1 dose-escalated oral M3814 plus oral etoposide combination trial as 3rd-line palliative therapy in ovarian cancer patients who have no other treatment options. A randomized phase 2 trial for would be anticipated to follow.

M3814 sensitizes cancer cells to radiotherapeutic effects, with a mean radiation dose enhancement factor of 2.2 in preclinical *in vitro* models (FaDu, MiaPaCa, and A549). Radiotherapy induces up to 40 dsDNA breaks per cell after 200 cGy exposure, making a DNA-PK inhibitor combination attractive. CTEP and Merck KGaA are interested in a phase 1 dose-escalated oral M3814 plus stereotactic ablative radiotherapy combination trial with or without avelumab (intravenous 10mg/kg q2weeks) as treatment in solid tumor patients who have liver metastases. CTEP is interested in using its γH2AX-NBS1 clinical assay as an early predictor of treatment response. Depending upon results from the Merck KGaA dose-finding M3814-avelumab study, a randomized phase 2 trial in advanced-stage refractory colorectal cancer with liver metastases might follow.

M3814 improves anthracycline-related pro-apoptotic effects in AML models. Doxorubicin and daunorubicin interact with DNA by intercalating and inhibiting topoisomerase II progression, preventing dsDNA breaks from being resealed (up to 10 dsDNA breaks per cell after clinical dose exposure). CTEP and Merck KGaA are interested in a phase 1 dose-escalated oral M3814 plus 7+3 chemotherapy combination trial as treatment for relapsed refractory AML patients who have blast crisis. CTEP is interested in exploring the clinical application of its apoptosis assay in assessing response to treatment in circulating and marrow post-therapy samples. CTEP would consider a single-arm or a randomized phase 2 trial in relapsed refractory AML afterward.

M3814 preclinical observations also provide rationale for a personalized medicine multiple arm trial that could be considered during the project team process. M3814 might sensitize *in vitro* cancer cells with wild-type BRCA status, wild-type P53, loss of PTEN, BRAF mutations, or Ras mutations due to their predilection for p16-mediated senescence and regrowth (Campisi and d'Adda di Fagagna, 2007). Based on this possibility, CTEP plans preclinical cell line experiments with these oncogenic phenotypes to further justify clinical trial basket studies. If found positive, CTEP and Merck KGaA are interested in a phase 1 dose-escalated then expansion cohort study of oral M3814 plus disease-specific approved therapies as treatment for molecularly-selected patients with relapsed refractory solid tumor or hematological malignancies.

<u>Biomarker Studies of Interest to CTEP</u>

CTEP is interested in the development of biomarker studies examining the effects of M3814 or other parameters of DNA damage response in tumor biopsies and other patient-derived materials obtained from patients receiving the agent. With its partners at Frederick National Laboratory, CTEP plans whole exome sequencing or ctDNA analyses of patient samples for central confirmation of gene-of-interest status. Although driver mutations have been a focus of cancer research, passenger mutational signatures, the imprints of DNA damage and DNA repair processes that have been operative during tumorigenesis and resistance, are also biologically informative. CTEP anticipates deep-dive mutational signature analyses as every mutation detected may be instructive. Also of special interest are quantitative multiplex assays that can examine the pharmacodynamic effects of M3814 on the repair kinetics of DNA damage foci (γ-H2AX / NBS1) or on the induction of pathways of senescence (p16) or apoptosis (caspase-3) from among tumor samples. Biomarker technology and assays measuring the effect of M3814-agent combinations *in vivo* are of interest for clinical development. Limited funding for these biomarker studies may be available through a CRADA agreement for M3814 between NCI CTEP and Merck KGaA (EMD Serono), and/or through a UM1 grant mechanism. PTMAs should specifically indicate whether biomarker funding is already available or being requested from NCI, if this is pertinent to the application.

A CTEP project team could make recommendations for limited preclinical studies for M3814 alone or in combination to examine biomarkers or to justify proposed clinical studies, as well as to plan biomarker studies to occur within the study period. If the project team requests such studies, a proposal with a budget will be requested from the appropriate project team translational researcher involved, and the studies may be funded through a UM1 supplement.

## M3814 Project Team Selection, Composition, and Tasks

The M3814 project team will meet regularly by WebEx to review available evidence, determine promising strategies, examine clinical trial designs to test those strategies, and to identify biomarkers to evaluate those strategies. The project team will be composed of intramural and extramural members. The extramural members will include clinician scientists with experience in phase 1 or 2 trial designs in ovarian, gastrointestinal, leukemia and other refractory solid tumor patients; translational scientists with expertise in DNA damage biomarker development; clinical pharmacologists with experience in phase 1 or 2 trial designs, and basic scientists with expertise in DNA-PK or the nonhomologous end joining repair pathway. Since the clinician scientists selected for the project team will be expected to lead the clinical trials that come out of this process, the evaluation criteria for the clinician scientists will include not only clinical trial expertise but also their documented record of success in accruing to and/or leading early phase clinical studies in the relevant indications, as represented in the NIH Biosketch.

Questions regarding this request for applications may be addressed to Charles Kunos, M.D., Ph.D. Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI (phone: 240-276-6565; FAX: 240-276-7894; e-mail: charles.kunos@nih.gov).

CTEP recognizes the importance of encouraging and supporting young investigators as they embark upon a clinical cancer research career. CTEP highly encourages Career Development Applications (CrDAs) from these investigators and their mentors to participate as Project Team members and to develop Career Development Letters of Intent (CrDLs) after conclusion of Project Team activities.

https://ctep.cancer.gov/protocolDevelopment/lois_concepts.htm

Project Team Member Applications (PTMAs) should contain a clear indication of the applicant's desired role on the M3814 project team (clinician scientist, translational scientist, clinical pharmacologist, or basic scientist). An NIH Biosketch containing a personal statement customized to this project should also accompany the PTMA. The PTMAs should be sent to the Protocol and Information Office (PIO) at the address below by **5:00 PM Eastern Time (ET), December 15, 2017**. The most recent version of the PTMA form, available on the CTEP Website (http://ctep.cancer.gov), must be used. PTMAs should be submitted electronically to:

PIO, CTEP/DCTD/NCI
E-mail: CTEPPTMASubmissions@mail.nih.gov

**Please note that Clinician Scientists may only participate through association with the ETCTN, an NCTN Group, or a consortium (see below), and will need to submit the PTMA through their ETCTN LAO's Coordinating Center or the Group/Consortium Operations office, as applicable**. That organization will then need to submit the Clinician's application to PIO on your behalf to confirm that they are in support of the proposal. Please allow sufficient time for your organization's review. Qualifying clinical institutions include:

- ETCTN Participating Institution (under UM1 grant)

- NCTN Group member institution (under U10 grant; Alliance, COG, ECOG-ACRIN, NRG Oncology, or SWOG)
- Institutional affiliation with the Pediatric Brain Tumor Consortium (PBTC), Adult Brain Tumor Consortium (ABTC), or Cancer Immunotherapy Trials Network (CITN)

**Basic** and **Translational Scientists** (including **Clinical Pharmacologists**) who belong to a participating ETCTN institution (Lead Academic Organization [LAO] or Affiliated Organization [AO]) **must** submit applications through your LAO's Coordinating Center. Please allow sufficient time for your organization's review. Basic and Translational Scientists from non-ETCTN-affiliated institutions may directly submit their applications to PIO.

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